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ORIGINAL COMMUNICATION

Sleep-wake cycle and effects of cabergoline monotherapy in de novo Parkinson's disease patients

An ambulatory polysomnographic study

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This study was performed at the Sleep Disorder Center of Tor Vergata University of Rome.

The authors have declared that no conflict of interest exists.

Abstract *Objective* To investigate the sleep-wake cycle and the effects of cabergoline monotherapy in a homogenous group of de novo Parkinson's Disease (PD) patients without confounding comorbid factors. *Design and participants* Twelve de novo patients affected by idiopathic PD underwent two ambulatory polysomnographic (A-PSG) monitoring sessions. The first was performed at baseline, and the second recording one-month after stable treatment with cabergoline monotherapy. Subjective daytime sleepiness was evaluated by means of the Epworth Sleepiness Scale. Data obtained in PD patients at baseline were compared with those obtained in 12 age- and sex-matched healthy subjects. *Results* Diurnal sleep parameters did not show significant differences between controls and PD patients at baseline. In PD patients, no significant changes in diurnal sleep were observed between baseline and cabergoline treatment. Regarding nocturnal sleep, patients at baseline showed a significantly lower sleep efficiency and a significantly higher Wakefulness After Sleep Onset than controls. With respect to baseline, a significant increase in REM latency and a significant reduction in REM sleep were observed during cabergoline treatment. *Conclusions* In the early stage of PD, the neurodegenerative process does not seem to be directly responsible for daytime somnolence, but it may be directly involved in the alteration of nocturnal sleep. Cabergoline monotherapy does not affect daytime sleep propensity and, despite clinical improvement, it *may have negative* effects on REM sleep.

Key words sleep · daytime somnolence · Parkinson's disease · cabergoline · polysomnography

Introduction

Patients affected by Parkinson's disease (PD) frequently complain about sleep-wake cycle disturbances; several factors, indeed, may impair nocturnal sleep. Sleep abnormalities can be due to PD-related motor phenomena such as nocturnal bradykinesia/akinesia and rigidity, resting tremor, dystonia/dyskinesias or nocturia, as well as concomitant sleep disorders such as restless leg syn-

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drome (RLS), periodic limb movements (PLMS), circadian rhythm alteration, sleep disorder breathing (SDB) and REM sleep behavior disorder (RBD) [1–3]. In addition, daytime sleepiness and sleep attacks have been recently described during both ergot and nonergot dopamine agonists use (DA) [4–6], as well as during levodopa treatment [7, 8]. At present, the relationship between sleep, sleepiness, antiparkinsonian treatment and PD is still debated [7, 9–13]. Despite numerous studies evaluating sleep in PD, it is not yet clear if sleep disorders are a consequence of the illness itself or if these disorders depend on other factors such as the pharmacologic treatment or comorbid conditions. Furthermore, polysomnographic recordings were obtained in relatively few studies carried out in PD patients, albeit they might be crucial to exclude concomitant sleep disorders commonly associated with PD.

Cabergoline (CBG) is an ergot-derived antiparkinsonian drug with both D1 and D2 receptor agonist action. Its efficacy, long half-life (65 h) and tolerability make this drug a valid therapeutic option in early PD [14]. Add-on CBG therapy has been reported to improve sleep quality in advanced PD [15, 16].

The aims of our study were (i) to investigate the sleep-wake cycle of a homogenous group of drug-naive idiopathic PD patients who were not affected by other confounding comorbid factors and (ii) to study the effects of cabergoline (CBG) monotherapy on diurnal and nocturnal sleep in this PD group considered as a prospective cohort.

