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'Sleep Attacks' or 'Unintended Sleep Episodes' Occur with Dopamine Agonists

Is This a Class Effect?

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Abstract

Controversial reports of sudden onset 'sleep attacks' resulting in road traffic accidents have recently been reported in patients with Parkinson's disease (PD) taking the non-ergot dopamine D_2 /D_3 receptor agonists pramipexole and ropinirole. These reports have generated considerable debate as the concept of 'sleep attacks' is disputed amongst sleep specialists and most believe that isolated 'sleep attacks' not preceded by warning on the background of chronic sleepiness or 'unintended sleepiness' do not exist. A series of case reports suggested that this phenomenon may not be exclusive to the non-ergot dopamine agonists such as pramipexole or ropinirole and indeed may occur with most dopaminergic agents. Recent evidence suggest that a 'sleepiness' or 'hypoactivity' reaction to dopaminergic therapy may be related to underlying dopamine deficiency of PD rather than a drug effect. In this report we provide the evidence for the phenomenon being a class effect attributable to all dopamine agonists currently employed in the management of PD.

Controversy surrounding excessive daytime sleepiness (EDS) in PD and the use of the Epworth Sleepiness Scale (ESS) in relation to PD is also discussed. In spite of variable reports, EDS is recognised to be common in PD and is likely to be related to both the disease process and drug therapy. Studies using multiple sleep latency tests have also reported differing results in PD although a recent study indicated that a subset of 'sleepy' patients with PD may experience pathological somnolence with resultant detrimental consequence on daytime and cognitive functions. We recommend that the issue of 'sleepiness' or 'sleep attacks' in PD should be routinely checked in all patients with PD and indirectly assessed by using either the ESS or the recently introduced Parkinson's Disease Sleep Scale. Those with reported 'sleep attacks' or 'unintended sleep episodes' and excessive daytime sleepiness while taking dopamine agonists or dopaminergic agents such as levodopa should have a review of their medication, should not be driving a car on their own and some may merit formal sleep architecture studies. The latter may identify sleep disorders such as secondary narcolepsy which may benefit from the use of a wakefulness promoting agent.

Recently, an observational, clinical series-type publication reported that 'sleep attacks' occur in patients with Parkinson's disease (PD) taking the non-ergot dopamine D_2/D_3 receptor agonists pramipexole and ropinirole.[1] The episodes were described as arising suddenly and without warning while patients were driving and resulted in road traffic accidents in all patients. The 'sleep attacks' ceased when pramipexole and ropinirole were discontinued. The publication of this report resulted in widespread concern in relation to safety of prescribing pramipexole and ropinirole and also led to driving restrictions being imposed upon individuals receiving these drugs. The situation was further compounded by the fact that the concept and terminology of 'sleep attacks' was disputed among sleep physicians.[2] Subsequently a series of case-reports and letters to journals have suggested that this phenomenon of dopaminergic drug–induced sleepiness may not be exclusive to the non-ergot dopamine agonists, and that 'sleep attacks' or 'unintended sleep episodes' are a potential adverse effect of other dopamine agonists including pergolide, bromocriptine, lisuride, piribedil, talipexole, and apomorphine as well as levodopa.[3-11]

1. Defining 'Sleep attacks'

Frucht et al.[1] characterised 'sleep attacks' following the use of non-ergot dopamine agonists as sudden irresistible overwhelming sleepiness without awareness of falling asleep. Following the original report of 'sleep attacks' many questioned the validity and terminology of such a phenomenon on pathophysiological grounds. Olanow et al.[2] also suggested that the term 'sleep attacks' is misleading as the implication is such episodes are unavoidable.

In the majority of reported cases, evidence for a lack of background sleepiness has been the patient or caregiver's recall. It has been argued that such reports may be erroneous as a period of amnesia on a background of chronic sleepiness, preceding sleep episodes may account for patients reporting 'sleep attacks' without warning. 'Sleep attacks' are not described by the American Sleep Disorders classification of sleep disturbances and have not been described previously in relation to PD or its treatment.[12] Furthermore, such sudden sleep episodes with absence of coexistent or chronic sleepiness do not exist in other sleep disorders such as narcolepsy or sleep apnoea. However, this issue is compounded by the fact that a recent study by Tan and colleagues[13] reported that irresistible sleepiness not preceded by obvious somnolence or warning was present in 14% of a Chinese PD population compared with <2% in controls. However, Rascol and colleagues[14] have emphasised the need for controlled studies as they found a similar prevalence of 'sleep attacks' in controls and patients with PD.[14] Arnulf and colleagues[15] performed polysomnography (PSG) in 54 French patients with PD and abnormal sleepiness [defined by multiple sleep latency (MSLT) of <5 minutes] was present in 50% of these patients while 39% demonstrated a narcolepsy-type pattern, a condition known to cause sudden sleepiness.[15] Interestingly, impairments of arousal state and resultant sleepiness had poor correlation with degree of disability or medication suggesting that the underlying disease process of PD rather than antiparkinsonian medications was responsible for sleep-wake cycle disorders.[16] However, two independent studies have suggested that in PD, sleepiness is likely to be related to dopaminergic drugs rather than the underlying disease process.[11,17]

