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ORIGINAL PAPER

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Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome

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Abstract In a single-blind, placebo-controlled crossover trial, the acute efficacy of the dopamine agonist pramipexole was investigated in 11 restless legs syndrome (RLS) patients by sleep laboratory methods, with a clinical follow-up for 4 weeks. In 3 nights (pre-treatment, placebo and drug night), objective sleep quality was determined by polysomnography (PSG), subjective sleep and awakening quality by rating scales, objective awakening quality by psychometry. Clinical follow-up consisted of completion of the International RLS Study Group (IRLSSG) Scale, Zung Depression (SDS) and Anxiety (SAS) Scale, Quality of Life Index, Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale. Concerning acute effects, an omnibus significance test for PSG variables demonstrated a global difference between placebo and pramipexole, but none between pre-treatment and placebo. Pramipexole 0.27 mg significantly decreased the target variable periodic leg movements (PLM)/h of sleep as well as all other RLS/PLM variables and improved objective sleep efficiency and subjective sleep quality as compared with placebo. In sleep architecture, sleep stages S1 and S2 and stage shifts increased, while slow-wave sleep and SREM decreased. After 4 weeks of therapy, the total scores of the IRLSSG questionnaire, sleep quality and daytime sleepiness, depression and quality of life also improved.

Thus, acute pramipexole markedly reduced PLM measures and slightly improved objective and subjective sleep quality. Follow-up ratings showed a moderate improvement of RLS and sleep quality, and to a lesser extent of daytime sleepiness, depression and quality of life. The psychopathological findings as well as acute sleep architecture changes are reminiscent of those seen after activating antidepressants.

Key words restless legs syndrome · polysomnography · psychometry · sleep quality · pramipexole

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Introduction

Although the restless legs syndrome (RLS) was described as early as in the 17th century by Thomas Willis (Willis 1686) and reemerged in the 19th century as a primarily psychiatric/psychosomatic disease called "anxietas tibiarum" (Whittmack 1881), it was only in 1945 that Ekbom reported the clinical entity, epidemiology, genetic and pathogenetic aspects of this common sensorimotor and sleep disorder (Ekbom 1945). In 1995 the International RLS Study Group defined 4 minimal clinical criteria for RLS: 1) desire to move the extremities often associated with leg paresthesia/dysesthesia, 2) motor restlessness, 3) worsening of symptoms at rest with at least temporary relief by activity, and 4) worsening of symptoms in the evening or during the night (Walters et al. 1995). A recent population-based survey mainly relying on these 4 clinical standard criteria reported an overall age-adjusted prevalence of RLS of 10 % (Rothdach et al. 2000). RLS was significantly associated with increased age. According to a recent epidemiological survey in Germany, 41 % of the sample reported mild to moderate sleep disturbances, while 4 % fulfilled the criteria of severe insomnia (Hajak 2001). RLS was found to be the fourth leading cause of insomnia after psychiatric disorders, drug abuse, and sleep-related breathing disorders (Coleman et al. 1982).

Treatment of RLS is carried out with substances of 4 classes: dopaminergic agents, which are considered the

drugs of choice, benzodiazepines, opioids and anticonvulsants (Hening et al. 1999, Saletu B et al. 2000, Saletu M et al. 2000, Saletu M et al. 2001). In conjunction with a dopa decarboxylase inhibitor (DDCI) such as carbidopa or benserazide, L-dopa proved to be efficacious in idiopathic and uremic RLS and was the first drug to be licensed for RLS in two European countries, Germany and Switzerland (Trenkwalder et al. 1995, Collado-Seidel et al. 1999). However, an end-of-dose morning rebound phenomenon (Guilleminault et al. 1993) and an earlier appearance of RLS symptoms in the afternoon, along with an increase in symptom severity ("augmentation") may be a limiting factor of L-dopa therapy (Allen and Earley 1996). Therefore, dopamine agonists are currently being favored in the treatment of RLS, especially in severe forms of the disease (Montplaisir et al. 2000). In polysomnographic studies, ergot dopamine agonists like pergolide (Wetter et al. 1999) and cabergoline (Stiasny et al. 2000), as well as the two non-ergot dopamine agonists, ropinirole (Saletu B et al. 2000; Saletu M et al. 2000) and pramipexole (Montplaisir et al. 1999), have been found efficacious in improving subjective and objective sleep quality of RLS patients. Pramipexole has a unique receptor selectivity for the dopamine D3 receptor subtype of the D2 subfamily of receptors. It has a moderate opioid affinity but no significant alpha- or beta-adrenergic or serotonergic activity. Its bioavailability is high (> 90 %). Elimination $t_{1/2}$ lies between 8 and 12 hours and is unaffected by renal function. A different profile in terms of clinical efficacy and adverse events can be expected as compared with ergolines. In contrast to the wealth of pharmacological long-term studies (Lin et al. 1998, Becker et al. 1998, Montplaisir et al. 2000) with pramipexole on RLS symptomatology and subjective sleep quality, the acute therapeutic effect of this drug on objective and subjective sleep and awakening quality has never been studied.

The aim of the present sleep laboratory study was to measure the acute effects of pramipexole as compared with placebo on objective and subjective sleep and awakening quality, with a follow-up on the clinical symptomatology in the subsequent 4 weeks.