Methods

Twelve de novo never treated (except for diagnostic pharmacological challenge) PD outpatients were consecutively enrolled in our study. Patients (mean age 59.1 ± 8.5 y.o., range 46–70; 6 males, 6 females) suffered from idiopathic PD, diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria. PD severity was assessed using the Hoehn and Yahr stage [17] and patients' clinical disability was assessed by the motor examination section of the Unified Parkinson's Disease Rating Scale (UPDRS III) [18]. The control group included 12 age- and sex-matched healthy subjects (58.5 ± 9.2 y.o., range 43–70, 6 males, 6 females). Caffeine, tobacco, alcohol use or medications interfering with the central nervous system were not allowed. Participants affected by neoplastic, endocrine, psychiatric, respiratory illness, dementia (Mini Mental State Examination < 27) and overweight subjects (Body Mass Index > 28) were excluded. The exclusion criteria included depression and anxiety, assessed by the Hamilton Anxiety Scale and the Hamilton Depression Rating Scale.

All patients gave their informed consent. Details on patients' demographic and clinical features are summarized in Table 1.

Patients underwent two 48-hour ambulatory polysomnographic (A-PSG) monitoring sessions in order to evaluate diurnal and nocturnal sleep. The first 24 hours of each monitoring session were considered as adaptation and only results from the remaining 24 hours were analyzed.

The first A-PSG monitoring session was performed at baseline, with drug-free patients. Afterwards, all patients started cabergoline (CBG) treatment (starting dose 0.5 mg per day). The daily dose of CBG was then increased stepwise by 0.5 mg per week to achieve a relevant improvement of parkinsonian symptoms (see Table 1). The second A-PSG was performed one month after stable CBG monotherapy (mean daily dosage 3 ± 1.3 mg, range 2–4.5 mg/day, administered at 8 AM in a single dose). The mean time-interval between the two A-PSGs was 68 ± 16 days, range 52–87.

Table 1 Demographic and clinical features of PD patients

Age	
mean ± SD (range)	59.1 ± 8.5 yrs (46–70)
Gender	
male	6 pts
female	6 pts
Reported disease duration	
mean ± SD (range)	13 ± 3 months (8–18)
H & Y	
mean ± SD (range)	1.37 ± 0.4 (1–2)
CBG daily dose	
mean ± SD (range)	3 ± 1.3 mg (2–4.5)
UPDRS (section III)	
Baseline	
mean ± SD (range)	14.6 ± 5.8 (9–20)

Prior to each A-PGS monitoring session a neurologist, blind to the study design, evaluated PD patients' clinical disability by means of the UPDRS-III; each patient was required to reply to a structured interview on nocturnal sleep patterns, daytime napping and somnolence. Moreover, patients were instructed to maintain the usual sleep schedule during the week prior to each evaluation day and to fill in a sleep log. In particular, they had to signal light "off", subjective sleep onset, light "on", sleepiness, voluntary napping or diurnal sudden sleep episodes.

Recordings were performed through an ambulatory dynamic polygraph (Halley System, EBNeuro, Florence, Italy). The signal was stored on a flash card utilizing a common average reference and a time constant of 0.3 s. Electrodes were positioned according to the 10–20 International System. Specifically, the montage consisted of two oculographic channels, three electromyographic channels (mental and anterior tibialis muscles) and eight EEG channels (F4, C4, O2, A2, F3, C3, O1, A1). Prior to the first recording session, patients underwent an ambulatory monitoring of oronasal airflow (thermocouples), thoracic and abdominal respiratory effort, ECG, oximetry and snoring by means of the Embletta system (Flaga, Reykjavik, Iceland) in order to exclude obstructive sleep apnea syndrome. The evaluation of subjective daytime sleepiness was carried out the day after each PSG recording by means of the Epworth Sleepiness Scale (ESS) [19]. Finally, a neurologist expert in sleep medicine, totally blind to treatments and subjects' identity, performed the sleep analysis according to Rechtshaffen and Kales' criteria [20].

REM sleep without atonia (RWA) was scored according to Lapierre and Montplaisir criteria [21].

Subjective and objective sleep parameters obtained in PD patients at baseline were compared with controls by means of a case-control study with the pairs one case-one control using a matched-pairs T-test. The same analysis was used in order to evaluate the effects of CBG on nocturnal and diurnal sleep parameters in PD patients as a prospective cohort. The non-parametric Wilcoxon matched-pairs test assessed clinical score differences in PD patients.

