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ORIGINAL COMMUNICATION

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The association of dopamine agonists with daytime sleepiness, sleep problems and quality of life in patients with Parkinson's disease
– A prospective study –

Abstract *Objective* Reports that dopamine agonists (DA) precipitate sudden daytime sleep episodes in Parkinson's disease (PD) patients have received widespread attention. It remains unclear if non-ergoline and ergoline DAs have differential sedating effects or if sedation rather represents a class effect of DAs. The aim of this study was the evaluation of sleep disturbances and the quality of life (QoL) in PD patients with different dopaminergic treatment strategies. *Patients and methods*. This analysis is part of the FAQT-study, a prospective German cohort study evaluating determinants of QoL in PD patients. A subgroup of 111 PD patients was evaluated twice, at baseline and after one year of follow-up, using standardised and validated questionnaires (Unified Parkinson's disease rating scale (UPDRS), Hoehn and Yahr classification, Center for Epidemiologic Studies Depression Scale (CESD), Short Form–36 (SF–36), Parkinson Disease Questionnaire (PDQ–39)). The impact of treatment strategies on sleep problems, daytime sleepiness, bad dreams and hallucinations, depression and QoL in PD patients was analysed separately for ergoline DAs, non-ergoline DAs and the patient group taking no DA. *Results* At baseline, sleep problems were reported by about one third of the patients with and without DA medication. Excessive daytime sleepiness (EDS) was higher in the two DA groups (ergoline 11.9 %, non-ergoline 9.1 %) than among patients not taking DAs (4.5 %). At follow-up, sleep problems in general had decreased among patients taking DAs continuously and among those newly taking DAs, while the sleep problems increased in patients discontinuing DAs. However, EDS had increased to 25 % in patients newly taking DAs, and decreased to 15.9 % in those taking them continuously. QoL scores at follow-up were slightly increased in the patient groups newly taking and discontinuing DAs (the latter except in physical functioning) while those on continuing DA-medication remained unchanged. *Conclusion* No differential effects of ergoline or non-ergoline DAs on sleep problems were found. Different dopaminergic treatment strategies did not influence QoL. Our results support the evidence that sedation may be rather a class effect of DAs.

Key words Dopamine agonists · Daytime sleepiness · Sleep · Parkinson's disease · Quality of life

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Introduction

Recent reports that dopaminergic medication, in particular the D_2 and D_3 receptor agonists pramipexole and ropinirole, precipitate daytime sleepiness with sudden sleep episodes in Parkinson's disease (PD) patients have received widespread attention [4, 10, 13, 15, 16, 18, 24, 25, 27, 29, 31]. Schapira, Ferreira and colleagues, Olanow and colleagues, and Arnold reported on the occurrence

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of sleep episodes in PD patients taking the ergoline dopamine agonists (DA) pergolide [4, 13, 25, 31], bromocriptine [13], lisuride [13], or piribedil [13]. In an earlier publication, Frucht and colleagues described sleep attacks in eight PD patients taking the non-ergoline DAs pramipexole or ropinirole, two more recently introduced DAs with D_2 and D_3 receptor activity [15]. Pirker and Happe, Einwächter, Ryan and colleagues, Hauser and colleagues, and Hoehn reported on further sleep episodes in PD patients taking ropinirole [27, 29] or pramipexole [10, 16, 18, 29] and regression after switching to an ergoline DA in some cases [10, 27]. It was suggested that the sedating effect of ropinirole and pramipexole may be due to their stronger D_3 receptor activity as compared with other DAs [15, 29]. However, other reports suggest that sedation may be rather a class effect of DAs in general [13, 24–27, 31].

We present results of a prospective study analysing the associations of daytime sleepiness, bad sleep, bad dreams and hallucinations with the quality of life (QoL) in PD patients with different DA treatment strategies.