Methods

Patients

Eleven patients (8 males, 3 females) aged between 35 and 74 years (mean 54.2 ± 13.6 years) with the ICD–10 diagnosis of RLS (G25.8) were included in the study.

From the 16 patients initially recruited from the outpatient clinic for sleep disorders of the Department of Psychiatry, University of Vienna, and the Sleep Laboratory Rudolfinerhaus, five were excluded due to the following reasons: sleep apnea, rapidly developing virus pneumonia, diabetic neuropathy, generalized anxiety disorder, or depression in a bipolar affective disorder II.

Inclusion criteria called for patients of either sex, satisfying the classification criteria for RLS (780.52–5), as determined by the ICSD (American Sleep Disorders Association 1997) and the International RLS Study Group (Walters et al. 1995), and showing stable symptoms during the 2 weeks before the study. The polysomnographic screening night had to reveal an abnormal PLM index (more than five PLM per hour of sleep).

Exclusion criteria were evidence of a medical or psychiatric disorder that might account for the primary complaint, signs of secondary RLS or other pathophysiologies such as obstructive sleep apnea or narcolepsy. Furthermore the following were excluded: pregnant or lactating women; women in the child-bearing period who were not applying adequate contraceptive methods; patients with a history of drug abuse or dependency including alcohol; patients requiring psychoactive medication or any other drug that might interfere with the study assessments; patients who were unable or unwilling to comply with the protocol; patients who worked at night.

Before entering the study, all patients had undergone a complete neuropsychiatric and general medical examination, including standard laboratory tests (blood cell count, creatinine, urea, uric acid, calcium, sodium, potassium, phosphate, LDH, liver enzymes, folic acid, iron, thyroid-stimulating hormone, T3/T4, glucose, transferrin, ferritin), electromyography (EMG) and nerve conduction velocity, to ensure that the selection criteria were fulfilled.

Patients had been suffering from RLS between 0.5 and 25 years (mean 7.9 ± 8.4 years). At the time of the investigations they had to have been free of psychotropic drugs for a period of five times the half-life of the psychoactive substance given last. Before the study, they had been treated with triazolam (n = 2), nitrazepam (n = 1), flunitrazepam (n = 1), amitriptyline (n = 1), fluoxetine (n = 1), ropinirole (n = 1) and rr-L-dopa (n = 1), while 3 patients had not received any neuropsychopharmacological agents.

The study was performed in accordance with the relevant guidelines of the Declaration of Helsinki, 1964, as amended in Tokyo, 1975, Venice, 1983, Hong Kong, 1989, and Somerset West, 1996. Informed consent was obtained. The study protocol was approved by the Institutional Review Committee.

Study design

The study was performed in two parts:

Part one was an acute, single-blind, placebo-controlled, unbalanced crossover trial with the evaluation of three sleep laboratory nights: a pre-treatment night, a placebo night and a drug night with an evening (9.00 p. m.) dose of 0.088 mg and a bedtime (10.30 p. m.) dose of 0.18 mg pramipexole. The split dose was chosen for reasons of tolerability and in order to be able to compare the data obtained with those of other dopaminergic compounds.

Part two consisted of an open follow-up period over 4 weeks, during which the optimal daily dose was titrated stepwise by 0.088 mg in weekly intervals. At each dosage increase, patients were instructed to go back to the previous dosage if they experienced persistent side-effects related to the medication.

Measures

Part one

Objective sleep quality. Sleep was recorded between 10.30 p. m. (lights out) and 6 a. m., using a 16-channel polygraph, including 3 EEG channels (C4-A1, Cz-O2, and C3-A2) according to the international 10/20 system, 2 electro-oculogram (EOG) channels (left/right), submental electromyogram (EMG) and tibialis anterior electromyogram of both legs (EMG), nasal and oral airflow, movements of the chest and abdomen, snoring, transcutaneous oxygen saturation and pulse rate. PLM parameters were subjected to a computer-assisted detection and scored visually based on the recommendation of the ASDA Atlas Task Force with the following criteria (ASDA Atlas Task Force 1993): 1) an EMG burst length between 0.5 and 5.0 seconds; 2) a movement amplitude > 25 % of a calibration movement; 3) an interval of 5 to 90 seconds between movements; 4) a minimum number of 4 consecutive movements required for a group of movements to be scored as PLM. PLM indices were subdivided into PLM/h of time in bed (PLM/h TIB), PLM/h of sleep (PLM/h TST), PLM-arousals/h of sleep, PLM/h of REM (PLM/h REM), PLM/h of NON-REM (PLM/h NREM), PLM/h of wake time (PLM/h W).

Arousals were subjected to a computer-assisted classification according to the following rules: minimum frequency change required, 2.5 Hz; min. frequency level, 6 Hz; required amplitude increase, 30 %, minimal duration, 3 s; maximal duration, 15 s; EMG ratio for REM, 2.0. Subsequently, arousals were visually scored on the basis of the EEG arousal scoring rules published by the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association (1992).

For sleep staging, thirty-second epochs were visually scored according to the criteria of Rechtschaffen and Kales (Rechtschaffen and Kales 1968).