Significance level was accepted at $p < 0.05$ (C.I. 95%).

Results

Clinical data

PD patients showed a significant clinical improvement in UPDRS-III score after CBG treatment vs baseline (5.9 ± 4.9 vs 14.6 ± 5.8; $p < 0.01$).

Subjective evaluation of daytime somnolence (Table 2)

ESS score did not show significant differences between control subjects and PD patients at baseline. In addition, PD patients did not show pathological ESS values or significant changes after CBG therapy with respect to baseline.

Diurnal PSG data (Table 2)

Seven out of 12 patients and six out of 12 controls showed a voluntary postprandial nap. No PD patient experienced sleep attacks or Sleep Onset REM Sleep (SOREM). Sleep parameters of diurnal sleep (i.e., Total Sleep Time-TST and number of naps) did not show statistical differences between controls and PD patients at baseline. With respect to baseline, PD patients did not show significant changes in diurnal sleep parameters after CBG monotherapy.

Nocturnal PSG data (Table 3)

PD patients at baseline had a lower Sleep Efficiency Index (SEI) (80.1 ± 9.8 vs 89.4 ± 3.7; $p < 0.01$) and an increased Wake After Sleep Onset (WASO) (17.5 ± 9.8 vs 8.3 ± 3; $p < 0.05$) with respect to the control group, without differences in other sleep macrostructure parameters.

In comparison to baseline values, a significant increase in REM Latency (204 ± 114 vs 118 ± 51.4; $p < 0.05$) and a significant reduction in REM sleep were observed during CBG treatment (7 ± 5 vs 11.9 ± 5.6; $p < 0.05$). We did not find any further significant difference in other macrostructure parameters.

RWA scored according to Lapierre and Montplaisir criteria [21] was detected in two out of 12 PD patients, even if none of them reported a clinical history suggesting RBD. Periodic Limb Movement Index (PLMI) was

Table 2 Diurnal sleep parameters and ESS score (Epworth Sleepiness Scale) in control group and PD patients, in basal condition and during CBG treatment

Sleep parameters	Control subjects mean ± SD (C.I. 95 %)	Patients, Baseline mean ± SD (C.I. 95 %)	p Control subjects vs Basal PD	Patients, CBG mean ± SD (C.I. 95 %)	p Basal PD vs CBG
ESS	5.8 ± 2.4 (4.3–7.3)	6.4 ± 2.9 (4.5–8.3)	0.45	6.7 ± 3.4 (4.4–8.9)	0.8
Diurnal TST	31.2 ± 34.8 (9–53.3)	33.7 ± 30.5 (14.3–53.2)	0.8	35.5 ± 38.8 (10.8–60.2)	0.89
N° of naps	0.5 ± 0.53 (0.16–0.8)	0.58 ± 0.51 (0.2–0.9)	0.67	0.5 ± 0.67 (0.2–0.9)	0.72

Table 3 Nocturnal sleep parameters of control subjects and PD patients in basal condition and during cabergoline therapy

