Excessive daytime sleepiness in PD

Excessive Daytime Sleepiness (EDS) in Parkinson's disease (PD) is an important issue that warrants serious attention because it can have adverse effects on the quality of life of both the patient and their carers. While many patients will respond to measures designed to treat 24 hour control of PD and improve nocturnal sleep, some may require pharmacological treatment. **Dr Doug MacMahon** looks at the causes of EDS, its diagnosis and management.

DR DOUG MACMAHON is a Consultant Physician at the Royal Cornwall Hospitals NHS Trust

Disordered sleep at night has long been recognised as a problem for people with Parkinson's disease (PD). In contrast Excessive Daytime Sleepiness (EDS) is frequently overlooked, even though it is reported by over half of patients and occurs significantly more often in people with PD than among age-matched controls in the general population[1-4]. Daytime somnolence can have serious adverse effects on the quality of life, functioning and safety not only of PD patients but also of their carers. Consequently, it is important for all doctors dealing with parkinsonian patients to understand how to manage EDS.

Causes of EDS

Any prolonged nocturnal sleep disturbance or sleep fragmentation will result in sleepiness the next day in healthy individuals, and many PD patients undoubtedly feel sleepy during the day because they have difficulty in falling asleep and maintaining sleep at night.

The problems with nocturnal sleep, reported by an estimated 60 to 98 per cent of PD patients, are due to several factors[5]; some are specific to PD while others relate to older people in general (*Table 1*). However as EDS is also reported in PD patients who do not experience disturbed nocturnal sleep[6], it is clear that other causal factors contribute to EDS associated with PD (*Table 2*).

Older PD patients are also affected by general age-related changes in sleep architecture. As people age, they tend to sleep less at night than younger people with more night-time arousal and awakening. In addition, although Rapid-Eye Movement (REM) sleep tends to be preserved in older people, the deepest stages of non-REM sleep are often reduced or absent. There are also age-related changes in the circadian rhythm of sleep, so that older people go to sleep earlier in the evening and wake earlier in the morning[7].

Some PD patients may have comorbid diseases, such as hypothyroidism, that cause daytime sleepiness. They are also likely to be taking several types of drugs that are associated with sleepiness during the day (*Table 2*). Indeed, reports of 'sleep attacks' in patients treated with dopamine agonists were responsible for an increased awareness of and interest in EDS associated with PD[8,9]. These episodes of irresistible sleepiness — some patients claimed to have fallen asleep at the wheel while driving[8] — are now considered to be a class effect of all dopaminergic drugs, but they may also, like EDS, be intrinsic to PD[12].

Recent research has identified changes in

Table 1. Causes of nocturnal sleep disturbance in people with PD[5,11]

Cause	Examples
Night-time PD-related symptoms (both motor and non-motor)	Classical motor symptoms: tremor, rigidity, cramps, difficulty turning over in bed Other PD-related symptoms: restless legs syndrome, periodic limb movement disorder, depression, anxiety, dementia, sleep apnoea, nocturia, REM sleep behavioural disorder
Comorbid conditions common in older people	Cardiac disease, respiratory disease, arthritis, prostatic disease, incontinence, obstructive sleep apnoea
Side-effects of medical treatment	Insomnia, change in sleep architecture, vivid dreams, nightmares, hallucinations.

sleep-wake regulation that are specific to PD and are associated with nocturnal and diurnal sleep problems. PD appears to result in structural changes to the brain that cause insomnia, hypersomnia and disturbed circadian rhythm[13]. The disease is also associated with neurochemical changes that affect several neurotransmitters thought to be involved in maintaining the sleep-wake cycle. These include not only dopamine[12] —which is well known to be deficient in the parkinsonian brain — but also a recently discovered neuropeptide called hypocretin[14].

The state of wakefulness involves two neuronal pathways. The first arises from the brainstem and is the classical centre of arousal or the Reticular Activating System (RAS). The second is a recently characterised projection from the hypothalamus, which incorporates the sleep-wake 'switch' that ensures that the brain is either 'on' (awake) or 'off' (asleep)[15].

The role of hypocretin seems to be to maintain the sleep-wake switch in the 'on' position and prevent inappropriate switching to 'off'. Reduced concentrations of hypocretin are therefore likely to result in narcolepsy with 'sleep attacks'[16]. Low levels of this neurotransmitter have indeed been reported in PD patients as well as in people with narcolepsy[14,17], and PD has been associated with narcolepsy (generally without cataplexy)[18].

Table 2. Causes of EDS in PD[10]

- Disturbed sleep at night (see *Table 1*)
- PD-related disturbance in sleep-wake regulation
- Age-related changes in sleep architecture and circadian rhythm
- Sedation caused by medication, including dopaminergic drugs, other anti-parkinsonian drugs (anticholinergics, amantadine), psychotropic drugs
- Endocrine dysfunction.

Diagnosing EDS

The first step is to ask whether the patient experiences excessive sleepiness during the day. Some health professionals do not enquire routinely about this symptom, since non-motor symptoms have until recently received much less attention than the classical motor symptoms associated with PD[19]. Similarly, some patients don't volunteer that they experience EDS because they and their carers may be unaware that their symptoms are related at least in part to their PD and may not be troubled by it.

Daytime sleepiness becomes 'excessive' and a problem that deserves further investigation and treatment if episodes of overwhelming tiredness, prolonged daytime naps and unintended sleep adversely affects the patient's or carers' daily quality of life, functioning and safety.