2. 'Sleep attacks' and the Non-Ergot Dopamine D_2/D_3 Receptor Agonists

In the original report of 'sleep attacks' by Frucht et al.,[1] eight male patients with PD had been taking pramipexole for an average of 7 months at a mean dose of 2.9 mg/day. The majority of patients, all classified as in Hoehn and Yahr stage II, were also taking levodopa. All eight patients fell asleep whilst driving, several while on the highway. An accompanying passenger verified events in 33% of cases. Four patients taking pramipexole were described to experience 'sleep attacks' during

other activities such as business meetings and telephone calls. Following road traffic accidents, pramipexole was discontinued in six patients and the dosage was reduced in the remaining two. Of note, no further 'sleep attacks' were reported by any of the patients. The authors reported similar episodes of sudden sleep onset in one patient with PD taking ropinirole 16 mg/day. Shortly after this initial report, a further series of identical 'sleep attacks' were described in nine PD patients taking pramipexole 0.75 to 4.5mg daily.[3] Similarly, 'sleep attacks' ceased once pramipexole had been discontinued. No patient in either series described 'sleep attacks' prior to the use of pramipexole despite previous treatment with carbidopa/levodopa and other dopamine agonists.

As both pramipexole and ropinirole share D_2/D_3 receptor affinity, much interest has focussed on whether the sudden onset sleepiness could be directly related to D_2/D_3 dopamine receptor agonism. This concept is augmented by the finding that talipexol, a selective D_2/D_3 receptor agonist available only in Japan, is also known to cause excessive drowsiness.[18] While the pathophysiology of 'sleep attacks' and the specific role of the non-ergot D_2/D_3 receptor agonists remains unclear, speculation surrounds involvement of the reticular activating system and more recently, involvement of the hypothalamic peptide, hypocretin/orexin. Most patients with sporadic narcolepsy have undetectable levels of hypocretin-1 in the cerebrospinal fluid[19] although preliminary studies in a small number of patients with PD have shown normal hypocretin levels in the cerebrospinal fluid.[20] Frucht et al.[1] suggest the biological effect in the patients they described is derived from the enhanced affinity of pramipexole and ropinirole for the D_3 receptor. Four patients in their series were taking 2 mg/day or less of pramipexole and the authors propose the drug potentially acts on presynaptic receptors, stimulated by low doses of the agonist, ultimately triggering 'sleep attacks' by down-regulating dopaminergic input to the reticular activating system. This hypothesis is supported by work from other groups proposing that analogous dysfunction of neuronal pathways may be responsible for episodes of cataplexy in narcolepsy.[21,22]

Olanow et al.[2,8] argued that 'sleep attacks' were likely to arise secondary to a presumed sedative effect of dopamine agonist therapy suggesting that the drugs predispose to continuous daytime sedation and drowsiness rendering patients susceptible to falling asleep in unintended situations. Individuals may be unaware of prodromal sleepiness, and fighting sleep behaviour due to the amnesic effects of the subsequent brief periods of sleep. Indeed sedative effects with dopamine agonists appear to be dose related and doses of pramipexole 2.9 mg/day (the average dose of pramipexole in Frucht's series[1]) have been shown to be associated with excess sedation in clinical trials.[1,8,22-25] High doses of dopamine agonists such as pramipexole or ropinirole are often used by many physicians and may be associated with excess sedation. This may be of particular importance to younger patients with PD. In a recent study using pramipexole in younger patients (average age 42 years), patients taking pramipexole had a significantly higher incidence of somnolence compared with patients taking placebo (36 *vs* 5.9%, respectively).[26] This observation raises the possibility that younger patients with PD dopamine agonist therapy may be more prone to somnolence. The underlying aetiology is unclear. As these patients are more likely to drive motor vehicles, the phenomenon of iatrogenic somnolence, or 'sleep attacks', may have considerable social and safety implications.

In a placebo-controlled, randomised, double-blind, crossover study in 20 healthy volunteers, ropinirole reduced time to sleep onset as measured by MSLT.[27] However, daytime rapid eye movement (REM) sleep episodes were not observed. Our own clinical experience suggest that drowsiness related to pramipexole or ropinirole is often linked to higher doses and rapid up-titration of these drugs during initiation of therapy. Analysis

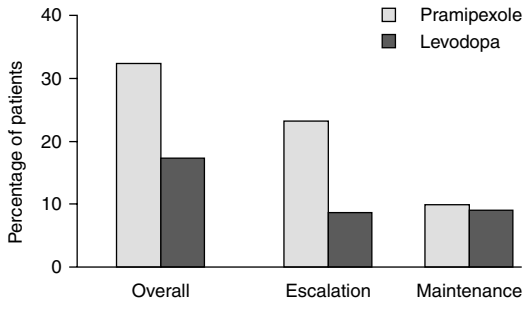

Fig. 1. Pramipexole versus levodopa. Somnolence by study phase (CALM-PD Study).

of reports of 'somnolence' from the recently published results of the CALM-PD (pramipexole versus levodopa monotherapy trial), suggest that somnolence occurred mostly during the rapid titration of pramipexole to the full dose of 4.5mg[28] (figure 1). A practical point would therefore be to avoid quick up-titration of dopamine agonists in patients with PD particularly those with pre-existing 'sleepiness'.