Total sleep time (TST) is the amount of actual sleep time in the total sleep period (TSP). TSP is the period of time measured from sleep onset until the final awakening. In addition to TST, TSP includes wake time (wake/TSP) and movement time. The number of awakenings refers to arousals to wakefulness during the TSP. The sleep efficiency index (SE) is the proportion of sleep in the recorded period and is calculated by dividing TST by the total time in bed (TIB), multiplied by 100. Sleep stages 1, 2, 3, 4 and REM are expressed in minutes and in percentages of the TST. Latency to stages 1, 2, 3 and 4 defines the period of time measured from lights-out to the appearance of sleep stage 1, 2, 3 and 4, respectively. REM latency is defined as clock time from the first epoch of stage 2 (followed by > 8 min sleep in the next 10 min) to the first REM period of at least 3 min. Wake before buzzer is the time spent awake from the final awakening until the buzzer. Stage shifts refer to the number of shifts from one stage to another during TIB.

Subjective sleep and awakening quality. After awakening, the patients completed the Self-Assessment of Sleep and Awakening Quality Scale (SSA) (Saletu B et al. 1987, 1991; Saletu and Saletu-Zyhlarz 2001), including a 100 mm Visual-Analog Scale (VAS) for RLS symptomatology. The VAS consisted of a line of 100 mm, on which the patient had to mark his present condition, distinguishing between "no symptoms at all" (left end) and "most severe symptoms" (right end).

Thymopsychic variables included subjective well-being in the evening and morning, based on the Von Zerssen Bf-S Scale (Von Zerssen et al. 1970), as well as drive, mood, affectivity and drowsiness in the morning, measured by means of 100 mm VASs.

Objective awakening quality (psychometry). Morning mental performance tests included the Grünberger Alphabetical Cancellation Test (Alphabetischer Durchstreichtest = AD) for quantification of attention (AD/total score), concentration (AD/E%; errors in percentage of the total score) and attention variability (AD/SV; difference between extreme scores), the Numerical Memory Test as well as the Grünberger Fine Motor Activity Test (right and left hand) for evaluation of changes in psychomotor activity and drive (Grünberger et al. 1977). Reaction time, reaction time variability (ms) and errors of omission and commission were determined by the computer-assisted reaction time apparatus.

Part two

Clinical follow-up rating before and after 4 weeks of therapy consisted of completion of:

- The 10-question IRLSSG Rating Scale for subjective assessment of the global severity of RLS (1–10 points = mild, 11–20 = moderate, 21–30 = severe, 31–40 = very severe), which is currently being validated.
- The Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire which assesses quality and disturbances of sleep over one month (Buysse et al. 1989).
- The Zung Self-Rating Depression Scale (SDS), a rating instrument for depressive syndromes (Zung et al. 1965).
- The Zung Self-Rating Anxiety Scale (SAS), a rating instrument for anxiety syndromes (Zung et al. 1976).
- The Quality of Life Index (QLI), a self-administered paper-and-pencil questionnaire for assessment of elementary components of general health-related quality of life (HRQoL) (Mezzich et al. 2000, Saletu B et al. in press).
- The Epworth Sleepiness Scale (ESS), a self-administered questionnaire to measure a subject's general level of daytime sleepiness (Johns 1991).

Statistics

Sample size determination was based on a preceding trial with the dopamine agonist ropinirole in RLS patients (Saletu B et al. 2000).

Statistical analysis was based on the concept of descriptive data analysis (DDA), as proposed by Abt (1988) and Ferber et al. (1999) for controlled clinical trials, which allows one confirmatory statement on a pre-selected variable based on previous findings (Saletu M et al. 2000).

Normal distribution was tested by means of the 1-sample Kolmogorov Smirnov Test. If in no cases the null hypothesis of normal distribution was rejected at $\alpha = 0.10$, a two-way ANOVA was used within each drug group. In the case of a violation of the assumption of normal distribution, a Wilcoxon test was used. The pre-selected null hypothesis was that there were no differences between pramipexole and placebo in terms of the primary target variable – the PLM index/hour of sleep (maximum error probability $\alpha = 0.05$). Differences between placebo and pre-treatment recordings were analyzed as well in order to consider the psychological effect of placebo treatment.

All other effects were tested descriptively. The null hypotheses were: there are no differences between pramipexole and placebo nights (error probability = 0.05). For correction of the alpha-inflation due to the multiple tests in the inter-night comparisons (41 tests concerning PSG and 22 concerning morning subjective and objective awakening quality), an omnibus significance test based on the binomial theorem was performed (Cross and Chaffin 1982). Thus, to reject the global null hypothesis, more than 5 out of 41 tests in PSG and 4 out of 22 in morning subjective and objective awakening quality had to be significant.

In the clinical follow-up, post-treatment scores were compared with pretreatment scores using Wilcoxon' s signed rank test.

Results

Subjects

All 11 patients completed the acute part of the study. The open 4-week follow-up period was completed by 10 patients. One patient was not compliant.

Dosage

In the acute single-blind, placebo-controlled part of the study, each patient received a night-time dose of 0.27 mg pramipexole. In the subsequent open titration phase, 5 patients remained on their initial dosage. Two patients reduced the dosage to 0.088 mg. Three patients increased pramipexole to 0.45 mg. Thus, after 4 titration weeks the mean dose of pramipexole was 0.28 ± 0.1 mg.