Sleep parameters	Control subjects mean ± SD (C.I. 95 %)	Patients, Baseline mean ± SD (C.I. 95 %)	p Control subjects vs Basal PD	Patients, CBG mean ± SD (C.I. 95 %)	p Basal PD vs CBG
TST (min)	420 ± 48 (389.4–451.4)	391.5 ± 58 (354.5–428.5)	0.08	368.2 ± 58 (331.0–405.4)	0.3
Sleep efficiency	89.4 ± 3.7 (87.0–91.7)	80.1 ± 9.8 (73.8–86.4)	0.009	85.7 ± 14.6 (76.4–95.0)	0.26
WASO %	8.3 ± 3 (6.3–10.3)	17.5 ± 9.8 (11.3–23.7)	0.017	11.9 ± 13.8 (3.1–20.7)	0.3
S1 %	8.1 ± 6.4 (4.0–12.3)	7.3 ± 8.2 (2.1–12.6)	0.7	8.4 ± 2.5 (6.2–10.6)	0.7
S2 %	52.5 ± 12.3 (44.7–60.4)	44.2 ± 13.9 (35.4–53.1)	0.09	53.4 ± 11 (46.3–60.5)	0.15
SWS %	18 ± 6.5 (13.8–22.2)	19.1 ± 7.6 (14.2–23.9)	0.2	19.3 ± 9.2 (13.4–25.2)	0.9
REM %	13.1 ± 4.8 (10.1–16.2)	11.9 ± 5.6 (8.3–15.5)	0.3	7 ± 5 (3.8–10.2)	0.03
Sleep latency (min)	12 ± 10.2 (5.6–18.6)	12.6 ± 7 (7.7–17.6)	0.86	13 ± 21 (1.1–26.6)	0.9
REM latency (min)	103.8 ± 42 (77.1–130.6)	118 ± 51.4 (85.4–150.8)	0.5	204 ± 114 (132.0–277.1)	0.03
No of awakenings	8.1 ± 9.2 (2.3–13.9	11.5 ± 10.7 (4.6–18.3)	0.3	8.5 ± 6.2 (4.6–12.6)	0.4
No of stage shifts	68 ± 32.2 (48.3–89.3)	78.4 ± 31.4 (58.4–98.4)	0.2	77.2 ± 40 (51.7–102.7)	0.9

Sleep stages are calculated as percentage to Sleep Period Time (SPT) = Time in Bed – Sleep Latency; *TST* Total Sleep Time; *WASO* Wake After Sleep Onset; *S1* Stage 1; *S2* Stage 2; *SWS* Slow Wave Sleep (Stage 3 + Stage 4); *REM* Stage REM; Sleep Efficiency = TST/TIB

not statistically different between PD patients and control subjects (9.8 ± 10 vs 8.3 ± 7) and PLM Arousal Index (PLMAI) was < 5/h in both groups.

Discussion

In this prospective open-label study we evaluated the effects of CBG monotherapy on sleep-wake cycle in de novo PD patients by means of A-PSG. Many studies have investigated the relationships between sleep, daytime somnolence and PD and most of them took into account nocturnal sleep and daytime somnolence separately, including samples of clinically heterogeneous patients, often in polytherapy [2, 3, 9, 22–25]. In addition, a few studies were performed by means of 24-hour polysomnographic monitoring in the patient's real-life settings, and some of them regarded single case reports [6, 12, 15, 26].

Our study evaluated the complete physiological sleep-wake cycle of drug-naive PD patients in their own natural and familiar environment, without possible perturbations and interferences induced by the laboratory setting. Moreover, our sample, although numerically limited, was clinically homogenous without several confounding factors such as medical, psychiatric and sleep comorbidities that could have affected previous studies.

In our study, PD patients at baseline showed a normal degree of diurnal sleep propensity as measured by subjective (ESS) and objective A-PSG data. These results are noteworthy, considering the high occurrence of daytime somnolence in PD with a prevalence ranging between 15 and 50 %, as reported in the literature [1, 2, 24, 27]. However, in some healthy subjects and PD patients, both at baseline and after dopaminergic treatment, we observed a postprandial voluntary nap configuring a biphasic sleep pattern similar to the one reported in elderly healthy subjects, a typical habit in Mediterranean countries [28, 29].

The mechanisms underlying the diurnal sleepiness in PD are still debated; several authors hypothesized a multifactorial genesis including antiparkinsonian treatment, the illness itself and the presence of concomitant sleep disorders [5, 9–11, 13, 24]. In addition, daytime sleepiness and sleep attacks have been ascribed to both ergot and nonergot DA [4–6] as well as to levodopa treatment [7, 8]. Interestingly, CBG therapy did not modify daytime sleep propensity evaluated by means of objective (PSG data) and subjective (ESS) parameters in our patients, similar to some previous reports [12, 15, 30]. Furthermore, we did not record sleep attacks and SOREMs either in baseline condition or during CBG monotherapy, so we excluded a narcolepsy-like phenotype reported in some PD patients [31, 32].

