

# Why Excessive Daytime Sleepiness is an Important Issue in Parkinson's Disease

Specialists are likely to see many patients with excessive daytime sleepiness (EDS) since disordered sleep is so common, especially with neurological conditions such as Parkinson's disease (PD), Alzheimer's disease and other types of dementia, other neurodegenerative conditions, peripheral neuropathy, neuromuscular disorders, depression, epilepsy and chronic pain syndromes.<sup>1</sup>

The corollary of impaired nocturnal sleep may be EDS. The issues related to excessive daytime sleepiness in PD attracted little attention until reports were published of patients treated with dopamine agonists falling asleep while driving.<sup>2</sup> These episodes of irresistible sleepiness - or 'sleep attacks' - initially were thought to be specifically related to dopamine agonists, but are now considered to be a class effect of all dopaminergic drugs and even of PD itself.<sup>3</sup> Much discussion has focused on the suddenness of their onset and whether they truly occur with no warning, and it has also been questioned whether the sleep attack is a distinct phenomenon or is indistinguishable from drug-induced somnolence or background levels of EDS.<sup>3,5</sup>

The consequence of this renewed interest in PD-related sleep pathology, and its effects on patients and their lives, has led to a greater focus on EDS yet the first systematic study of sleepiness in PD was published only a couple of years ago.<sup>6</sup> Given that excessive sleepiness can have profound, detrimental effects on an individual's day-to-day functioning, their safety and overall quality of life, as well as affecting the lives of their family and carers, it is now being appreciated that EDS in PD is a wide-reaching problem with important implications.

This article looks at the issue of EDS in patients with PD and explores the reasons why patients might suffer from daytime somnolence and what steps could be taken to manage it.

## EDS in PD - a sizeable problem

Daytime sleepiness is common but often unrecognised<sup>1</sup> and appears to be a frequent complaint of PD patients: one community-based study indicated that around 15% of PD patients might be affected by EDS, compared to only 1% of elderly controls.<sup>7</sup> However, this could underestimate the size of the problem, as subsequent studies have

reported much higher figures: Ondo et al<sup>8</sup> found "abnormally high" sleepiness scores in half of the PD patients they studied; similarly, an incidence of 51% was seen in a study of over 600, highly-functional PD patients without dementia;<sup>5</sup> and in another study of PD patients, being evaluated for quality of life, 72% showed symptoms of increased daytime somnolence.<sup>9</sup>

## EDS in PD patients - what causes the problem?

It would be logical to assume that a key reason why patients may suffer from excessive sleepiness during the day is because they are not getting enough good quality sleep at night. Whilst this is largely true, it does not give the full picture in PD: many factors can have an influence on PD patients' daytime alertness.<sup>4</sup>

PD patients may not get the right amount, or the right type, of sleep because of sleep disruption or disturbances (interference with getting to sleep and/or fragmentation of sleep during the night) and alterations of sleep architecture, where the patterns and relative amounts of REM and non-REM sleep change.

Sleep disturbances are very common in PD, affecting from 60% to 98% of patients<sup>10</sup> and can be caused by a wide range of factors (see Table 2). One frequent cause is sleep-disordered breathing: Arnulf et al detected moderate-to-severe obstructive sleep apnoea syndrome (OSAS) in 20% of PD patients, even though obesity was rare in this particular study.<sup>6</sup> However, although EDS has been attributed to sleep fragmentation, it can also be seen in patients with normal sleep efficiency who do get enough sleep at night.<sup>11</sup> PD patients may have daytime somnolence because of dysfunction of their sleep-wake mechanisms: in such patients, the underlying disease process is thought to affect the neuronal pathways and/or neurotransmitter functions that maintain the balance between the sleep and waking states, causing EDS.

Additional factors, such as sedating drugs, or comorbid disease e.g. thyroid disorders, must also be borne in mind when looking for causes of EDS.



**Doug MacMahon** is Consultant Physician with special responsibility for the elderly, Royal Cornwall Hospital NHS Trust. He has particular interests in PD, community care and rehabilitation. He has written extensively on PD, its management, and on health-care policy for older people.