Findings based on DDA statistics – confirmatory part

The target variable "PLM/h TST", tested by the confirmatory approach of the DDA, improved significantly from 35.0 ± 55.5/h under placebo to 8.2 ± 6.1/h under 0.27 mg pramipexole. The median of the pramipexole-induced changes, expressed in percent of the placebo values, was 78 %.

Findings based on DDA statistics – descriptive part

In order to answer the question whether or not there is an overall difference in objective PSG variables and morning subjective and objective awakening quality between pramipexole and placebo, an omnibus significance test based on the binomial theorem was performed, which corrects for the alpha-inflation due to the multiple tests in the inter-group comparison. Since 17 tests out of 41 PSG variables ($n_{sig} > 5$; $p < 0.05$) were significant, the global null hypothesis that in objective sleep quality there is no difference between pramipexole and placebo was rejected. There was no overall difference between placebo and pre-treatment, as only 3 variables showed significant findings. On the other hand, concerning morning subjective and objective awakening quality, only 2 out of 22 variables exhibited significant alterations after both placebo and pramipexole administration. Thus, in the morning no significant global differences between placebo and pramipexole were detected ($n_{sig} > 4$; $p < 0.05$).

Sleep initiation and maintenance (polysomnographic findings)

Pramipexole 0.27 mg induced a significant improvement in TST and sleep efficiency as compared with placebo (Table 1). In addition, nocturnal wake time and wake time before the buzzer decreased significantly. There were no changes from pre-treatment to placebo, with the exception of a shortened latency to stage S2 (min). The medians of pramipexole-induced changes, as expressed in percent of the placebo values, may be seen in Table 1 (e. g., under pramipexole sleep efficiency improved by 19 % as compared with placebo).

Sleep architecture (polysomnographic findings)

Under treatment with pramipexole, RLS patients showed a significant increase in sleep stages S1 and S2 (both min and %) and stage shifts, while S4 (min and %), slow-wave sleep (S3 + S4, min and %) and SREM (min and %) decreased in comparison to placebo (Table 2).

In contrast, sleep stage S4 (%) and slow-wave sleep (S3 + S4 min) increased significantly under placebo as compared with pre-treatment. The medians of pramipexole-induced changes, as expressed in percent of the placebo values, may be seen in Table 2.

Periodic leg movements

The total number of PLM, PLM/h of time in bed, and PLM/h of REM and NREM were significantly reduced after pramipexole as compared with placebo (Table 3). PLM/h of wake time (PLM/h W) were also significantly improved. Changes in the average PLM interval (s), the standard deviation of the PLM intervals and the PLM-arousal index did not reach the level of statistical significance. There were no changes from pre-treatment to placebo. The medians of pramipexole-induced changes, as expressed in percent of the placebo values, may be seen in Table 3.

Respiratory and arousal variables

Under pramipexole the apnea-hypopnea index decreased significantly, while the arousal index increased significantly as compared with placebo (Table 4). The O_2-desaturation index showed a significant decrease from pre-treatment to placebo and remained unchanged thereafter. The medians of pramipexole-induced changes, as expressed in percent of the placebo values, may be seen in Table 4.

Table 1 Sleep initiation and maintenance after acute administration of 0.27 mg pramipexole as compared with placebo in RLS patients

Variables	Mean ± sd		Wilcoxon (p) Plac v Pre	Mean ± sd Pram (N = 11)	Wilcoxon (p) Pram v Plac	Median % Pram v Plac
	Pre (N = 11)	Plac (N = 11)				
Latency to S1 (min) ↓	41.8 ± 87.3	12.3 ± 4.8	0.133	8.3 ± 8.2	0.078	–67
Latency to S2 (min) ↓	66.6 ± 96.6	33.3 ± 62.6	**0.013**	12.6 ± 9.1	0.187	–39
Latency to S3 (min) ↓	96.2 ± 121.8	83.4 ± 125.1	0.253	77.0 ± 125.1	0.500	7
Latency to S4 (min) ↓	161.6 ± 166.2	126.7 ± 164.0	0.267	170.5 ± 186.9	0.328	17
Latency to SREM (min) ↓	156.9 ± 113.3	137.5 ± 126.5	0.107	109.6 ± 74.9	0.361	25
Wake within TSP (min) ↓	113.0 ± 91.7	104.7 ± 89.9	0.297	62.0 ± 46.0	**0.019**	–41
Wake before buzzer (min) ↓	10.2 ± 29.4	32.6 ± 69.5	0.155	3.3 ± 8.5	**0.023**	–100
Awakenings (N) ↓	19.6 ± 88.9	21.6 ± 7.0	0.187	24.7 ± 8.5	0.153	17
Total sleep period (min) ↑	398.0 ± 85.4	406.2 ± 69.6	0.447	440.8 ± 11.8	**0.002**	4
Total sleep time (min) ↑	284.6 ± 102.7	301.1 ± 90.9	0.212	377.6 ± 49.5	**0.017**	18
Sleep efficiency (%) ↑	63.3 ± 22.8	66.7 ± 20.1	0.187	83.5 ± 10.6	**0.002**	19

↑ ↓ Direction of improvement
Pre Pre-treatment, *Plac* Placebo, *Pram* Pramipexole, *sd* standard deviation

Table 2 Sleep architecture after acute administration of 0.27 mg pramipexole as compared with placebo in RLS patients

