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## **Sleepiness in Parkinson's disease**

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## **Abstract**

Excessive daytime sleepiness is a disabling and vital problem in patients with PD. It affects around 33% patients and culminates in sleep attacks (without prodroma) in 1 to 4% of the patients. When monitored, these patients may have short, narcolepsy-like naps with abnormal intrusion of REM sleep during daytime (and hypnagogic hallucinations as wakeful dreams) are observed in 33-41% patients, while other patients display naps with non REM sleep. Although insomnia, sleep apnea and periodic leg movements are common in these patients, there is no clear link between the night events and the level of sleepiness. Patients treated with dopamine agonists are two to three fold more exposed to sleep attacks than those on levodopa, with large variability between patients. Sleepiness may exist, to a lesser degree, before the onset of parkinsonism and before the use of dopamine agents, suggesting that other, disease-dependant factors contribute to the sleepiness. Most arousal systems are indeed damaged in PD brains, including the locus coeruleus (noradrenalin), the pedunculo-pontine nucleus and the basal forebrain (acetylcholin), the median raphe (serotonin), and the lateral hypothalamus (orexin), while histamine activity dopamine arousal system are normal. Treating patients with stimulants such as modafinil is only partially efficacious, while trials of anti-H3 drugs and sodium oxybate seem more active. Eventually, the recent stimulation of the pedunclopontine nucleus has stimulant or sedative effects in patients, depending on the frequency of stimulation. These results provide new insights into the mechanisms of arousal in PD.

**Keys words:** Parkinson's disease, sleepiness, sleep, narcolepsy, pedunclopontine nucleus.

Driving with excessive daytime sleepiness (EDS) exposes the driver, as well as other road users, to a major risk of accident. This safety issue applies to the conditions exposing to acute sleepiness (eg sleep deprivation, single use of sedative drug) and to chronic diseases with excessive daytime sleepiness (eg sleep apnea syndrome, narcolepsy). In addition, subjects with EDS have altered quality of life, decreased attention, and may be irritable and depressed. Since patients with Parkinson's disease (PD) have difficulty walking and using the public transportations, they are keen to frequently use their car, at least before they become too bradykinetic [1]. Ten years ago, EDS and sleep attacks were documented in PD drivers using non-ergot D2-D3 agonists ropinirole and pramipexole [2]. Soon after, this abnormal sleepiness was evidenced as a common (although neglected before) side-effect of all classes of dopamine agonists, and sometimes of levodopa alone and other PD medications. These observations have prompted numerous studies on the frequency, type, causes and treatment of excessive sleepiness in PD.

### **Sleepiness is frequent and potentially dangerous in Parkinson's disease**

Excessive daytime sleepiness is defined as a disabling trend to nod or fall asleep in various circumstances (reading, while attending a meeting, while working) that interferes with familial, professional and social life. It should be differentiated from fatigue (a state of extreme tiredness, weakness or exhaustion, either mental or physical or both) and from apathy (a lack of interest or emotion). Due to the high risk of accident in sleepy drivers, the level of daytime sleepiness must be regularly checked in patients with PD, especially when the dopaminergic treatment is changed. Sleepiness is easily self-assessed using the Epworth sleepiness scale, an instrument that scores the tendency to fall asleep (from 0 to 3) during 8 everyday situations [3]. The score ranges from 0 to 24, and abnormal somnolence is considered as a value greater than 10 [4]. A score greater than 7 has a 75% sensitivity (and a 50% specificity) in PD for predicting a risk of driving accident [5]. The scale has been validated in large populations of patients with PD. Case-controlled epidemiological studies performed in various countries consistently

document higher sleepiness scores and higher percentage (16 to 74%, usually around one third) of subjects with abnormal somnolence in PD patients than in age- and sex-matched controls [6-8]. The incidence of sleepiness is 6% per year in a prospective series [9]. Sleepiness may precede PD onset, as sleepy adults in a large Asian longitudinal study develop 3.3 times more frequent PD later in life [10].

Patients with PD may also experience sleep attacks, or ‘sudden onset of sleep, without prodroma’. Examples of sleep attacks include patients falling asleep during stimulating life conditions, such as eating a meal (the head drooping in the plate), walking, attending work, while carrying a child in an escalator, and in the most dangerous situation, while driving a car. Between 1% and 4% of patients with PD report having experienced sleep attacks while driving [5, 11].