### Correspondence to:

Dr Doug MacMahon,  
Camborne-Redruth Hospital,  
Redruth,  
Cornwall,  
TR15 3ER.  
Tel: 01209 881634,  
Email: Doug.MacMahon@  
cornwall.nhs.uk

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**Table 1: Causes of excessive daytime sleepiness in PD**  
(Adapted from Olanow et al<sup>1</sup>)

<ul style="list-style-type: none"> <li>Disturbed nocturnal sleep resulting from PD-related motor symptoms, parasomnias, sleep disorders, coexisting medical conditions</li> </ul>
<ul style="list-style-type: none"> <li>PD-related disturbance in sleep-wake regulation</li> </ul>
<ul style="list-style-type: none"> <li>Age-related changes in sleep architecture and alterations in circadian rhythm</li> </ul>
<ul style="list-style-type: none"> <li>Medications that can cause sedation, such as:               <ul style="list-style-type: none"> <li>dopaminergic drugs e.g. levodopa, dopamine agonists, selegiline</li> <li>other antiparkinsonian drugs e.g. anticholinergics, amantadine</li> <li>psychotropic drugs e.g. benzodiazepines, antidepressants, neuroleptics</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>Endocrine dysfunction e.g. hypothyroidism</li> </ul>

**Table 2: Factors contributing to sleep disturbance in PD**  
(Adapted from Comella, 2003<sup>10</sup>; Chaudhuri, 2003<sup>11</sup>)

<ul style="list-style-type: none"> <li>Nocturnal recurrence of PD symptoms e.g.</li> </ul>	Tremor Akinesia (e.g. difficulty turning over in bed) Rigidity Painful cramps
<ul style="list-style-type: none"> <li>Conditions often associated with PD e.g.</li> </ul>	Depression, anxiety Restless legs syndrome Periodic limb movement syndrome Dementia Sleep apnoea Nocturia Parasomnias e.g. nightmares, somnambulism
<ul style="list-style-type: none"> <li>Other comorbid disorders commonly seen in older people e.g.</li> </ul>	Arthritis and other painful conditions Cardiac disorders. Respiratory diseases
<ul style="list-style-type: none"> <li>Side-effects of medication (antiparkinsonian or other drugs)</li> </ul>	Insomnia Changes in sleep architecture Sleep-related effects such as vivid dreams, nightmares, hallucinations Withdrawal effects

## EDS in PD - an outcome of sleep-wake dysregulation?

Whilst much is still unknown, there have been great advances in sleep research recently that have helped define the multiple neural pathways, transmitters and cell groups involved in the regulation of sleep and wakefulness. This has provided a better understanding of the relationship between PD and daytime somnolence, and how new medications could offer improved treatment options for the symptom of EDS.

The neuropathology of PD can lead to structural changes of the sleep-wake centres causing insomnia, hypersomnia or circadian rhythm disturbances.<sup>13</sup> Similarly, it can cause neurochemical changes affecting not only dopamine, but a range of neurotransmitters now known to be involved in the modulation of the sleep-wake cycle. In the past, dopamine was not considered to be a modulator of the sleep-wake state, but discovery of the extensive striatal and thalamocortical connections of midbrain dopaminergic neurones suggests that dopamine does have such a role.<sup>14</sup>

Wakefulness and sleep (and the transition from one state to the other) are regulated by neuroanatomical, neurochemical and circadian systems, but no single brain centre is responsible for the whole sleep-wake cycle.<sup>13</sup> 'Being awake' involves two, parallel pathways that activate the cortex: one arises from neurones in the brainstem - the classical reticular activating system (RAS); the other a newly-characterised, neuronal projection from the hypothalamus that incorporates the sleep-wake 'switch'.<sup>15,16</sup> The latter involves three distinct hypothalamic structures that play a key role in promoting either sleep or wakefulness: the ventrolateral preoptic area (VLPO - sleep-promoting), the tuberomammillary nucleus (TMN - wake-promoting) and the suprachiasmatic nuclei (SCN - site of the 'internal clock' that regulates circadian rhythm).