Variables		Mean ± sd Pre (N = 11)	Mean ± sd Plac (N = 11)	Wilcoxon (p) Plac v Pre	Mean ± sd Pram (N = 11)	Wilcoxon (p) Pram v Plac	Median % Pram v Plac
Sleep stage	1 (%)	17.2±7.1	20.2±18.4	0.430	20.2±7.8	0.164	15
	1 (min)	45.5±21.4	51.3±25.6	0.430	73.5±17.8	**0.002**	48
Sleep stage	2 (%)	49.0±6.7	43.8±10.1	0.066	61.9±13.9	**0.003**	40
	2 (min)	138.3±51.1	135.0±55.4	0.267	233.9±63.4	**0.002**	67
Sleep stage	3 (%)	8.7±4.2	8.3±3.5	0.480	5.6±6.3	0.070	–47
	3 (min)	24.4±12.7	27.2±15.5	0.282	21.7±26.7	0.208	–38
Sleep stage	4 (%)	6.8±6.2	9.9±9.2	**0.047**	2.7±3.4	**0.009**	–89
	4 (min)	22.4±25.9	31.4±30.3	0.057	10.4±14.0	**0.011**	–85
Sleep stage	3 + 4 (%)	15.5±7.5	18.3±10.2	0.091	8.2±8.3	**0.004**	–55
	3 + 4 (min)	46.8±32.7	58.6±37.9	**0.013**	32.2±31.2	**0.006**	–50
Sleep stage	REM (%)	18.3±4.6	17.7±7.0	0.288	9.7±6.7	**0.004**	–45
	REM (min)	54.0±26.0	56.3±28.1	0.288	37.9±28.3	**0.008**	–40
Movement time (min)		0.4±0.7	0.4±0.4	0.432	1.0±1.3	0.087	50
REM latency (min)		90.3±59.8	104.2±81.0	0.395	97.0±72.6	0.361	23
Stage shifts (N)		98.6±41.6	108.1±40.4	0.055	156.9±56.1	**0.003**	18

Pre Pre-treatment, *Plac* Placebo, *Pram* Pramipexole, *sd* standard deviation

Table 3 Periodic leg movements (PLM) after acute administration of 0.27 mg pramipexole as compared with placebo in RLS patients

Variables	Mean ± sd Pre (N = 11)	Mean ± sd Plac (N = 11)	Wilcoxon (p) Plac v Pre	Mean ± sd Pram (N = 11)	Wilcoxon (p) Pram v Plac	Median % Pram v Plac
PLM (total #)	272.3±250.3	327.7±326.2	0.115	117.7±81.0	**0.005**	–63
Index PLM/h TIB	36.3±33.3	43.4±42.7	0.133	15.7±10.8	**0.005**	–63
PLM during sleep (total #)	113.1±140.1	155.5±243.4	0.143	50.4±39.9	0.091	–69
Index PLM/h TST (normal:0–5/h)	33.7±58.8	35.0±55.5	0.329	8.2±6.1	**0.031**	–78
Index PLM/h REM	14.1±30.2	18.4±33.7	0.054	4.3±7.8	**0.033**	–100
Index PLM/h NREM	37.9±62.9	37.8±61.7	0.297	8.5±6.2	**0.037**	–78
PLM during wake (total #)	159.2±134.1	172.3±111.1	0.329	67.4±67.4	**0.004**	–52
Index PLM/h W	59.9±29.6	72.4±38.6	0.143	44.4±28.6	**0.021**	–29
PLM average interval (s)	34.2±9.5	36.6±9.3	0.297	38.6±14.6	0.329	14
PLM interval sd (s)	27.3±7.7	28.7±11.0	0.297	29.3±11.0	0.430	–2
PLM-arousal index	2.7±2.8	4.2±4.6	0.107	1.4±1.3	0.073	–77

Pre Pre-treatment, *Plac* Placebo, *Pram* Pramipexole, *sd* standard deviation

Table 4 Respiratory variables and arousal index after acute administration of 0.27 mg pramipexole as compared with placebo in RLS patients

Variables	NR	Mean ± sd Pre (N = 11)	Mean ± sd Plac (N = 11)	Wilcoxon (p) Plac v Pre	Mean ± sd Pram (N = 11)	Wilcoxon (p) Pram v Plac	Median % Pram v Plac
Apnea-hypopnea index (#/h sleep)	0–10	7.7±7.5	6.3±4.9	0.239	2.8±2.3	**0.013**	–54
O_2 desaturation index (#/h sleep)	0–5	4.0±6.3	1.8±3.9	**0.026**	2.2±3.7	0.390	44
Snoring index (#/h sleep)	0–20	14.3±15.3	12.7±17.7	0.267	11.3±8.3	0.395	26
Arousal index (#/h sleep)		17.4±9.2	15.5±8.1	0.187	24.5±16.3	**0.017**	44

Pre Pre-treatment, *Plac* Placebo, *Pram* Pramipexole, *NR* normal range, *sd* standard deviation

Subjective sleep and awakening quality and thymopsychic measures

Subjective sleep quality showed a significant improvement from a score of 17.0 ± 4.3 under placebo to 12.3 ± 4.2 under 0.27 mg pramipexole (Table 5). The median of the pramipexole-induced changes in this variable, expressed in percent of the placebo values, was –26 %. The RLS-VAS improved from 55.1 ± 37.5 mm in the placebo night to 28.6 ± 33.7 in the pramipexole

night, with a median change of 87 %. No other significant effects on subjective sleep and awakening quality were found. There were no changes from pre-treatment to placebo.