3. Do 'Sleep attacks' Occur with Other Dopamine Agonists?

In a recent study of 236 patients with idiopathic PD (106 men and 130 women, Hoehn and Yahr stage I to IV), systematic questioning about the occurrence of 'sleep attacks' during the preceding week yielded a positive response in 72 patients (30.5%).[29] Questions focussed on the four specific characteristics of 'sleep attacks' as defined in the original description by Frucht et al.,[1] that is episodes are: (i) sudden; (ii) irresistible; (iii) overwhelming; and (iv) occur in the absence of warning signs. Dysautonomia was clinically defined as present in 57 of all PD patients (24.2%). Of note, sleep attacks were significantly more frequent in dysautonomic (70.0%) than non-dysautonomic (17.8%) patients. In fact autonomic failure was identified as the factor most significantly associated with sleep attacks, followed by use of dopamine agonists. Odds ratio values were significantly elevated for all dopamine agonists used in this study, although the number of patients treated with lisuride or piribedil was too low for the authors to reach a definite conclusion with these. Use of ropinirole was associated with the highest risk, followed by bromocriptine. The results of this study suggest that 'sleep attacks' occur frequently among patients with PD attending outpatient movement disorders clinic and that the phenomenon is not exclusive to a particular dopamine agonist.

In another study, Epworth Sleepiness Scale (ESS, an eight point scale to assess daytime sleepiness) was administered to 303 patients with PD and ESS >10 was reported in approximately 50% of patients and sleepiness occurred with similar rates in those taking pramipexole, ropinirole and pergolide.[30] Worryingly, 22% of those who drove cars reported falling asleep while driving and these patients had high ESS scores. However, these observations are contradicted by Hobson et al.[31] who studied 600 Canadian patients with PD with a modified version of ESS and reported infrequent occurrence of sudden onset sleep while driving. These authors also concluded that ESS has poor sensitivity for predicting a tendency to fall asleep while driving. Carbonari et al.[32] have also reported that increased somnolence is uncommon in non-demented patients with PD.

A recent cross sectional, longitudinal study on daytime sleepiness, sleep disturbances, and the quality of life in 111 patients with PD taking different dopamine replacement therapies suggested sedation was a class effect of dopamine agonists.[33] In this study the impact of therapy on daytime sleepiness was analysed separately for ergot dopamine agonists (pergolide 0.075 to 5 mg/day, cabergoline 1 to 8 mg/day, bromocriptine 5 to 30 mg/day and lisuride 0.2 to 30 mg/day), non-ergot dopamine agonists (ropinirole 1.5 to 35 mg/day and pramipexole 0.36 to 8 mg/day) and levodopa monotherapy. At 1-year follow-up EDS was reported by 14% of the ergot dopamine agonist group, 25% of the non-ergot dopamine agonist

group, and 0% of patients receiving levodopa monotherapy.

A community-based study of 245 patients with PD reported a 15.5% prevalence of excessive daytime sleepiness (EDS), compared with 1% of healthy age-matched controls.[34] Tandberg et al.[34] propose mild excessive daytime sleepiness infers an increase in daytime sleepiness with a propensity to falling asleep on a limited number of occasions daily. Severe EDS, in contrast, causes incapacitating daytime somnolence. Cognitive impairment induced by EDS, is likely to constitute a health hazard predisposing to lapses of attention, poor memory, susceptibility to occupational and motor vehicle accidents, impaired work performance and reduced quality of life.[35]

Work from our own group comparing three groups of patients with PD taking pramipexole (± levodopa), cabergoline (± levodopa), or levodopa monotherapy, no significant differences were identified in ESS scores between the three groups.[36,37] Scores of greater than 16, indicative of excessive daytime sleepiness in the original report by Johns,[37] were evenly distributed throughout treatment groups, particularly in older patients with advanced disease. The study demonstrated that EDS is not unique to pramipexole therapy and occurs with both cabergoline and levodopa. Results from this study also suggested that increasing age, advanced disease, and higher treatment dose appeared to be important predictors for EDS.

Sanjiv et al.[38] compared the prevalence of daytime sleepiness in 160 patients with PD taking levodopa alone, levodopa with bromocriptine, levodopa with ropinirole, levodopa with pramipexole, and 40 healthy control individuals. The group employed the ESS, and a modified ESS, asking directly about falling asleep suddenly with no prior warning. Results revealed no significant difference in modified ESS scores among the four PD groups, and significantly higher scores in all groups of patients with PD compared with healthy adult controls. The study, however, does not exclude the possibility that the neurodegenerative process of PD, irrespective of treatment, is responsible for the daytime somnolence. Furthermore, these results have not been corroborated by other studies. A recent study from our own group recently reported the results of the tolerability profile of cabergoline, the longest acting ergot dopamine agonist, in young, elderly, and very elderly patient with PD.[39] In this study of 202 patients, somnolence was identified as being a rare adverse effect of cabergoline within the dose range of 2 to 6 mg/day, irrespective of age.