### The sleep-wake 'flip-flop' switch

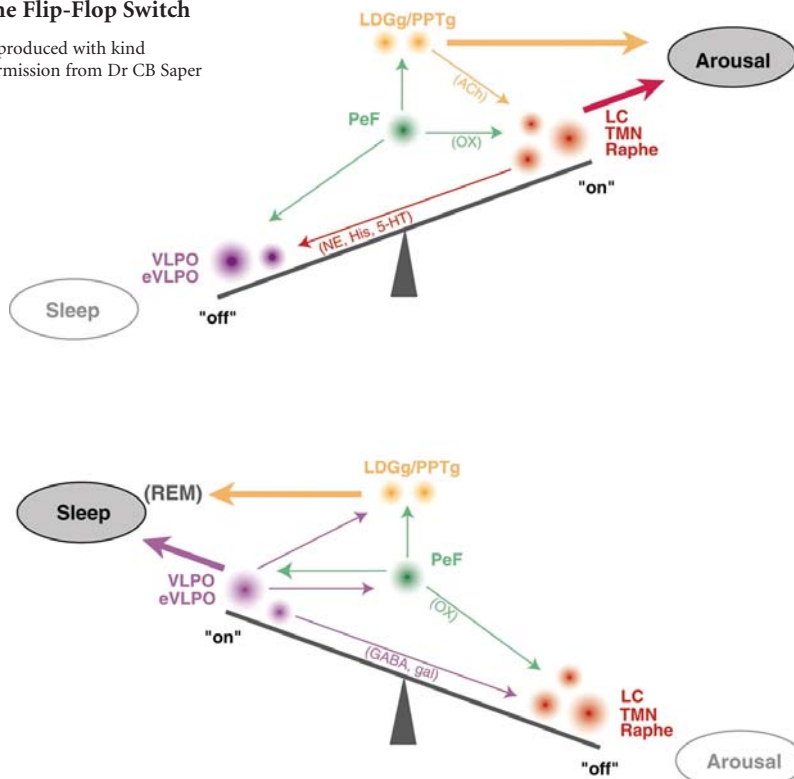
One model of the normal sleep-wake cycle proposes that VLPO and TMN neurones inhibit each other, thus causing oscillations between wakefulness and sleep in a rhythm determined by the internal clock in the SCN. This is elegantly described by Saper et al<sup>17</sup> who discuss the concept of a reciprocal switching circuit - or 'flip-flop' switch - which means the brain can be either 'on' (calm wakefulness) or 'off' (asleep). The two halves of the flip-flop circuit, by each strongly inhibiting the other, create a feedback loop that is bi-stable, meaning there are two possible stable patterns of firing, with a tendency to avoid intermediate states (see Figure 1).

The self-reinforcing firing patterns of the flip-flop switch produce a degree of resistance to switching when one side is firing briskly, which confers stability to the system. So, what flips the switch? When major influences come into play, such as circadian sleep drive or an accumulated homeostatic need for sleep, the relative balance of mutual inhibition might gradually shift. When this pressure to change becomes great enough, the same feedback properties that allow the flip-flop circuit to resist change will suddenly yield and rapidly produce a reversal of the firing patterns. The flip-flop switch therefore changes behavioural state infrequently but rapidly, in contrast to the homeostatic and circadian inputs, which change continuously and slowly.

The relatively recent discovery of the neuropeptide, hypocretin (orexin), has thrown further light on how stability of this switch is maintained. It is now thought that hypocretin neurones might act as a 'finger', pressing the flip-flop switch into the 'wakeful' position, and preventing inappropriate switching into the 'sleep' position.

### The Flip-Flop Switch

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It would follow that an unstable switch could lead to insomnia or to unwanted, rapid transitions into sleep during wakefulness, e.g. as seen in narcolepsy.<sup>16</sup> Indeed, low levels of hypocretin have been implicated in the pathology of narcolepsy<sup>18</sup> and, more recently and relevantly, also in the pathogenesis of EDS in PD.<sup>19</sup>

### EDS in PD - evaluating the problem

It is normal to experience bouts of daytime sleepiness from time to time, for instance, after a very late night, and the propensity for daytime somnolence and need for naps increases as part of the normal ageing process. These problems are accentuated in PD patients,<sup>4</sup> but when does sleepiness become 'excessive' or pathological? If there are episodes of overwhelming tiredness, extended daytime naps and unintended sleep episodes that interfere with patients' (and carers') day-to-day activities, then the sleepiness warrants further investigation.