Mental performance in the morning

Concerning mental performance in the morning there were no significant differences between pramipexole and placebo (Table 6). Fine motor activity of the left hand increased and errors of omission decreased from pre-treatment to placebo.

Clinical follow-up

RLS symptomatology

RLS symptomatology, as rated by the IRLSSG, improved from a severe pre-treatment score of 23 ± 7 to a moderate score of 13 ± 10 after 4 weeks of therapy (Table 7). The median of the pramipexole-induced changes, expressed in percent of the pre-treatment value, was –34 %.

Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS)

After 4 weeks of therapy with pramipexole, the Pittsburgh Sleep Quality Index (PSQI) had significantly decreased from 13.5 ± 3 to 7.7 ± 3, which corresponds to a median change of 46 %. The a priori normal Epworth Sleepiness score also showed a significant decrease.

Table 5 Subjective sleep/awakening quality and thymopsychic measures after acute administration of 0.27 mg pramipexole as compared with placebo in RLS patients

Variables	Mean ± sd		Wilcoxon (p) Plac v Pre	Mean ± sd Pram (N = 11)	Wilcoxon (p) Pram v Plac	Median % Pram v Plac
	Pre (N = 11)	Plac (N = 11)				
Sleep quality (score) ↓	17.5 ± 5.0	17.0 ± 4.3	0.480	12.3 ± 4.2	**0.004**	–26
Awakening quality (score) ↓	20.2 ± 6.0	19.4 ± 5.5	0.132	18.7 ± 5.5	0.297	–4
Somatic complaints (score) ↓	7.1 ± 2.4	7.0 ± 2.0	0.392	8.6 ± 3.5	0.053	14
SSA – total (score) ↓	44.8 ± 10.9	43.4 ± 8.6	0.395	39.6 ± 10.2	0.091	–9
RLS – visual analog scale	47.1 ± 33.1	55.1 ± 37.5	0.200	28.6 ± 33.7	**0.006**	–87
Well-being evening (score) ↓	25.1 ± 16.9	25.5 ± 17.3	0.118	28.6 ± 15.6	0.179	3
Well-being morning (score) ↓	26.4 ± 17.4	28.6 ± 17.7	0.380	27.5 ± 17.9	0.460	–1
Drive (mm) ↓	53.0 ± 31.3	63.0 ± 22.3	0.057	56.5 ± 28.7	0.238	–5
Mood (mm) ↑	57.4 ± 27.5	55.3 ± 25.4	0.361	48.1 ± 30.0	0.077	–7
Affectivity (mm) ↑	53.5 ± 30.5	48.7 ± 29.8	0.203	59.8 ± 30.1	0.465	–2
Drowsiness (mm) ↓	65.5 ± 30.2	56.5 ± 27.0	0.175	58.6 ± 27.9	0.465	4

↑ ↓ Direction of improvement
Pre Pre-treatment, *Plac* Placebo, *Pram* Pramipexole, *sd* standard deviation

Table 6 Mental performance in the morning after acute administration of 0.27 mg pramipexole as compared with placebo in RLS patients

Variables	Mean ± sd		Wilcoxon (p) Plac v Pre	Mean ± sd Pram (N = 11)	Wilcoxon (p) Pram v Plac	Median % Pram v Plac
	Pre (N = 11)	Plac (N = 11)				
Attention (score) ↑	439.1 ± 133.8	440.0 ± 150.4	0.430	426.3 ± 145.7	0.500	2
Concentration (% errors) ↓	5.6 ± 6.9	3.8 ± 3.2	0.395	3.9 ± 2.8	0.395	28
Attention var. (score) ↓	15.4 ± 2.6	14.8 ± 6.1	0.322	15.6 ± 7.7	0.465	–4
Numerical memory (N) ↑	4.2 ± 1.3	4.6 ± 1.4	0.235	4.9 ± 1.4	0.286	0
Fine motor activity RI ↑	36.3 ± 9.0	38.5 ± 8.1	0.120	36.5 ± 11.7	0.157	–4
Fine motor activity LE ↑	28.3 ± 8.0	32.8 ± 6.2	**0.016**	30.6 ± 7.8	0.077	–8
Fine motor activity RI+LE ↑	64.6 ± 16.6	71.3 ± 13.7	0.052	67.1 ± 19.1	0.121	–7
Reaction time (RT) (ms) ↓	603.4 ± 118.9	567.5 ± 98.9	0.257	592.5 ± 87.3	0.111	2
RT variability (ms) ↓	122.3 ± 43.9	109.1 ± 38.4	0.459	112.8 ± 30.5	0.361	2
RT errors/commission (N) ↓	6.9 ± 5.6	6.0 ± 7.6	0.277	5.0 ± 8.3	0.078	–58
RT errors/omission (N) ↓	1.9 ± 2.3	0.6 ± 1.0	**0.034**	1.2 ± 0.3	0.051	–100

↑ ↓ Direction of improvement
Pre Pre-treatment, *Plac* Placebo, *Pram* Pramipexole, *sd* standard deviation

Table 7 Changes in clinical variables after 4 weeks of treatment with pramipexole 0.28 ± 0.1 mg h.s. as compared with pre-treatment