### **A sleepy intrinsic phenotype in PD**

When daytime sleep is monitored in patients with excessive sleepiness using five sequential in lab nap opportunities scheduled every two hours (the multiple sleep latency tests), more than half of them fell asleep within a mean 5 min, which is considered pathological [12, 13]. Moreover, 41% sleepy patients would fall asleep at least twice directly in REM sleep, an abnormal pattern mostly observed in primary narcolepsy [12]. In addition, one third of the patients were not aware that they had been sleeping, despite they had long episodes of sleep [14]. In PD patients with severe hallucinations, abnormal irruptions of REM sleep episodes can be timely associated, during night-time and daytime with the visual hallucinations, as are the hypnagogic hallucinations in primary narcolepsy [15]. Sleepiness may be more frequent in patients with advanced disease [6]. Sleep deprivation, a condition observed when patients with PD are kept awake at night by restless legs, akinesia or painful dystonia, is a classical cause of somnolence. In large groups of patients with PD however, the longer sleep time at night is associated with more severe daytime sleepiness, an association suggestive of central hypersomnia [12, 13, 16]. Similarly, sleep apnea (observed in 20-30% PD patients [17]), periodic leg movement during sleep and sleep fragmentation do not correlate with the severity of daytime sleepiness [12, 13, 16], suggesting they do not contribute much to the mechanisms of sleepiness. Patients with REM sleep behavior disorder have no more EDS than those without these behaviors, despite their REM sleep may be disrupted by the violent enacted dreams [18].

### **Arousal systems are damaged in PD**

If there is evidence of central hypersomnia in PD, one may look for damage in arousal systems. Most of them are indeed affected by neuronal loss and Lewy bodies in PD brains (Table 1). They include the noradrenaline neurons in the locus coeruleus [19], the serotonin neurons in the raphe [19], the cholinergic pedunculopontine nucleus [20], the cholinergic neuron in the basal forebrain [19], and the orexin neurons (also affected in primary narcolepsy) in the hypothalamus [21, 22]. Despite this important cell loss (and as already observed for dopamine), the cerebrospinal levels of orexin are normal in PD. The cell loss in arousal systems is variable [20], raising the possibility that there are subtypes of the disease with greater or lesser loss of neurons. In contrast, the wake-active dopamine neurons in the ventral periaqueductal gray matter, and the histamine neurons in the hypothalamus are intact in PD brains [23, 24]. They could be appropriate targets for central nervous system stimulants.

## **Sedative effect of dopamine agonists**

The mechanisms of sleepiness in PD may include a complex drug-disease interaction. Sleep attacks have indeed first been described in patients using the new non-ergot dopamine agonists drugs pramipexole and ropinirole [2]. Patients using a dopamine agonist have a twice higher risk of sleep attacks than those using levodopa alone [25]. The risk of sleep attack is similar using ergotic (bromocriptine, pergolide) or non-ergotic (pramipexole, ropinirole) agonists. When a single dose is given to healthy volunteers, pramipexole is however more sedative than levodopa and bromocriptine [26]. The peak effect occurs between 3h30 and 5h30 after the drug intake and is not related to hypotension [26]. The risk increases with increasing daily dosage, especially during the escalation phase [27], and decreases with drug withdrawal. The recent trials of D2-D3 dopamine agonists with prolonged release (transdermal rotigotine and ropinirole 24-h prolonged release) as adjunct therapy also show more frequent sleepiness in the treated group than in the placebo group, but no sleep attacks yet [28, 29]. Around 10% of patients with idiopathic restless leg syndrome also experience somnolence induced by small doses of ropinirole or pramipexole [30, 31], suggesting that this is a dopamine agonist class effect. In contrast, levodopa is more rarely sedative [12], although de novo patients become more sleepy after receiving for one year levodopa or a dopamine agonist [32]. Why drugs that are supposed to stimulate the arousal dopamine system (and do so when given at bedtime [33]) are on the contrary sedative ? [Please reword the previous sentence] This effect cannot be explained, at these high doses, by the biphasic effect (presynaptic sedative effect at low dose, post-synaptic alerting effect at high dose) of dopamine agonists that has been described in animals [34]. Rather, a different selectivity for D1 or D2 receptors may be in cause. D1 agonist and small doses of dopamine increase the firing of orexin neurons in rat hypothalamus, while high concentrations of dopamine and D2 agonist decrease or can even block this firing [35]. If one extends this concept to PD, one may imagine than patients with a partial orexin deficiency would be sedated by D2-D3 agonists or high doses of levodopa.