Current PD scales, such as the United PD Rating Scale (UPDRS) and the PD Quality of Life Scale, are limited in terms of sleep-related questions. A Parkinson's Disease Sleep Scale (PDSS) has recently been developed for assessing the different factors contributing to sleep disturbances, particularly motor symptoms.<sup>20</sup> However,

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whilst frequency of falling asleep is included, it does not focus on daytime sleepiness.

A useful instrument for evaluating EDS, by assessing the likelihood of patients dozing off in a range of lifestyle situations, is the Epworth Sleepiness Scale (ESS) - a quick and easy-to-use questionnaire for the patient and/or carer that does not require technical measurements or the involvement of a sleep laboratory (see Figure 2).<sup>21</sup>

Objective confirmation of EDS - usually regarded as an Epworth score of 11 or more - can be obtained by the MSLT (Multiple Sleep Latency Test), but this may not be practicable for most cases as it requires the use of a sleep laboratory. Therefore, unless a primary sleep disorder (such as narcolepsy) is suspected, the ESS provides a useful evaluation tool.

**Managing the PD patient with ES**

A systematic approach will help build a picture of the patient and their EDS and enable identification of the possible cause - or causes :

- o establish the presence of EDS using the Epworth Sleepiness Scale
- o identify contributing medical or psychological factors - nocturnal PD-associated symptoms and comorbid complaints, including sleep disorders such as OSAHS (obstructive sleep apnoea/hypopnoea syndrome)
- o identify iatrogenic factors by reviewing all current medication

Useful measures to help overcome night-time sleep disturbances or their consequences include:<sup>11</sup>

**Non-pharmacological interventions**

- Improving sleep hygiene - making simple recommendations to help the patient create a mental / physical state and environment conducive to falling and staying asleep.

**Pharmacological interventions**

- Adjusting medication to ensure control of PD symptoms throughout the night. Slow-release L-dopa can

help, but patients with advanced PD are particularly vulnerable to vivid dreams or sleep fragmentation by L-dopa. In these patients, sustained treatment with dopamine agonists such as nocturnal apomorphine, or an evening dose of cabergoline can be effective

- Avoiding excessive dosage of dopaminergic medication. Reducing the night-time dose or taking it earlier in the evening can reduce the risk of sleep onset insomnia, parasomnias and nocturnal myoclonus. Selegiline and amantadine can have stimulant effects which disturb sleep, so these drugs should not be taken later than noon.
- The use of stimulants such as dexamfetamine and methylphenidate could be considered in those cases where daytime sleepiness persists even when nocturnal symptoms and adverse effects from treatment are controlled. However, they are not licensed for such use and their drawbacks are well-known - high abuse potential, limitations in prescribing due to their Controlled Drug status, their tendency to interfere with sleep by decreasing total sleep time and REM sleep, as well as cardiovascular and other side effects.
- Use of a selective wakefulness-promoting agent, modafinil, which is chemically and pharmacologically unrelated to CNS stimulants. Whilst stimulants have a 'blanket' effect on both the RAS and hypothalamic sleep-wake system, modafinil is more selective - specifically affecting the latter - and thus avoiding the motor hyperactivity, hyperarousal and jitteriness often associated with amphetamines.<sup>16</sup>

**Combating EDS in PD with a specific wakefulness-promoting agent - modafinil**

Whilst its mode of action is yet to be clarified, modafinil appears to exert its effects specifically on the hypothalamic sleep-wake system: increasing wake-promoting neuronal activity in the TMN and decreasing sleep-promoting neuronal activity in the VLPO, thus inducing 'calm wakefulness'.<sup>16</sup> Modafinil is well-established as a first-