It must be emphasised that in spite of the widespread use of ESS for assessing EDS in PD, ESS is not specific to PD and workers have reported that ESS may not be a useful instrument to identify patients at risk of sudden sleep episodes.

In a series of diagnostic apomorphine tests performed over a 3-year period on 68 patients with PD, two patients (2.9%) experienced 'narcolpetic like attacks' whilst performing motor tasks.[7] These episodes occurred 25 minutes after administration of the drug and ceased after 10 minutes and provided evidence for 'sleep attacks' arising following acute administration of apomorphine. In clinical practice, our own observations suggest that drowsiness following apomorphine injection is a common occurrence, particularly with use of higher doses in older patients with PD and patients with advanced PD.[40] Transient drowsiness, usually accompanied by yawning, is also commonly seen during apomorphine challenge testing in PD.

4. Pathophysiology

Abnormalities of sleep architecture, sleep fragmentation and excessive daytime sleepiness appears to be common problems in patients with PD.[16,34,35,41,42] The nucleus tractus solitarius, a major brainstem autonomic nucleus, is thought to be closely implicated with abnormal sleep function in PD.[42] Furthermore, presynaptic dopaminergic deficit has been closely linked to sleep disorders.[16] In addition to problems related to progression of disease, in PD, nocturnal sleep can be disrupted due to a combination of motor, urinary, and

neuropsychiatric symptoms, all of which may result in increased daytime sleepiness or paradoxic increasing daytime alertness with enhanced sensitivity to sedating medications.[43-45] Dopaminergic agents, and particularly dopamine agonists have a complex effect on the sleep/wake cycle and the final effect is dependent on variables such as dopamine receptor subtypes, differential dopamine receptor affinity of dopamine agonists and dose. In rodents, administration of dopaminomimetic agents produces a biphasic effect, with low doses leading to sedation possibly via pre-synaptic activation while high doses produce arousal via the post-synaptic receptors.[27,46] Indeed, recent work by Nishino and co-workers[21] in a canine model of narcolepsy has demonstrated that systemic administration of small doses of D_2 receptor agonists aggravates cataplexy, suggesting an effect on presynaptic autoreceptors. Furthermore, local infusion of D_3 specific dopamine receptor agonists into the ventral tegmental area and lateral globus pallidus/putamen produces identical effects in this animal model.[22] However, in patients with PD, dopamine agonists have been shown to cause sedation at doses effective for post-synaptic activation, which based on animal work should lead to an arousal state. The cause of this discrepancy is unclear and may be due to species-related differences. However, the fact that several studies have now demonstrated sedation with various dopamine agonists including apomorphine and also levodopa, suggest that dopaminergic drug induced 'sleepiness' occurs in PD and is likely to be related to the underlying disease process and dopamine neuronal loss in addition to a 'somnolent' effect of virtually all dopaminergic drug including levodopa[11,27,47] (table I).

Sedation and drowsiness have been reported as adverse events in clinical trials of dopamine agonists including pramipexole, ropinirole, and pergolide.[17,23-27,50-59] In a recent meta-analysis of four clinical trials comparing patients with PD taking pramipexole or ropinirole with those taking placebo, the pooled relative risk (RR) of somnolence with dopamine agonist therapy was 4.98 [95% confidence interval (CI) 1.79 to 13.89].[47] A meta-analysis of seven further trials in which patients with PD were taking pramipexole or ropinirole in conjunction with or levodopa monotherapy revealed a pooled RR of somnolence of 2.06 (CI 1.47 to 2.88) with dopamine agonist therapy.[47] The authors of this study concluded that patients

Table I. Reports of sedation/'sleep attacks' related to dopamine agonist and levodopa treatment in Parkinson's disease

Dopamine agonists/levodopa	Trial design	Effects observed	References
PPX/ROP	Clinical observation	'Sleep attacks' and RTA	1
PPX/ROP	Clinical observation	'Sleep attacks' and RTA	3
Pergolide	Case report	Sleep attack	4
Pergolide	Case report	Sleep attack	6
Ergot DA/non-ergot DA/levodopa	Cross sectional longitudinal study	14% EDS with ergot DA, 25% with non-ergot DA	32
Apomorphine	Clinical observation	Sleep attacks	7
Apomorphine	Open study	Sedation	47
Levodopa	Double-blind, placebo-controlled, crossover study	Sedation	11
CBG/PPX/levodopa	ESS and clinical observation	EDS with CBG/PPX and levodopa	35
PPX	Case report	Somnolence	23
ROP	Randomised, placebo-controlled study in healthy subjects using MSLT	Reduced time to sleep onset	26
Pergolide	PSG, case report	EDS	17
Pergolide	24h PSG, case report	Narcolepsy type sleep attacks	48