Variables	Pre-treatment (mean ± sd)	Post-treatment after 4 weeks (mean ± sd)	Wilcoxon (p)	Median % Pre v Post
IRLSSG Severity Scale	23.2 ± 6.5	13.0 ± 10.1	**0.004**	–34
Pittsburgh Sleep Quality Index	13.5 ± 3.1	7.7 ± 3.0	**0.003**	–46
Self-rating Depression Scale	45.6 ± 11.7	37.0 ± 11.6	**0.006**	–11
Self-rating Anxiety Scale	37.6 ± 10.4	36.2 ± 8.9	0.078	–5
Quality of Life Index	5.8 ± 1.9	6.7 ± 2.1	**0.014**	16
Epworth Sleepiness Scale	7.6 ± 4.3	7.0 ± 3.8	**0.008**	–14

sd standard deviation

Zung Self-Rating Depression (SDS) and Anxiety Scale (SAS), Quality of Life Index (QLI)

Post-treatment scores of the SDS and QLI showed a significant improvement as compared with pretreatment. For the SAS no differences between pre- and post-treatment were observed.

Adverse events

All 11 patients completed the study. Minor side-effects possibly related to the therapy were nausea (n = 2), headache (n = 1) and vertigo (n = 2).

Discussion

In our acute, placebo-controlled investigations pramipexole induced a significant decrease in the target variable PLM/h of sleep by 78 %. Concerning overall objective quality of sleep, an omnibus significance test demonstrated a global superiority of pramipexole over placebo, as 17 out of 41 PSG variables showed a significant immediate effect of this treatment regimen. Sleep efficiency improved by 19 % as compared with placebo. In the morning only subjective sleep quality and RLS symptomatology improved in comparison to placebo. The latter itself did not induce any significant changes as compared with pre-treatment, except for 3 out of 41 PSG variables (shortened latency to S2, increased slow-wave sleep and decreased desaturation index) and 2 out of 22 morning psychometric variables (improvement in fine motor activity left and errors of omission in the reaction time task). Objective sleep quality after acute administration of pramipexole had never before been measured by means of polysomnography in an acute randomized placebo-controlled trial. In contrast to the well-documented beneficial effects of the drug on subjective RLS and sleep symptomatology (Lin et al. 1998, Becker et al. 1998, Montplaisir et al. 2000), sleep laboratory studies with chronic pramipexole in doses of up to 0.75 mg have not succeeded in objectifying an effect on sleep continuity, such as total sleep time, number of awakenings or sleep efficiency, although PLM variables returned to normal values. This lack of significant improvement was due to the small sample size and the large standard deviations on these variables, as suggested by the author (Montplaisir et al. 1999). However, these findings are consistent with 4 controlled polysomnographic studies on L-dopa, which on the one hand all showed a significant improvement of PLM and subjective sleep quality, but one the other hand failed to demonstrate an improvement of objective sleep efficiency (Brodeur et al. 1988, Kaplan et al. 1993, Trenkwalder et al. 1995, Saletu M et al. 2002b). Due to its short elimination half-life, L-dopa/benserazide seems to be more effective in the first hours after drug intake than at the end of the night (Trenkwalder et al. 1995, Kaplan et al. 1993), as it improves PLM, which mostly occur in the first half of the night, but not sleep efficiency, which is calculated over the whole night. In contrast to L-dopa, ergot dopamine agonists like pergolide (Wetter et al. 1999) and cabergoline (Stiasny et al. 2000) improved sleep efficiency determined by PSG. The non-ergot dopamine agonist ropinirole (Saletu B et al. 2000), with a shorter elimination half-life of 6 h improved sleep efficiency by only 8 % as compared to an improvement of 19 % under pramipexole with an elimination half-life of 8 h, while interestingly both drugs induced a similar improvement of PLM/h of sleep (75 and 78 %, respectively). Therefore, one may argue that dopaminergic agents with a short half-life, especially L-dopa, have a more pronounced effect on movement disorders than insomnia, which may reflect another shortcoming of this first approved RLS therapy, apart from a higher risk and extent of the augmentation phenomenon as compared with dopamine agonists (Allen and Earley 1996).

In sleep architecture, acute administration of 0.27 mg pramipexole increased sleep stages S1 and S2 and stage shifts, while slow-wave and REM sleep decreased significantly as compared with placebo. Significant differences as compared with placebo were observed with several dopamine agonists, which again is in contrast to our recent study results with a combination treatment of 100 mg regular-release (rr) and 100 mg sustained-release (sr) L-dopa/benserazide in RLS, showing no influence of this drug on sleep architecture (Saletu M et al., 2002b). In a study on pergolide, an ergoline dopamine agonist with a potent activity on presynaptic D2 and postsynaptic D1 and D2 dopamine receptors, given in mean daily doses of 0.51 mg 2 hours before bedtime, Wetter et al. (1999) noted a significant improvement of

TST, TSP and SE, an increase in the number of spontaneous awakenings and S2, a decrease in S3 + S4 as well as an improvement of subjective sleep quality. These findings indicate that relatively low doses of pergolide may alter the distribution of non-REM sleep towards more light sleep. This is also in agreement with our own results on the dopamine agonist ropinirole, which showed an increase in S2 and stage shifts as well as a tendency towards an attenuation of S3 + S4 (Saletu B et al. 2000). Also the increase in the number of arousals seen in the present study, as well as in the above-mentioned pergolide and ropinirole studies, can be seen as a consequence of the postulated drug effect on the D2 receptors. Like in the present study, in that of Montplaisir, pramipexole was also found to prolong REM sleep latency and decrease REM sleep time, mimicking antidepressant effects, as suggested by the author (Montplaisir et al. 1999). The decrease in SREM and SWS (stages with reduced muscle tone) observed after pramipexole in the present study could also explain the improvement of the apnea/hypopnea index, which may be of relevance in sleep-related breathing disorders, a frequent comorbidity of PLM and RLS (Saletu and Saletu-Zyhlarz 2001).