Patients and methods

This cross-sectional and longitudinal study of the association of DAs with daytime sleepiness, sleep problems and QoL in PD patients was embedded in the FAQT Study (Determinants of Quality of Life of Parkinson's Disease Patients in Ambulatory Care). For FAQT, 209 consecutive PD patients without dementia were recruited in 10 German university hospital out-patient clinics, fulfilling conventional diagnostic criteria for PD [20, 22]. All patients were interviewed and examined between November 1997 and February 1999. A subgroup of 111 PD patients who provided complete information on QoL scores and medication at baseline and after one year of follow-up were included. This group did not differ in age, disease severity, depression, medication, and duration of the disease from those participants (n=98) without follow-up. All patients were neurologically examined and evaluated using the following instruments: Unified Parkinson's Disease Rating Scale (UPDRS) [12], Hoehn and Yahr classification [19], German versions of Short Form–36 (SF–36) [37], Parkinson Disease Questionnaire (PDQ–39) [28], and the Center for Epidemiologic Studies Depression Scale (CESD – 10-item short form) [2]. SF–36 is a questionnaire that contains eight categories of items related to QoL. We analysed three sub-scores of the SF–36, physical functioning, general health and mental health. Standardised instruments were used to assess (Instrumental) Activities of Daily Living, utilisation of medical care, and medications. The impact of different antiparkinson dopaminergic treatment strategies on daytime sleepiness, sleep related problems and QoL in PD patients was tested separately for ergoline DAs (including pergolide, cabergolide, bromocriptine, and lisuride), non-ergoline DAs (including ropinirole and pramipexole) and no DA at all with regard of the levodopa dose.

The PDQ–39, containing the two questions about daytime sleepiness and bad dreams and hallucinations, was not used in all study centers at the baseline examination. Therefore, baseline data of these two aspects are based on 53 patients with baseline assessment of the PDQ–39. At follow-up, all analysed patients filled in the following three questions concerning sleep related problems: 1) Have you had problems of falling asleep unexpectedly at daytime during the last month? 2) Have you had bad night-time sleep during the last week? and 3) Have you had bad dreams or hallucinations during the last month? For question 1) and 3) (part of the PDQ–39), the subjects were asked to respond to items on a five-point scale ranging from 0, "not at all/never," to 4, "very much/always". For question 2) (part of the CESD), subjects were required to indicate response to items on a four-point scale ranging from 0 "never/rarely (less than 1 day)," to 3, "very much/always (5 to 7 days). Excessive daytime sleepiness (EDS) was defined as being present if question 1) was answered with "often" or "always". Bad sleep was defined to be present if question 2) was answered with "often" or "always", meaning three or more days during the last week. Bad dreams and hallucinations were defined to be present if question 3) was answered with "often" or "always".

We used non-parametric and parametric methods in the statistical analyses. Differences in the UPDRS and CESD scores were tested using Wilcoxon signed ranks test for two and Kruskal-Wallis test for more than two groups. Differences in interval level data (e. g. age, levodopa dose) were tested using Student's t test (two groups) or one-way ANOVA (more than two groups). Percentage differences were tested using chi square test. Results are presented with p-values. P-values < 0.05 were considered statistically significant.

Results

Descriptive data

111 PD patients (50 female, 61 male, mean age 64.1 ± 10.3 years) were included in this analysis. At baseline, 38 % of all patients were classified as having severe PD ($\geq$ 21 points in the UPDRS-motor-score). Mean Hoehn and Yahr stage was 2.6 ± 1.0 with a range of 1 to 5. About 45 % of the patients had more than 10 points in the CESD, the cut-off value for suspected depression. 34 % reported bad sleep more than 3 days during the last week, 10 % reported EDS, and 18 % reported frequent bad dreams and hallucinations. The socio-demographic and clinical data in relation to different DA treatment strategies for baseline examination are presented in table 1. Additional medication (e. g. other drugs used in PD including e. g. amantadine, selegiline, budipine, and biperiden; antihypertensive drugs, antacids, antiplatelet drugs, anticoagulants, drugs used in diabetes, bronchodilators, lipid-lowering drugs) was equally distributed among the different groups. The frequency of prescribed drugs for PD, depression, sleep disorders, and psychosis is given in table 2. There is a slight increase in drug prescriptions at follow-up, mainly in antiparkinson medication, antidepressants and atypical neuroleptics. Only tri- and tetracyclic antidepressants were used at baseline. At follow-up, only two patients received selective serotonin reuptake inhibitors. No relation of antidepressive drugs, atypical neuroleptics and hypnotics with sleep related problems and EDS was observed.