CBG = cabergoline; **DA** = dopamine agonists; **EDS** = excessive daytime sleepiness; **ESS** = Epworth sleepiness scale; **MSLT** = multiple sleep latency test; **PPX** = pramipexole; **PSG** = polysomnography; **ROP** = ropinirole; **RTA** = road traffic accident.

with PD using pramipexole or ropinirole are at a higher risk of experiencing somnolence relative to patients taking placebo and that patients taking levodopa in conjunction with either dopamine agonist are at greater risk of somnolence than those taking levodopa alone.[47] Two separate studies have identified an increased risk of somnolence in patients with PD taking pergolide compared with those taking placebo (15.1 *vs* 5.8% and 10 *vs* 3%, respectively).[17,47] Ulivelli et al.[49] performed 24 hour polysomnographic characterisation of pergolide-induced sleepiness in a single patient with PD and reported an excessive 14 hour total sleep and increased REM sleep. Without pergolide, they noted 8.2 hour normal sleep. Our own clinical experience also suggests that pergolide can lead to somnolence similar to that experienced following use of pramipexole or ropinirole. Analysis of a 5-year randomised trial comparing cabergoline monotherapy with levodopa monotherapy in early PD revealed similar and low rates of somnolence with cabergoline and levodopa.[60,61] Our own figures addressing tolerability profile and somnolence rates with cabergoline also suggest a favourable therapeutic profile of cabergoline in elderly and the very elderly patients with PD.[39]

5. Evidence from Multiple Sleep Latency Testing Studies

In a recently reported interim analysis, Bliwise et al.[41] described results of multiple sleep latency testing in 16 patients with PD having EDS (as defined by the ESS). Five were treated with pergolide and levodopa, one with pergolide, pramipexole and levodopa, three with ropinirole and levodopa, and one with pramipexole. Patients were divided into two groups, those describing 'unintended sleep episodes' (USE), and those without USE. The mean sleep latency for the without USE group was 7.0 ± 7.6 minutes while that for the USE group was 8.2 ± 5.9 minutes, the prevalence of pathological sleepiness was 60 and 55%, respectively. Of note USE were observed with a variety of dopamine agonists and appeared to be associated with a background of EDS comparable with that seen in the non-USE patients but greater than that in the general population.

Using MSLT, Ferreira et al.[27] investigated the sedative effects of ropinirole in a placebo-controlled, randomised, double-blind study of 20 healthy adults. Oral ropinirole 1.5mg at 7.30am and 11.30am, or placebo, were assessed on two separate days, with a two week washout period. Results demonstrated significantly lower mean sleep latency with ropinirole compared with placebo. The results provide quantitative evidence to support the sedative effect of ropinirole, independent of disease-related sleep dysfunction.

A series of individual case reports have identified increased frequency of sudden sleep episodes following introduction of pergolide therapy in patients with PD. Some reports suggest the episodes may be dose related, while a recent paper hinted that pergolide may increase sleep drive.[17,49] One such report, in which polysomnography was performed, revealed severe reduction in sleep efficacy, slow wave sleep, and REM sleep suppression in a patient taking a relatively modest dose of pergolide, 0.9 mg/day.[17] However, paradoxically, a change in dopamine agonist therapy to ropinirole resulted in increase in the MSLT as well as increases in psychomotor speed and mental flexibility. The authors of this report suggest drug-induced modification of sleep and wakefulness in PD cannot be classified as specific and that switching between different agonists can be a possible treatment strategy.

Ebersbach et al.[62] performed polysomnographic recordings for 48 hours in a 62-year-old patient with PD who described 'sleep attacks' leading to falls.[62] The patient was taking levodopa, cabergoline, entacapone, budipine, metixene, and amantadine. Two daytime 'sleep attacks' lasting 2.5 to 3.0 minutes were detected with a latency to S2 of less than 1 minute. The episodes of sleep onset were described as sudden and irresistible. MSLT and HLA-DR2 serotyping excluded other potential causes of sudden sleep episodes such as

narcolepsy. Results from such reports suggest a specific neurophysiological substrate for 'sleep attacks' in idiopathic PD and reaffirms the concept that such episodes are not confined to the non-ergot dopamine agonists.

Results of a recent study of MSLT in 'sleepy' PD patients by Arnulf et al.[15] have already been alluded to.[15] Contrary to the above report, these workers have reported that up to 39% of these patients may exhibit a narcolepsy-type phenotype. Administration of dopamine agonists in these patients may therefore, lead to unintended sleep episodes.