Our findings about the lack of EDS in PD subjects, before and after CBG monotherapy, indicate that, at an early stage of the illness, both PD itself and CBG treatment may not cause EDS. Indeed, we hypothesize that the etiopathogenesis of daytime somnolence may be attributed to several different factors such as medical, psychiatric and sleep comorbidity and polytherapy, typical of the advanced phases of the pathology.

As concerns the nocturnal sleep pattern, a reduction of sleep stability and continuity was observed in our de novo PD patients, as documented by a decrease of SEI and an increase of WASO, compared to controls; no other macrostructural parameters were impaired.

The low percentage of RWA observed in our series (16.6 %), with respect to previous reports, may be due to the earlier stage of the illness of our patients [33]. Furthermore, our sample of PD patients showed a mildly increased PLMI similar to control subjects. This result is in line with a recent paper demonstrating that PLMI increase may be part of the normal aging process associated with the loss of dopaminergic function [34].

Previous PSG studies reported that sleep alterations are common, even if a pathognomonic hypnic PD pattern does not exist. In particular, sleep fragmentation with frequent awakenings, increase in WASO, arousals and sleep latency, reduction of SE, TST, Slow Wave Sleep (SWS), REM latency and REM sleep, were variably described [9, 13, 23, 35]. Such abnormalities were not observed in other studies [36]. These conflicting findings are probably due to the different methodological protocols applied, including heterogeneous samples of patients, disease duration, therapy and comorbidity.

In the present study, the dopaminergic treatment introduction, although indirectly improving the hypnic structure through a decrease of nocturnal hypokinesia, caused a further alteration of nocturnal sleep structure. In particular, CBG produced a significant increase in REM latency and a reduction in REM sleep. CBG-induced negative effect on REM sleep is in line with two previous studies reporting REM suppression in patients taking apomorphine and pergolide, respectively [37, 38]. Studies on CBG effects on nocturnal sleep are few and have reported discordant results, probably because of the heterogeneity of the case series including dopaminergic polytherapy, higher severity of disease and add-on CBG therapy [15, 16].

The actions of DA medications on sleep are complex since they may induce opposite effects on the sleep-wake cycle, which are dose- and receptor-dependent. High dose DA enhance wake and suppress REM sleep via D1-like postsynaptic receptor [39], while low dosage dopamine agonists promote sleep via D2-like receptor [5].

The nocturnal sleep alteration in drug naive PD patients without medical, psychiatric and sleep comorbidity, whose motor function is not seriously compromised, and the persistence of sleep abnormalities in spite of the clinical improvement induced by dopaminergic therapy, suggest that the disease per se may be responsible for

this hypnic impairment. In PD patients, indeed, the neurodegenerative process involves not only dopaminergic neurons of substantia nigra-pors compacte [10], but it precociously affects also other neuronal populations such as serotoninergic neurons of Dorsal Raphe nuclei, noradrenergic cells of Locus Coeruleus, and cholinergic neurons of Peduncolo-Pontine Nuclei, which are directly involved in sleep-wake cycle and REM/NREM alternation [40]. Hence, the clinical improvement induced by the dopaminergic treatment, not accompanied by any amelioration of the hypnic pattern, seems to suggest that in PD the nocturnal sleep impairment represents a self-running and independent disorder, probably due to early degeneration of different non-dopaminergic neurotransmittorial pathways [40].

In conclusion, our study highlights the clinical relevancy to take into account the occurrence of nocturnal sleep alterations in the early stage of PD, since they may contribute to affect precociously the patients' quality of life.

Although our results are limited by the small number of patients, they suggest that PD itself may be directly involved in the alteration of nocturnal sleep, whereas it does not seem to be directly responsible for daytime somnolence in the early stage. Finally, CBG monotherapy does not seem to affect daytime sleep propensity, but it may induce negative effects on REM sleep.