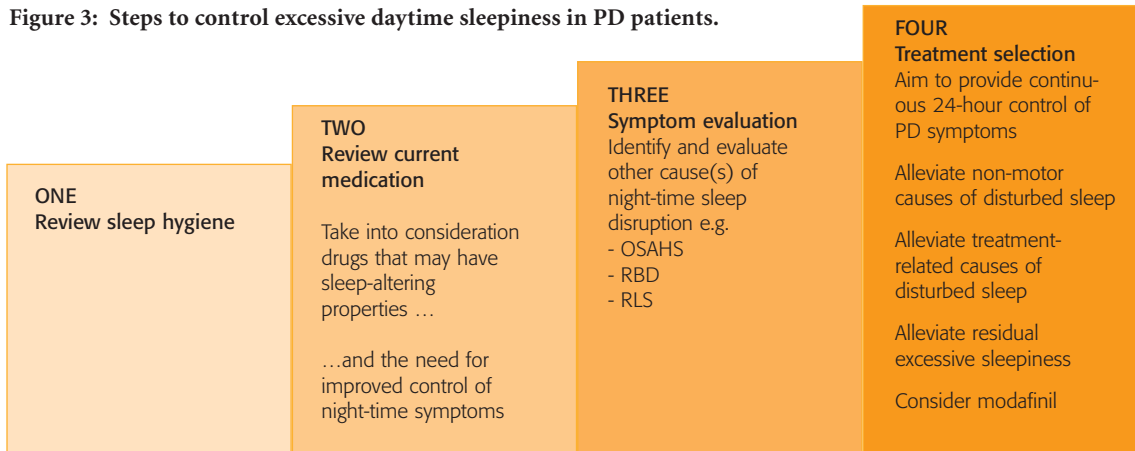
**Figure 2: The Epworth Sleepiness Scale<sup>21</sup>**

Questionnaire				
Situation	Chance of dozing (0-3)			
1. Sitting and reading	0	1	2	3
2. Watching TV	0	1	2	3
3. Sitting, inactive in a public place e.g. a theatre or a meeting	0	1	2	3
4. As a passenger in a car for an hour without a break	0	1	2	3
5. Lying down to rest in the afternoon when circumstances permit	0	1	2	3
6. Sitting and talking to someone	0	1	2	3
7. Sitting quietly after a lunch without alcohol	0	1	2	3
8. In a car, while stopped for a few minutes in the traffic	0	1	2	3

Patients are asked to rate their chance of dozing off in each situation, giving them a ranking of between 0 (would never doze) and 3 (high chance of dozing). Total scores range from 0 to 24. Scores > 10 indicate excessive sleepiness. Patients with scores > 15 should be referred to a specialist centre.

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Figure 3: Steps to control excessive daytime sleepiness in PD patients.



OSAHS – obstructive sleep apnoea/hypopnoea syndrome, RBD - REM behaviour disorder and RLS - restless legs syndrome.

line, symptomatic treatment for EDS associated with narcolepsy and, more recently, is proving to be a useful agent in other medical conditions where EDS is a symptom.

The efficacy of modafinil in improving the symptom of EDS in patients with narcolepsy and other sleep disorders raised the question of whether it could resolve this troublesome and common symptom in other conditions, such as PD. A number of small studies and case reports using modafinil in single daily doses between 200 – 400 mg have shown it to be a well-tolerated addition to antiparkinsonian medication in patients with EDS, relieving excessive sleepiness with no detrimental effect on PD symptoms noted.<sup>22-26</sup>

The most extensive study was a 7-week, placebo-controlled, crossover study of modafinil 200 mg/day, followed (after a 1-week wash-out period) by a 4-week, open-label trial of modafinil 200 mg/day for the first week and 400mg/day for the remainder.<sup>22,23</sup> In both studies, Epworth Sleepiness Scale (ESS) scores were significantly improved in patients on modafinil ( $p=0.039^{22}$ ;  $p=0.002^{23}$ ) and, in the open-label extension, patient- and physician-rated Clinical Global Impression of Change

(CGI-C) scores for improvement in wakefulness were also significant ( $p=0.015$  and  $p=0.003$ , respectively). Modafinil was very well tolerated, with no significant changes in blood pressure or vital signs.

Importantly, modafinil does not appear to have a detrimental effect on the underlying disease as, when assessed, parkinsonian symptoms did not seem to be worsened in any of the studies. In fact, one study reported that some patients were able to tolerate the necessary increments in their dopamine agonist dosage only after receiving modafinil.<sup>24</sup>

### Conclusions

Improving patients' quality of life is a key factor to consider when reviewing PD treatment plans. With up to 98% of PD patients reporting problems with sleep disturbances,<sup>10,12</sup> the management of these disturbances and any consequent excessive sleepiness should be a priority. By using the steps outlined above and simple evaluation tools, such as the Epworth Sleepiness Scale, the physician should be able to effectively manage and treat sleep disturbances and excessive daytime sleepiness in PD.