6. Recommendations for Practice

Initial reports of 'sleep attacks' following use of the non-ergot dopamine agonists (pramipexole and ropinirole) in PD have heightened awareness amongst physicians and consumers about this potentially serious adverse reaction which may lead to job-related and road traffic accidents. Advisory agencies now provide cautionary warnings for prescribing of these drugs. The British National Formulary, for example warns, 'Sudden onset of sleep has been observed with dopamine agonists such as pramipexole and ropinirole. Patients starting treatment with any of the dopamine agonists should be warned of the possibility of excessive daytime sleepiness'.[63]

Routine use of validated clinical scales such as the ESS (table II) may be useful in detecting patients experiencing excessive daytime sleepiness although the usefulness of ESS remains controversial. High scores (greater than 10 to 12) may indicate susceptibility to the sedative effects of dopamine agonist therapy. Additionally, use of objective measures to quantify nocturnal sleep disturbance in PD such as the newly devised PD sleep scale may be useful in identifying individuals potentially susceptible to excessive daytime sleepiness.[45,64]

Based on the evidence presented in this review, it appears that sleepiness in PD is common and may be an effect of all dopaminergic drugs (table I) and thus a class effect. The following points summarise management issues in relation to dopamine agonist therapy and sleepiness in PD:

- Sleepiness in PD is common and occurs due to the underlying disease process.
- In PD, sleepiness may be aggravated by a 'hypoactivity' reaction to dopaminergic drugs.
- Sleepiness induced by dopamine agonists is not related to any specific agonists but is a class effect.
- Sleepiness may be precipitated by any dopamine agonists particularly in patients with preexisting chronic sleepiness. In some patients dopamine agonists may unmask severe sleepiness which may masquerade as a 'sleep attack' similar to a narcoleptic event.
- Available indirect evidence suggests that cabergoline may have lesser somnolent effect in comparison to other agonists both in the young and the elderly.
- Although controversial, we feel that sleepiness in PD patients can be indirectly assessed by the ESS and those with scores above 10 should be advised to take caution while driving, and should not drive alone or long distances.
- PD patients with a history of unintended sleep episodes without perceived warning should not drive.

Table II. Epworth Sleepiness Scale[37]

How likely are you to doze off or fall asleep during the following situations in contrast to just feeling tired?
For each of the situations listed below give yourself a score of 0 to 3 where 0 = would never doze, 1 = slight chance, 2 = moderate chance, 3 = high chance[a]
• Sitting and reading
• Watching television
• Sitting inactive in a public place
• As a passenger in a car for an hour without a break
• Lying down to rest in the afternoon
• Sitting and talking to someone
• Sitting quietly after lunch
• In a car while stopped in traffic

a Scores >16 equal severe daytime sleepiness.

- Risk of somnolence due to dopamine agonists could be avoided by slow up-titration of the drugs (occasionally slower than recommended titration regime) particularly in the elderly.
- 'Sleepy' PD patients should undergo polysomnography and in some (with a narcolepsy-type phenotype) use of wakefulness promoting drugs such as modafinil may be effective. Selegiline may also be effective.
- If excessive sleepiness or unintended sleep episodes occur with a specific agonist, switchover to another alternative agonist may be useful.
- Concurrent sedating medications and drugs interfering with the metabolism of dopamine agonist, such as antidepressants, antihistamines, antipsychotics, and excess alcohol consumption, should be avoided.

Identification of alternative substrates such as hypocretin and pathological states such as secondary narcolepsy in PD has the potential of radically altering our perception of 'sleepiness' and is essential for elucidating the underlying pathophysiology of somnolence and unintended sleep episodes with dopamine agonists. Only then can recommendations be reliably provided to patients taking these agents.