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References

1. Tandberg E, Larsen JP, Karlsen K (1998) A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord 13(6): 895–899
2. Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J (2001) Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology 57(8):1392–1396
3. Tan EK, Lum Sy, Fook-Chong SM, Teoh ML, Yih Y, Tan L, Tan A, Wong MC (2002) Evaluation of somnolence in Parkinson's disease: comparison with age- and sex-matched controls. Neurology 5(3):465–468
4. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S (1999) Falling asleep at the wheel: motor vehicle mishaps in person taking pramipexole and ropirinole. Neurology 52(9): 1908–1910
5. Ferreira JJ, Galitzky M, Montastruc JL, Rascol O (2000) Sleep attacks and Parkinson's disease treatment. Lancet 355(9212):1333–1334
6. Ulivelli M, Rossi S, Lombardi C, Bartalini S, Rocchi R, Giannini F, Passero S, Battistini N, Lugaresi E (2002) Polysomnographic characterization of pergolide-induced sleep attacks in idiopathic PD. Neurology 58(3):462–465
7. Homann CN, Wenzel K, Suppan K, Ivanic G, Kriechbaum N, Crevenna R, Ott E (2002) Sleep attacks in patient taking dopamine agonists: review. BMJ 324(7352):1483–1487
8. Garcia-Borreguero D, Schwarz C, Larrosa O, de la Llave Y, Garcia de Yebenes J (2003) L-DOPA-induced excessive daytime somnolence in PD: a placebo-controlled case with MSLT assessment. Neurology 61(7): 1008–1010
9. Poewe W, Hogl B (2000) Parkinson's disease and sleep. Curr Opin Neurol 13(4):423–426
10. Rye DB, Jankovic J (2002) Emerging views of dopamine in modulation sleep/wake state from unlike source: PD. Neurology 58(3):341–346
11. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, Lacomblez L, Golmard JL, Derenne JP, Agid Y (2002) Parkinson's disease and sleepiness: an integral part of PD. Neurology 58(7):1019–1024
12. Romigi A, Brusa L, Marciani MG, Pierantozzi M, Placidi F, Izzi F, Sperli F, Testa F, Stanzione P (2005) Sleep episodes and daytime somnolence as result of individual susceptibility to different dopaminergic drugs in a PD patient: a polysomnographic study. J Neurol Sci 228(1):7–10
13. Garcia-Borreguero D, Lardosa O, Bravo M (2003) Parkinson's disease and sleep. Sleep Med Rev 7(2):115–129
14. Fariello RG (1998) Pharmacodynamic and pharmacokinetics features of cabergoline. Rationale for use in Parkinson's disease. Drugs 55(Suppl 1):10–16
15. Romigi A, Stanzione P, Marciani MG, Izzi F, Placidi F, Cervellino A, Giacomini P, Brusa L, Grossi K, Pierantozzi M (2006) Effect of cabergoline added to levodopa treatment on sleep-wake cycle in idiopathic Parkison's disease: an open label 24-hour polysomnographic study. J Neural Transm 113(12):1909–1913
16. Hogl B, Rothdach A, Wetter TC, Trenkwalder C (2003) The effect of cabergoline on sleep, periodic leg movements in sleep, and early morning motor function in patients with parkinson's disease. Neuropsychopharmacology 28:1866–1870
17. Hoehn MH, Yahr MD (1967) Parkinsonism: onset, progression and mortality. Neurology 17:427–442
18. Fahn S, Elton RL, Members of the UPDRS development committee Unified Parkinson's disease rating scale (1997) In: Fahn S, Marsden CD, Calne DB, Goldstein M (eds) Recent development in Parkinson's disease, Vol. 2 MacMillan Healthcare Information: Florham Park, NJ, pp 153–163; 293–304
19. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14(6): 540–545
20. Rechtshaffen A, Kales A (1968) A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. UCLA Brain Information Service/Brain Research Institute, Los Angeles
21. Lapierre O, Montplaisir J (1992) Polysomnographic features of REM sleep behavior disorder: development of a scoring method. Neurology 42(7): 1371–1374