When evaluating EDS, it is helpful to use the Epworth Sleepiness Scale (ESS). It is a simple eight-item questionnaire that quickly assesses the

likelihood that the patient will fall asleep during a range of daily activities (*Table 3*)[20], or some exemplary questions derived from it. Patients are asked to rate their chance of dozing during each activity based on a scale of 0 (never fall asleep) to three (high chance of falling asleep). An Epworth score of 11 or more usually confirms that the patient has EDS.

Most General Practitioners (GPs) should be aware of the basic principles of managing a sleep disorder, but they may require the local PD service to assess the patient so that they can manage drug treatment and look at the patient's sleep hygiene. Occasionally further specialist sleep clinic assessment or investigation may be required, especially if a primary sleep disorder such as narcolepsy or obstructive sleep apnoea is suspected. The investigation of choice in this context is a polysmnogram, but few physicians have access to such instruments that need a full sleep laboratory and in most cases, a clinical approach will have to suffice.

Treating EDS

The control of EDS involves a systematic approach (*Table 4*) designed to overcome sleep disturbance at night and to promote wakefulness during the day. Careful enquiry will help to diagnose PD-related symptoms and comorbid problems that may be interfering with nocturnal sleep (*Table 1*).

At the same time, reviewing all current medication will help to identify any drug that may be responsible for promoting wakefulness at night and sleepiness during the day. Non-pharmacological approaches designed to improve night-time sleep in the general population are also applicable to PD patients. These measures include simple advice on sleep hygiene that should help to improve nocturnal sleep and reduce daytime sleepiness (*Table 5*).

Adjusting PD medication can also help to improve sleep by controlling PD symptoms at night. Controlled-release levodopa is an option in

Table 3. The Epworth Sleepiness Scale[20]

Situation	Chance of dozing (0-3)			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place, e.g. theatre or a meeting	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after a lunch when you've had no alcohol	0	1	2	3
In a car, while stopped in traffic	0	1	2	3

Total scores range from 0 to 24, 0 = never doze; 3 = high chance of dozing
Score ≥11 indicate EDS. Refer patients with scores ≥15 to a specialist centre.

Table 4. A systematic approach to controlling EDS in PD

- Advise patient and carer about sleep hygiene measures (*Table 5*)
- Review all current medication in order to identify iatrogenic causes of nocturnal sleep disturbance or EDS
- Consider the possibility of other causes of nocturnal sleep disturbance (see *Table 1*)
- Initiate treatment: adjust PD medication to provide 24-hour control of symptoms; treat other potential causes of disturbed nocturnal sleep; adjust any medication that may be causing sleepiness during the day or sleep disturbance at night; consider modafinil.

Table 5. Sleep hygiene measures

- Go to bed only when sleepy
- Try to maintain regular hours for sleep and wakefulness
- Do not nap during the day, especially close to bedtime
- Avoid sleeping-in after a poor night
- Use the bed primarily for sleep – do not watch television or work in the bedroom
- Ensure a comfortable temperature – neither too hot nor too cold
- Do not lie in bed awake for prolonged periods
- If unable to sleep or fall back to sleep within 20 minutes, get up and engage in relaxing activity until drowsy then return to bed. Repeat as necessary (note: this will only be possible in PD patients whose motor symptoms are well controlled at night)
- Avoid excessive liquid and heavy meals in the evening
- Do not exercise within three to four hours of bedtime
- After midday avoid caffeine, alcohol and tobacco.

some patients with nocturnal akinesia but these drugs may cause vivid dreams or sleep fragmentation in some patients.

An evening dose of a longer-acting dopamine agonist such as cabergoline may offer a better option in these patients. However, it can also cause similar problems itself and also has been suggested as a cause of fibrotic ergot-related reactions. Alternatively, altering the timing or dose of night-time dopaminergic medications can help to prevent problems in falling asleep, parasomnias (such as sleep walking) and nocturnal muscle spasms (myoclonus). Other PD treatments—for example, selegiline—should not be taken after midday as its metabolites may act as stimulants.

Morning doses of stimulant drugs such as dexamfetamine and methylphenidate have been used when EDS persists even when night-time sleep disturbance and iatrogenic causal factors have been controlled. However, this usage is unlicensed and there are limitations on prescribing these controlled drugs. Amphetamines are also associated with a high potential for abuse, cardiovascular and other adverse effects, and a tendency to decrease total sleep time and REM sleep.

Modafinil is an alternative pharmacological treatment for EDS. Chemically and pharmacologically distinct from stimulants, modafinil is a wake-promoting agent that has become a first-line, symptomatic treatment for EDS in narcolepsy and has been shown to relieve EDS in patients with PD[21-23].

In a seven-week, randomised, placebo-controlled crossover study, modafinil 200mg once daily significantly improved Epworth Scores[22]. However in another study, although modafinil was shown to not alter motor symptoms and was well tolerated, it failed to significantly improve EDS in PD compared with placebo[24].

When used to treat EDS in PD patients, modafinil is usually administered as a once-daily 200mg dose – titrating if necessary to 400mg once daily. However, elderly patients should start on the lower dose of 100mg a day. The agent is generally well tolerated in people with PD and it is not associated with worsening of parkinsonian symptoms[21]. Furthermore, since it appears to act selectively on the hypothalamic sleep-wake system, modafinil does not cause the hyperactivity and hyperarousal often seen with amphetamines due to their general effects on the brain[16].

Conclusion

The quality of life of patients and family carers is an especially important consideration when managing the symptoms of a chronic, progressive illness such as PD.