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References

1. Frucht S, Roger JD, Greene PE, et al. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999; 52: 1908-10
2. Olanow CW, Schapira AH, Roth T. Waking up to sleep episodes in Parkinson's disease Mov Disord 2000; 15: 212-5
3. Hoehn MM. Falling asleep at the wheel: motor vehicle mishaps in people taking pramipexole and ropinirole [letter]. Neurology 2000; 54: 275
4. Schapira AH. Sleep attacks (sleep episodes) with pergolide. Lancet 2000; 355: 1332-3
5. Ferreira JJ, Galitsky M, Montastruc JL, et al. Sleep attacks and Parkinson's disease treatment. Lancet 2000; 355: 1333-4
6. Jiminez-Jiminez FJ, Sayed Y, Garcia-Soldevilla MA, et al. 'Sleep attacks' induced by pergolide. Parkinsonism Related Disord 2001; 7: S59
7. Homann CN, Wenzel K, Suppan K, et al. Sleep attacks after acute administration of apomorphine [abstract]. Mov Disord 2000; 15 Suppl. 3: P585
8. Olanow CW, Schapira AHV, Roth T. Falling asleep at the wheel: motor vehicle mishaps in people taking pramipexole and ropinirole [editorial]. Neurology 2000; 54: 274
9. Chamraj SC, Schulzer M, Stoessl J, et al. Daytime sleepiness and antiparkinson treatment [abstract]. Neurology 2001; 56 (3): A213
10. Stover NP, Okun MS, Watts RL. 'Sleep attacks' and excessive daytime sleepiness (EDS) in Parkinson disease: a survey of 200 consecutive patients [abstract]. Neurology 2001; 56 (3): A213
11. Andreu N, Chale JJ, Senard JM, et al. L-dopa induced sedation: a double blind cross-over controlled study versus triazolam and placebo in healthy volunteer. Clin Neuropharmacol 1999; 22: 15-23
12. American Sleep Disorders Association. International classification of sleep disorders revised: diagnostic and coding manual. Rochester (MN): American Sleep Disorders Association, 1997
13. Tan EK, Lum SY, Fook-Chong SMC, et al. Evaluation of somnolence in Parkinson's disease: comparison with age and sex matched controls. Neurology 2002; 3: 465-8
14. Rascol O, Ferreira JJ, Desboeuf K, et al. Sleep disruption, daytime somnolence, and 'sleep attacks' in Parkinson's disease: a clinical survey in PD patients and age-matched healthy volunteers [abstract]. Neurology 2001; 56 (3): A212
15. Arnulf I, Konofal E, Mereno-Andreu M, et al. Clinical profiles of somnolence in Parkinon's disease. Neurology. In press
16. Rye DB, Jankovic J. Emerging views of dopamine in modulating sleep/wake state from an unlikely source: PD. Neurology 2002; 58 (3): 341-6
17. Saletu MT, Glatzl S, Brandauer E, et al. Pergolide induced insomnia and daytime sleepiness in a patient with Parkinson's disease resolved by switching to ropinirole [abstract]. Sleep 2001; 24: A370
18. Nakamishi T, Kowa H, Mizuno Y, et al. The clinical evaluation of B-HT 920 (talipxole hydrochloride) in Parkinson's disease: a multicentred double-blind comparative study vs bromocriptine mesilate. Clin Eval 1993; 21: 50-110
19. Nishino S, Ripley B, Overeem S, et al. Hypocretin (orexin) deficiency in human narcolepsy. Lancet 2000; 355: 39-40
20. Ripley B, Overeem S, Fujuki N, et al. CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. Neurology 2001; 57: 2253-8
21. Nishino S, Arrigno J, Valtier D, et al. Dopamine D2 mechanisms in canine narcolepsy. J Neurosci 1999; 11: 2666-71
22. Reid M, Tafti M, Nishino S, et al. Local administration of dopaminergic drugs into the ventral tegmental area modulates cataplexy in the narcolpetic canine. Brain Res 1996; 733: 83-100
23. Pinter MM, Pogarell O, Oertel WH. Efficacy, safety and tolerability of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double blind, placebo controlled, randomised, multicentre study. J Neurol Neurosurg Psychiatry 1999; 66: 436-41