22. Olanow CW, Schapira AH, Roth T (2000) Waking up to sleep episodes in Parkinson's disease. Mov Disord 15(2):212–215
23. Wetter TC, Collado-Seidel V, Pollmacher T , Yassouridi SA, Trenkwalder C (2000) Sleep and periodic leg movement pattern in drug-free patient with Parkinson's disease and multiple system atrophy. Sleep 23(3):361–367
24. Factor SA, McAlarney T, Sanchez-Ramos JR, Weiner WJ (1990) Sleep disorders and sleep effect in Parkinson's disease. Mov Disord 5(4):280–285
25. Hogl BE, Gomez-Averalo G, Garcia S, Scipioni O, Rubio M, Blanco M, Gershanik OS (1998) A clinical, pharmacologic, and polysomnographic study of sleep benefit in Parkinson's disease. Neurology 50(5):1332–1339
26. Manni R, Terzaghi M, Sartori I, Mancini F, Pacchetti C (2004) Dopamine agonists and sleepiness in PD: review of the literature and personal findings. Sleep Medicine 5:189–193
27. Chaudhuri KR, Pal S, Brefel-Courbon C (2002) 'Sleep attacks' or 'unintended sleep episodes' occur with dopamine agonists: is this a class effect? Drug Saf 25(7):473–483
28. Carskadon MA, Dement WC (1992) Multiple sleep latency tests during the constant routine. Sleep 15(5):396–399
29. Gigli GL, Placidi F, Diomedi M, Maschio M, Silvestri G, Scalise A, Marciani MG (1996) Sleep in healthy elderly subjects: a 24-hour polysomnographic study. Int J Neurosci 85(3–4): 263–271
30. Del Dotto P, et al. (2003) Bedtime cabergoline in Parkinson's disease patients with excessive daytime somnolence induced by dopamine agonists. Neurol Sci 24(3):170–171
31. Rye DB, Johnston LH, Watts RL, Bliwise DL (1999) Juvenile Parkinson's disease with REM sleep behavior disorders, sleepiness and daytime REM onset. Neurology 53(8):1868–1870
32. Arnulf I, Bonnet AM, Damier P, Bejjani BP, Seilhean D, Derenne JP, Agid Y (2000) Hallucinations, REM sleep and Parkinson's disease: a medical hypothesis. Neurology 55(2):281–288
33. Gagnon JF, Bedard MA, Fantini ML, Petit D, Panisset M, Rompre S, Carrier J, Montplaisir J (2002) REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. Neurology 59(4):585–589
34. Carrier J, Frenette S, Montplaisir J, Paquet GJ, Drapeau C, Morettini J (2005) Effects of Periodic Leg Movements during sleep in middle-aged subjects without sleep complaints. Mov Disord 20(9):1127–1132
35. Bergonzi P, Chiurulla C, Gambi D, Mennuni G, Pinto F (1975) L-dopa plus dopa-decarboxylase inhibitor. Sleep organization in Parkinson's syndrome before and after treatment. Acta Neurol Belg 75(1):5–10
36. Brunner H, Wetter TC, Hogl B, Yassouridis A, Trenkwalder C, Friess E (2002) Microstructure of the non-rapid eye movement sleep electroencephalogram in patients with newly diagnosed Parkinson's disease: effects of dopaminergic treatment. Mov Disord 17(5): 928–933
37. Cianchetti C, Masala C, Mangoni A, Gessa GL (1980) Suppression of REM and delta sleep by apomorphine in man: a dopamine mimetic effect. Psychopharmacology (Berl) 67(1): 61–65
38. Askenasy JJ, Yahr MD (1984) Suppression of REM rebound by Pergolide. J Neural Transm 59(2):151–159
39. Charles R (2002) Dopamine agonists and sleep in Parkinson's disease. Neurology 58:71–78
40. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K (2004) Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 318(1):121–134