Sleep questions with regard to dopaminergic treatment

The percentages of patients with bad sleep, EDS, and bad dreams and hallucinations are presented in tables 1 and 2, stratified by different dopaminergic treatment strate-

Table 1 Socio-demographic and clinical data of 111 Parkinson's disease patients divided for different dopamine agonist treatment strategies at baseline examination

	Ergoline DA N=67	Non-ergoline DA N=22	No DA N=22	p
Age, years	63.5 ± 10.8	66.4 ± 8.3	63.7 ± 10.7	n. s.[1]
Sex, % female	46.3	45.5	40.9	n. s.[2]
Duration of PD, years	7.6 ± 5.7	8.1 ± 5.1	5.9 ± 5.5	n. s.[1]
Hoehn & Yahr stage, medians	3.0	3.0	3.0	n. s.[3]
UPDRS motor score, medians	17.0	20.0	18.5	n. s.[3]
CESD total score, medians	9.0	11.0	9.0	n. s.[3]
Total number of medication	4.4 ± 1.9	4.3 ± 1.8	4.1 ± 2.0	n. s.[1]
Number of antiparkinson medication	3.0 ± 1.1	2.6 ± 1.0	2.2 ± 1.4	0.02[1]
Levodopa dose, mg	399 ± 279	332 ± 319	419 ± 267	n. s.[1]
CESD: Sleep problems, %	31.3	36.4	38.1	n. s.[2]
PDQ–39: Excessive daytime sleepiness, %[#]	11.9	9.1	4.5	n. s.[2]
PDQ–39: Bad dreams and hallucinations, %[#]	19.4	9.1	22.7	n. s.[2]
SF–36: General health score	44.9 ± 15.9	43.9 ± 12.7	46.3 ± 15.1	n. s.[1]
SF–36: Mental health score	59.2 ± 15.3	54.9 ± 20.0	61.1 ± 15.0	n. s.[1]
SF–36: Physical functioning score	48.0 ± 31.9	51.5 ± 31.3	48.7 ± 33.9	n. s.[1]

[1] One-way ANOVA for differences between groups, [2] Chi square test for differences between groups, [3] Kruskal Wallis test for differences between groups.
[#] based on 53 patients with baseline assessment of the PDQ-39

Table 2 Frequency of prescriptions for selected drugs in Parkinson's Disease patients (n=111)

Medication	Baseline		Follow-up (12 months)	
	n	(%)	N	(%)
Levodopa plus benserazide	63	56.8	66	59.5
Levodopa plus carbidopa	52	46.8	55	49.6
Ergoline dopamine agonists	67	60.4	67	60.4
Non-ergoline dopamine agonists	22	19.8	24	21.6
No dopamine agonist at all	22	19.8	20	18.0
Other antiparkinson drugs	86	77.5	94	84.7
Antidepressants	12	10.8	20	18.0
Hypnotics (e. g. benzodiazepines)	4	3.6	4	3.6
Atypic Neuroleptics	2	1.8	6	5.4

gies. At baseline, 11.9 % of the patients taking an ergoline DA, 9.1 % of the patients taking a non-ergoline DA, and 4.5 % of the patients without a DA medication reported EDS. The corresponding percentages at follow-up were 13.6 %, 25 %, and none. Patients with DAs showed a significantly higher occurrence of EDS than patients without taking DAs (Fisher's exact test, p=0.036) at follow-up, but not at baseline (p=0.102). No significant difference of EDS between both DA groups was observed, neither at baseline nor at follow-up. There were no significant differences in sleeping badly and in having bad dreams or hallucinations at baseline and after one year in the different therapeutic groups. However, there was a trend of a higher occurrence of bad sleep in patients taking no DA.

Sleep questions with regard to alterations of dopaminergic treatment

Eighty-three patients were continuously prescribed a DA in the time period of 12 months between baseline and follow-up, six patients had discontinued taking a DA, and eight patients newly started to take a DA during the examination period (table 3). Significantly less patients with a newly prescribed DA and less patients without a change of DA reported bad sleep after one year. Patients who had discontinued taking a DA, however, had an increased frequency of bad sleep after one year. No significant changes of EDS and bad dreams and hallucinations were observed between treatment groups. Also, there were no significant associations of the levodopa dose with EDS and sleep and dream disturbances.