### References

- Guilleminault C, Brooks SN. Excessive daytime sleepiness. A challenge for the practising neurologist. *Brain* 2001;124:1482-1491.
- Frucht S, et al. Falling asleep at the wheel: Motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999;52:1908.
- Homann CN, et al. Sleep attacks in patients taking dopamine agonists: review. *Brit Med J* 2002;324:1483-7.
- Olanow CW, et al. An algorithm (decision tree) for the management of Parkinson's disease(2001): Treatment Guidelines. *Neurology* 2001;56(Suppl 5):S1-S88.
- Hobson DE, et al. Excessive Daytime Sleepiness and Sudden-Onset Sleep in Parkinson Disease. A Survey by the Canadian Movement Disorders Group. *JAMA* 2002;287:455-463.
- Arnulf I, et al. Parkinson's disease and sleepiness. An integral part of PD. *Neurology* 2002;58:1019-1024.
- Tandberg E, et al. Excessive Daytime Sleepiness and Sleep Benefit in Parkinson's Disease: A Community-Based Study. *Mov Disord* 1999;14:922-7.
- Ondo WG, et al. Daytime sleepiness and other sleep disorders in Parkinson's disease. *Neurology* 2001;57:1392-6.
- Happe S, et al. The Association between Disease Severity and Sleep-Related Problems in Patients with Parkinson's Disease. *Neuropsychobiology* 2002;46:90-6.
- Comella CL. Sleep Disturbances in Parkinson's Disease. *Curr Neurol Neurosci Rep* 2003;3:173-180.
- Garcia-Borreguero D, et al. Parkinson's disease and sleep. *Sleep Med Revs* 2003;7:115-129.
- Chaudhuri KR. Nocturnal symptom complex in PD and its management. *Neurology* 2003;61(Suppl 3):S17-S23.
- Abdelgabar A, Sharma J. Sleep Disorders in Parkinson's Disease. *Int J Clin Pract* 2003;57:781-7.
- Rye DB, Jankovic J. Emerging views of dopamine in modulating sleep/wake state from an unlikely source: PD. *Neurology* 2002;58:341-6.
- Stahl S. Psychopharmacology of Wakefulness: Pathways and Neurotransmitters. *J Clin Psychiatry* 2002;63:551-2.
- Stahl S. Awakening to the Psychopharmacology of Sleep and Arousal: Novel Neurotransmitters and Wake-Promoting Drugs. *J Clin Psychiatry* 2002;63:467-8.
- Saper CB, et al. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci* 2001;24:726-731.
- Nishino S, et al. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* 2000;355:39-40.
- Drouot X, et al. Low levels of ventricular CSF orexin/hypocretin in advanced PD. *Neurology* 2003;61:540-543.
- Chaudhuri KR, et al. 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.
- Johns MW. A New Method for Measuring Daytime Sleepiness: The Epworth Sleepiness Scale. *Sleep* 1991;14:540-545.
- Adler CH, et al. Randomized Trial of Modafinil for Treating Subjective Daytime Sleepiness in Patients with Parkinson's Disease. *Mov Disord* 2003;18:287-293.
- Adler CH, et al. An Open-Label Extension Study of Modafinil for the Treatment of Daytime Sleepiness in Patients with Parkinson's Disease. *Sleep* 2002;25(Abst Suppl):A251.
- Nieves AV, Lang AE. Treatment of Excessive Daytime Sleepiness in Patients With Parkinson's Disease With Modafinil. *Clin Neuropharmacology* 2002;25:111-114.
- Ondo WG, et al. Excessive Daytime Sleepiness in Parkinson's Disease: A Double-Blind, Placebo-Controlled Parallel Design Study of Modafinil. *Neurology* 2002;58 (Suppl 3):A434.
- Högl B, et al. Modafinil for the Treatment of Daytime Sleepiness in Parkinson's Disease: A Double-blind, Randomized, Crossover, Placebo-controlled Polygraphic Trial. *Sleep* 2002;25:62-66.