Insomnia patients have a significantly higher risk of psychiatric disorders, especially depression, anxiety disorders or alcoholism (Backhaus et al. 2001). The authors proved that primary insomniacs treated with short-term cognitive behavioral therapy showed significant decreases in depression and anxiety.

Our clinical follow-up rating before and after 4 weeks of therapy also included the Zung Self-Rating Depression Scale (SDS) (Zung et al. 1965), which improved significantly as compared with the pre-treatment score. In a recent study, we showed that RLS patients demonstrated significantly higher depression and anxiety scores as well as lower quality of life than a sex- and age-matched normal control group (Saletu M et al. 2002a). Moreover, brain mapping of the vigilance-controlled EEG demonstrated a trend towards a decrease in total power, an increase in absolute delta and absolute and relative alpha–2 power, a decrease in absolute and relative alpha–1 power, an acceleration of the dominant frequency and the alpha centroid and a slowing of the delta/theta centroid. These findings are characteristic of dissociated vigilance changes described in depression (Saletu B et al. 1996). Interestingly, in a recent double-blind, placebo-controlled parallel-group study, pramipexole was tested in 174 patients with major depression (Corrigan et al. 2000). As compared with the placebo group, patients receiving 1.0 mg of the dopamine agonist per day showed significantly better values than at baseline in the Hamilton Psychiatric Rating Scale for Depression and the Montgomery-Asberg Depression Rating Scale. In the same study, pramipexole demonstrated a similar or more statistically consistent improvement than fluoxetine 20 mg. The most obvious improvements were seen with 5.0 mg pramipexole, although there was a high drop-out rate in this sample due to dose-related side-effects. Corrigan's results support the monoaminergic theories of depression, which suggest that a dysregulation of systems involving dopamine, in addition to serotonin and norepinephrine, may cause major depression (Siever and Davis 1985). Theoretically, higher doses of pramipexole may act as a direct agonist at the postsynaptic receptor to relieve symptoms of depression.

Pramipexole proved to be active in diverse tests of animal behavior simulating symptoms of depression, including Willner's Anhedonia Test (Willner et al. 1994) and the Fixed Interval Test (Schaefer et al. 1996). These tests showed indications of antidepressant properties after a dose of 0.1 mg/kg. According to pharmacological studies in humans and animals, the dopamine system is involved in the modulation of sleep and waking. In rats the dopamine receptor agonists apomorphine, bromocriptine and pergolide were found to induce biphasic effects, depending on the doses administered (Monti et al. 1988). Small doses decreased wakefulness and increased SWS and REM sleep, whereas higher doses resulted in the opposite. In our present study we showed a partial antidepressive effect in the SDS rating scale and in sleep architecture, characterized by a decrease in SREM with a mean daily dose of 0.28 ± 0.1 mg after 4 titration weeks. However, even in these low doses pramipexole decreased SWS significantly, which is not in agreement with our suggested key-lock principle in the diagnosis/treatment of nonorganic insomnia related to depression. As RLS patients as well as patients with major depression exhibit a lack of SWS as compared with normal controls (Saletu B et al. 2000, Saletu-Zyhlarz et al. 2001, 2002), a therapeutically beneficial drug should increase deep sleep stages.

Our present findings with pramipexole on RLS and mood symptomatology not only reflect a comorbidity of RLS with depression, but also suggest a dopaminergic dysfunction in the pathogenesis of these two central nervous system diseases. In addition, several antidepressive agents may induce or worsen RLS or PLM (Ware et al. 1984, Paik et al. 1989, Bakshi 1996). Therefore, especially for daily clinical routine, further evidence based on placebo-controlled, long-term trials in regard to a successful monotherapy of pramipexole in RLS patients with concomitant affective disorders seems necessary.

In the second part of our study, RLS symptomatology was rated using the new severity scale of the IRLSSG, which is currently being validated. After 4 weeks of therapy, total scores of the IRLSSG questionnaire improved from a severe to a moderate form of RLS. Further improvements were found in subjective sleep and awakening quality, suggested by a significant decrease in the Pittsburgh Sleep Quality Index, and in quality of life, indicated by a significant increase in the Quality of Life Index (QLI).

In conclusion, acute administration of pramipexole markedly reduced PLM measures and showed slight effects on objective and subjective sleep quality. A 4-week treatment, evaluated by subjective ratings, moderately

improved RLS symptomatology and sleep quality, and to a lesser extent also daytime sleepiness, depression and quality of life. The psychopathological findings as well as acute sleep architecture changes are reminiscent of those seen after activating antidepressants (Saletu B et al. 1991, Saletu and Saletu-Zyhlarz 2001).

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