Disease severity, depressive symptoms and quality of life

At baseline, 49.2 % of patients without DA, 58.3 % of patients taking an ergoline DA, and 58.8 % of patients taking a non ergoline DA were classified in Hoehn and Yahr stages ≥ 3. There were no significant differences concerning disease severity, depression scores, and QoL in the different DA treatment groups, both cross-sectionally and longitudinally (table 1). However, the group discontinuing DAs reported lower QoL scores for all three sub-scores (table 3).

Discussion

Reports on DAs, in particular the D_2 and D_3 receptor agonists pramipexole and ropinirole, precipitating daytime sleepiness with sudden sleep episodes in PD patients have become of increasing interest among physicians and patients. It was speculated that the sedating effect of the non-ergoline DAs may be due to their stronger D_3 receptor activity as compared to ergoline DAs [15, 29]. Our results rather support the evidence that sedation may be a class effect of DAs in general [13, 24–27, 31].

We did not observe significant differences in disease severity, depressive symptoms, and QoL in patients with different DA treatment strategies, neither cross-sectionally nor longitudinally. EDS was generally more frequent

Table 3 Socio-demographic and clinical data of 111 Parkinson's disease patients stratified by dopamine agonist treatment status at baseline examination and at follow-up (12 months)

	DA continuously prescribed N=83	No DA at baseline, newly prescribed at follow-up N=8	DA at baseline, discontinued at follow-up N=6	p for difference between treatment strategies
Age at baseline, years	64.1 ± 9.9	61.4 ± 12.3	66.5 ± 15.3	n. s.[1]
UPDRS motor score, medians				
Baseline	18.0	18.5	17.0	n. s.[3]
Follow-up	18.0	18.2	13.0	n. s.[3]
CESD total score, medians				
Baseline	9.0	10.5	10.0	n. s.[3]
Follow-up	9.0	10.5	15.0***	n. s.[3]
Total number of medication				
Baseline	4.3 ± 1.8	3.9 ± 2.3	5.3 ± 1.8	n. s.[1]
Follow-up	4.7 ± 1.8**	5.3 ± 2.1	6.0 ± 2.0	n. s.[1]
Number of antiparkinson medication				
Baseline	3.0 ± 1.1	2.3 ± 1.6	2.5 ± 1.1	n. s.[1]
Follow-up	2.7 ± 1.1**	2.8 ± 1.0	2.5 ± 1.2	n. s.[1]
Levodopa dose, mg				
Baseline	362.3 ± 269.7	434.4 ± 297.6	660.4 ± 421.6	0.04[1]
Follow-up	469.4 ± 258.3**	385.9 ± 137.2	300.2 ± 291.5	n. s.[1]
Sleep problems, %				
Baseline	33.7	50.0	16.7	n. s.[2]
Follow-up	22.0	0*	33.3	n. s.[2]
Excessive daytime sleepiness, %				
Baseline[#]	25.0	0	0	n. s.[2]
Follow-up	15.9	25.0	0	n. s.[2]
Bad dreams and hallucinations, %				
Baseline[#]	15.0	0	0	n. s.[2]
Follow-up	8.5	12.5	33.3	n. s.[2]
General health, score				
Baseline	45.0 ± 15.1	47.8 ± 18.1	42.3 ± 15.2	n. s.[1]
Follow-up	44.9 ± 13.2	48.2 ± 15.7	44.1 ± 20.4	n. s.[1]
Mental health, score				
Baseline	58.6 ± 16.5	54.9 ± 12.8	50.0 ± 18.9	n. s.[1]
Follow-up	60.5 ± 16.6	58.3 ± 18.2	54.0 ± 15.8	n. s.[1]
Physical functioning, score				
Baseline	50.7 ± 31.0	49.8 ± 35.8	39.2 ± 35.6	n. s.[1]
Follow-up	49.0 ± 30.3	50.7 ± 33.00	35.8 ± 25.2	n. s.[1]

* p for difference between baseline and follow-up = < 0.05; ** p for difference between baseline and follow-up = < 0.01; *** p for difference between baseline and follow-up = 0.06.