24. Hauser RA, Gauger L, Anderson WM, et al. Pramipexole induced somnolence and episodes of daytime sleep. Mov Disord 2000; 15: 658-63
25. Rascol O, Brooks DJ, Korczyn AD, et al. A five year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinriole or levodopa. N Engl J Med 2000; 342: 1484-91
26. Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson's disease. JAMA 1997; 278: 125-130
27. Ferreira JJ, Galitzky M, Thalamas C, et al. Effect of ropinirole on sleep onset: a randomised, placebo controlled study in healthy volunteers. Neurology 2002; 58 (3): 460-1
28. Parkinson Study Group. Pramipexole *vs* levodopa as initial treatment for Parkinson's disease: a randomised controlled trial. JAMA 2000; 284: 1931-8
29. Montastruc JL, Brefel-Courbon C, Senard JM, et al. Sudden sleep attacks and antiparkinsonian drugs: a pilot prospective pharmacoepidemiological study. Clin Neuropharmacol 2001; 24: 181-3
30. Ondo WG, Vuong KV, Khan H, et al. Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology 2001; 57: 1392-6
31. Hobson DE, Lang AE, Martin WR, et al. Excessive daytime sleepiness and sudden onset sleep in Parkinson's disease: a survey by the Canadian Movement Disorders group. JAMA 2002; 287 (4): 455-63
32. Carbonari E, DeNoteris R, De Gasperi D, et al. Daily somnolence and night sleep in Parkinson disease: role of treatment and disease severity [abstract]. Neurology 2001; 56 (3): A213
33. Happe S, Berger K. The influence of dopamine agonists on daytime sleepiness, sleep disturbances, and quality of life in patients with Parkinson's disease [abstract]. Sleep 2001; 24: A371
34. Tandberg E, Larsen JP, Karlsen K. Excessive daytime sleepiness and sleep benefit in Parkinson's disease: a community based study. Mov Disord 1999; 14: 922-7
35. Factor SA, McAlarney T, Sanchez Ramos JR, et al. Sleep disorders and sleep effect in Parkinson's disease. Mov Disord 1999; 5: 280-5
36. Pal S, Bhattacharya KF, Agapito C, et al. A study of excessive daytime sleepiness and its clinical significance in three groups of Parkinson's disease patients taking pramipexole, cabergoline, and levodopa mono and combination therapy. J Neural Transm 2001; 108: 71-7
37. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991; 14: 540-5
38. Sanjiv CC, Schulzer M, Mak E, et al. Daytime somnolence in patients with Parkinson's disease. Parkinsonism Related Disord 2001; 7 (S2001): 283-6
39. Appiah-Kubi L, Forbes A, Gunawardena D, et al. The tolerability and efficacy of sustained dopaminergic therapy using cabergoline mono or adjunctive therapy in 202 elderly and young PD patients. A 2 year clinical observational study [abstract]. Parkinsonism Related Disord 2001; 7 (S2001): S28
40. Reuter I, Flowers J, Agapito C, et al. Risk and benefit of outpatient apomorphine challenge test in parkinsonism [abstract]. Mov Disord 1998; 13 Suppl. 2: 112
41. Bliwise DL, Borchert LD, Cantor C, et al. Excessive daytime sleepiness (EDS) in Parkinson's disease (PD) patients with unintended sleep episode (USE) when treated with dopaminergic agents (DS). Parkinsonism Related Disord 2001; 7 (S2001): P-TU-170
42. Chaudhuri KR. Autonomic dysfunction in movement disorders. Curr Opin Neurol 2001; 14: 505-11
43. Pal S, Lomax C, Pezzella FR, et al. The relationship of Parkinsonian nocturnal disability and excessive daytime sleepiness in Parkinson's disease. Parkinsonism Related Disord 2001; 7 (S2001): S50
44. Wetter TC, Collado-Seidel V, Pollmacher T, et al. Sleep and periodic leg movement patterns in drug-free patients with Parkinson's disease and multiple system atrophy. Sleep 2000; 23: 363-7
45. Chaudhuri KR, Pal S, Bridgman K. Achieving 24-hour control of Parkinson's disease symptoms: use of objective measures to improve nocturnal disability. Eur Neurol 2001; 46 Suppl. 1: 3-10
46. Monti JM, Hawkins M, Jantos H, et al. Biphasic effects of dopamine D-2 receptor agonists on sleep and wakefulness in the rat. Psychopharmacology (Berl) 1988; 95: 395-400
47. Etminan M, Samii A, Takkouche B, et al. Increased risk of somnolence with the new dopamine agonists in patients with Parkinson's disease. A meta-analysis of randomised controlled trials. Drug Saf 2001; 24 (1): 863-8
48. Bassi S, Albizzati MG, Frattola L, et al. Dopamine receptors and sleep induction in man. J Neurol Neurosurg Psychiatry 1979; 42: 458-60
49. Ulivelli M, Rossi S, Lombard C, et al. Polysomnographic characterization of pergolide-induced 'sleep attacks' in an idiopathic PD patient. Neurology 2002; 58: 460-1
50. Barone P, Bravi D, Barmejo-Pareja F, et al. Pergolide monotherapy in the treatment of early PD: a randomised controlled study. Pergolide Monotherapy Study group. Neurology 1999; 53 (3): 573-9
51. Lledo A, Quail D, van Laar T, et al. An analysis of the efficacy and safety of pergolide monotherapy in the treatment of Parkinson's disease [abstract]. Neurology 1999; 52 Suppl. 2: A408
52. Olanow CW, Fahn S, Muenter M, et al. A multicenter double blind placebo controlled trial of pergolide as an adjunct to sinemet in Parkinson's disease. Mov Disord 1994; 9: 40-7
53. Shannon KM, Bennet JP, Friedman JH, et al. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. Neurology 1997; 49: 724-8
54. Adler CH, Sethi KD, Hauser RA, et al. Ropinirole for the treatment of early Parkinson's disease. Neurology 1997; 49: 393-9
55. Rascol O, Brooks D, Brunt E, et al. Ropinirole in the treatment of early Parkinson's disease: a 6 month interim report of a 5 year L-dopa controlled study. Mov Disord 1998; 13: 39-45
56. Sethi KD, O'Brien CF, Hammerstad JP, et al. Ropinirole for the treatment of early Parkinson's disease. Arch Neurol 1998; 55: 1211-6
57. Brooks DJ, Abbott RJ, Lees AJ, et al. A placebo-controlled evaluation of ropinirole, a novel D2 agonist, as sole dopaminergic therapy in Parkinson's disease patients. Clin Neuropharmacol 1998; 21: 101-7
58. Lieberman A, Olanow CW, Sethi K, et al. A multicentre trial of ropinrole as adjunct treatment for Parkinson's disease. Neurology 1998; 51: 1057-62

59. Rascol O, Lees AJ, Senard JM, et al. Ropinirole in the treatment of levodopa-induced motor fluctuations in patients with Parkinson's disease. Clin Neuropharmacol 1996; 19: 234-45
60. Rinne UK. A 5 year double blind study with cabergoline versus levodopa in the treatment of early Parkinson's disease. Parkinsonism Related Disord 1999; 5: 84
61. Rinne UK, Bracco F, Chouza C, et al. Cabergoline delays the onset of motor complications: results of double-blind levodopa-controlled trial. Drugs 1998; 55 Suppl. 1: 23-30
62. Ebersbach G, Norden J, Tracik F. Sleep attacks in Parkinson's disease: polysomnographic recordings. Mov Disord 2000; 15: 89
63. British National Formulary. 42nd ed. London: British Medical Association, 2001
64. Chaudhuri KR, Pal S, Trenkwalder C, et al. Development of a novel scale for assessment of nocturnal disabilities in Parkinson's disease [abstract]. J Neurol Neurosurg Psychiatry 2001; 70: 281

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