## **How to treat excessive daytime sleepiness in PD**

Finding and treating the cause of excessive daytime sleepiness in PD requires an interview on nocturnal disturbances, hallucinations, and recent changes in dopaminergic and psychotropic treatment. If there is no recent change in the treatment, a night-time sleep monitoring (with video monitoring and tibialis anterior electromyography), if possible followed by multiple sleep latency tests, is very informative [36]. These tests may document severe sleep apnea, major nocturnal akinesia, dystonia, restless legs, periodic leg movements, REM sleep behavior disorder, slow alpha background rhythm, or a central disorder of arousal. If the efforts to reduce the sedative drugs (clonazepam, other benzodiazepines, dopamine agonists, sedative antidepressants, opioids) are without effect or worsen the motor symptoms, the solution could be to add a stimulant during daytime. The list of stimulants includes caffeine (and in the future some other adenosine receptor antagonists), modafinil, methylphenidate, sodium oxybate and anti-H3 drugs. Modafinil, a drug routinely used in primary narcolepsy and sleepiness of various causes, is well tolerated in PD patients [37], and has interesting neuroprotective effects in animal models of dopamine depletion [38]. The alerting effect is, however, limited in PD, with two-third of non- responders[37]. Sodium oxybate (or GHB) is used at night in primary narcolepsy, as high doses increase deep slow wave sleep and reduce the subsequent daytime sleepiness. A similar benefit has been recently demonstrated in an open trial in 20 PD patients with excessive sleepiness [39]. The slow wave sleep duration doubled, and the Epworth sleepiness score decreased by -7 after the intake of 9

g of sodium oxybate twice a night, with no change in disability scores. GHB is however a respiratory and central nervous depressant, and can cause, alone or associated with alcohol, some confusional states blocks dopamine release and cell firing, and dopamine stores accumulate, possibly explaining increased alertness after the drug has cleared. Methylphenidate, a potent stimulant blocking the catecholamine reuptake and increasing dopamine levels in the brain, seems to be useful for ameliorating cognition, apathy, and gait in small, open-labeled series of patients with PD [40]. Studies are however lacking before its use could be recommended in patients with daytime sleepiness. Drugs blocking the presynaptic reuptake of histamine (anti-H3 drugs) are developed as stimulants in narcolepsy and PD [41]. In a recent double-blind, placebo-controlled, dose-ranging study, a 20 mg dose of tiprolisant (an anti-H3 drug) reduced subjective sleepiness and Epworth score by -5 points [42]. Eventually, the recent use of the pedunclopontine nucleus as a target for deep brain stimulation in PD patients with freezing provides unexpected insights into the sleep and alertness mechanisms in humans. Stimulating this area with low frequency increases REM sleep during the night [43, 44], while patients report they feel more alert during daytime [45]. On the contrary, using high frequency stimulation (possibly blocking this nucleus) induces an immediate sedation and sleep onset [46]. Via their massive projection to the thalamus, the cholinergic neurons of the pedunclopontine tegmental nucleus, together with the adjacent laterodorsal tegmentum nucleus, play a critical role in switching behavioral states from non-REM sleep to stages involving cortex activity, including wakefulness and REM sleep [47]. These preliminary results open new insights into controlling alertness and sleep in PD.

In conclusion, excessive daytime sleepiness in PD probably results from a complex drug/disease interaction. Researches are now focused on the dopamine/orexin interactions, on new pharmacological means to increase alertness, and on the fascinating effects on sleep and alertness of the pedunculo-pontine nucleus area stimulation.

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**Table 1** : Arousal systems in Parkinson's disease

Nucleus	Neurotransmitter	Cell loss in PD brains, %	Reference
Locus coeruleus	Noradrenaline	40-50%	[48]
Raphe median	Serotonin	20-40%	[48]
Ventral periaqueductal gray matter	Dopamine	9%	[24]
Pedunculopontine nucleus	Acetylcholine	57%	[20]
Tubero-mammillary nucleus	Histamine	Unchanged enzymatic activity	[23]
Lateral hypothalamus	Orexin (hypocretin)	23-62%	[21, 22]
Basal forebrain	Acetylcholine	32-93%	[48]