[#] based on 46 patients with baseline assessment

[1] One-way ANOVA for differences between groups and Student's t-test for differences between baseline and follow-up within one group.

[2] Chi-square test for differences between groups and two-sample proportion test for differences between baseline and follow-up within one group.

[3] Kruskal Wallis test for differences between groups and Wilcoxon signed ranks test for differences between baseline and follow-up within one group.

in patients taking a DA. The patient group newly started on DA during the examination period decreased its sleep problems in general but reported more often EDS and bad dreams and hallucinations. However, owing to the small number of cases, these findings did not reach statistical significance and did not allow separate analysis for the two DA groups. The levodopa dose did not show any significant association to EDS and sleep disturbances.

Others have found that also levodopa can induce sedation [3] and occasionally improve sleep in PD patients [6]. In our study, patients without a change of DAs had a significant increase in the levodopa dose while those who were newly started on DA reduced their levodopa dose. This finding underlines the clinically important chance of reducing or omitting levodopa when taking a DA [7, 17], but obviously only for a short period of continuous treatment.

Rye and co-workers described a decreased sleep latency and an increased frequency of sleep-onset REM periods in 27 PD patients in the multiple sleep latency test. None of these patients took a non-ergoline DA, only seven of the patients took an ergoline DA, and a detrimental effect of the ergoline DA pergolide as well as the levodopa dose upon daytime alertness was not detected [30]. However, numbers were very small in this study. In a community-based study from Norway, 15.5 % of PD patients but only 1 % of healthy elderly and 4 % of older patients with diabetes mellitus reported to experience EDS, whereas the frequency of mild daytime sleepiness was similar [34]. Factor and co-workers also found that EDS and dozing, but not napping, are more frequent in PD patients than in elderly controls [11]. There was no difference in the levodopa dose in patients with EDS and mild daytime sleepiness but a somewhat higher frequency of EDS among patients taking a DA than among those without [34]. Pal and co-workers described no differences in the Epworth sleepiness scale in PD patients taking either pramipexole, cabergoline or levodopa monotherapy in a more recent study (Pal et al. 2001).

These findings are in line with our results. Based on the significant relation of male gender with EDS at follow-up in patients taking non-ergoline DAs (p=0.008), one might hypothesise that EDS could be increased because of altered muscle activity during the night. However, polysomnographic studies are necessary to further investigate this issue.

Our finding of a high prevalence of depressive symptoms in association with bad sleep supports previous findings [1, 5, 8, 9, 14, 21, 23, 32, 33, 35, 36]. But because of the use of a single question, no differentiation between various reasons for sleep-related problems was possible in this study. However, it underlines the important impact on sleep disturbances in PD patients and the need of effective antidepressive treatment.

Our study has several strengths and limitations. The strength of this study is a high number of 111 consecutive, rather unselected PD patients followed prospectively. The study had the ability to assess depressive symptoms and QoL with standardised methods parallel to the assessment of sleep problems. Changes in treatment strategies could be thoroughly documented. Since this was an observational study, the number of patients who discontinued or newly started DA was rather small and did not allow the analysis of differential effects of the two DA groups. Although EDS rather seems to be a class effect, the potential to induce EDS may be higher in non-ergoline DAs since its increase during the follow-up period was 175% as compared with 14% in ergoline DAs. We did not have the chance to include healthy controls because the FAQT study was designed to prospectively evaluate determinants of QoL of PD patients in ambulatory care.

The increased number of concomitant medications at follow-up did not show a direct relation with sleep related problems and EDS. This increase was most likely caused by disease progression and intensified care during study participation.

We conclude that EDS as well as sleep and dream disturbances are frequent findings in PD patients. Our results suggest that sedation is a class effect of DAs rather than specific to non-ergoline or ergoline DAs and that QoL does not significantly differ between various DA treatment strategies. Our findings also suggest that an optimised therapy with DAs plays an important role in decreasing the frequency of bad sleep in general but can increase EDS as well as bad dreams and hallucinations.

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