J Neural Transm (2003) 110: 125–150

Journal of Neural Transmission

Sleep disturbances in Parkinsonism

Review

J.J.M. Askenasy

Department of Neurology, Sackler School of Medicine, Tel-Aviv University, Israel

Accepted July 2002

Summary. The present article is meant to suggest an approach to the guidelines for the therapy of sleep disturbances in Parkinson's Disease (PD) patients.

The factors affecting the quality of life in PD patients are depression, sleep disturbances and dependence. A large review of the literature on sleep disturbances in PD patients, provided the basis for the following classification of the sleep-arousal disturbances in PD patients.

We suggest a model based on 3 steps in the treatment of sleep disturbances in PD patients. This model allowing the patient, the spouse or the caregiver a quiet sleep at night, may postpone the retirement and the institutionalization of the PD patient.

I. Correct *diagnosis* of sleep disorders based on detailed anamnesis of the patient and of the spouse or of the caregiver. One week recording on a symptom diary (log) by the patient or the caregiver. Correct diagnosis of sleep disorders co morbidities. Selection of the most appropriate sleep test among: polysomnography (PSG), multiple sleep latency test (MSLT), multiple wake latency test (MWLT), Epworth Sleepiness Scale, actigraphy or video-PSG.

II. The nonspecific therapeutic approach consists in:

a) *Checking the sleep effect on motor performance*, is it beneficial, worse or neutral.

b) *Psycho-physical assistance.*

c) *Dopaminergic adjustment* is necessary owing to the progression of the nigrostriatal degeneration and the increased sensitivity of the terminals, which alter the normal modulator mechanisms of the motor centers in PD patients. Among the many neurotransmitters of the nigro-striatal pathway one can distinguish two with a major influence on REM and NonREM sleep. REM sleep corresponds to an increased

cholinergic receptor activity and a decreased dopaminergic activity. This is the reason why REM sleep deprivation by suppressing cholinergic receptor activity ameliorates PD motor symptoms. L-Dopa and its agonists by suppressing cholinergic receptors suppress REM sleep. The permanent adjustment according to the progression of the degenerative process of the disease will diminishe aggravation.

The following types of sleep-arousal disturbances have to be considered in PD patients:
– *Sleep Disturbances*
Light Fragmented Sleep (LFS)
Abnormal Motor Activity During Sleep (AMADS)
REM Behavior Disorders (RBD)
Sleep Related Breathing Disorders (SRBD)
Sleep Related Hallucinations (SRH)
Sleep Related Psychotic Behavior (SRPB)
– *Arousal Disturbances*
Sleep Attacks (SA)
Excessive Daytime Sleepiness (EDS)
Each syndrome has to receive a score according to its severity

III. The specific therapy consists in: LFS: Benzodiazepines & Nondiazepines. AMADS: Clonazepam, Opioid, Apomorphine infusion; RBD: Clonazepam and dopaminergic agonists; SRBD: CPAP, UPPP, nasal interventions, losing weight; SRH: Clozapine, Risperidone; SRPD: Nortriptyline, Clozapine, Olanzepine; SA–adjustment; EDS-arousing drugs. Each therapeutic approach must be tailored to the individual PD patient.

Keywords: Sleep-arousal disturbances, light fragmented sleep, abnormal motor activity during sleep, REM behavior disorders, sleep related breathing disorders, sleep related hallucinations, sleep related psychotic behavior, sleep attacks, excessive daytime sleepiness.

Introduction

Parkinson's Disease (PD) is a basal ganglia disease of unknown origin. The disease is classified according to the degree of severity in stages described by Hoehn and Yahr and its rating is performed almost by means of the Unified Parkinson's Disease Rating Scale (UPDRS).

The prevalence of disturbed sleep in Parkinson's Disease (PD) was found to vary, according to an objective rating, from 60%–98% (Lees et al., 1988; Nausidea et al., 1982). The factors affecting the quality of life in PD patients are depression, sleep disturbances and dependence (Menza and Rosen, 1995). A succinct description of what is called normal sleep will facilitate the delimitation of disturbed sleep in PD patients.

Normal sleep is a cyclic succession of two different states, the silent sleep state or nonrapid eye movement (NonREM) sleep and the active or the rem eye movement (REM) sleep. The NonREM sleep is a cyclic succession of four

stages, first two (I,II) are also named light sleep and last two (III–IV) deep sleep or slow wave sleep (SWS). SWS is restorative and a protein synthetiser, while REM sleep is an energy consumer. Both are vital, with crucial importance for the well being. Their precise functions are not yet known.

During sleep, motor activity is present under the classical two states of relaxation and contraction at an unconscious level. In NonREM sleep *relaxation* is characterized by a regressive gradient muscle tone, paralleling the deepness of sleep, randomally populated by isolated motor unit potentials. The NonREM sleep muscle *contractions* consist in hypnic jerks mostly at the onset of sleep and postural shifts at stage changes. The hypnic jerk consists in a abrupt muscle action flexing movement, generalized or partial and asymmetric, which may cause arousal, with an illusion of falling. Electromyographically it displays complexes of 250 msec. in various skeletal muscles, predominantly in the limbs. The postural shifts at stage changes involve multiple skeletal muscles. They are more frequent in childhood 4,7/hour at the age 8 to 12 years old, decreasing toward 2,1/hour at 65–80 years old.

In *NonREM sleep* the motor register displays a motionless state with reduced responsiveness at all levels. A gabaergic inhibition originating in reticular centers, generates inhibitory postsynaptic potentials (IPSPs) blocking the synaptic transmission at the thalamus level, with deafferentation of the motor cortex. During slow wave sleep, due to a greater neuronal synchronization, gabaergic blockade of the thalamus, and hyperpolarisaton of the motor unit through descending inhibitory postsynaptic potentials, the neurons fire at their lowest level, thus explaining the lesser responsiveness to afferent impulses.

In *REM sleep* – an unstable state – excitatory and inhibitory responses coexist. The hyperpolarisation of the alpha neuron motors through small and large IPSPs originating in the nucleus pontis oralis and the nucleus reticularis gigantocellularis of the pons and medulla oblongata, results in the motor atonia of REM sleep. The inhibitory tone at the final motor pathway being at its maximal level, allows the enhancement of the motor and sensory cortices, red nucleus and cerebellum cellular activity, resulting in the dream state. The bursts of phasic REM movements arise from superimposed excitatory postsynaptic potentials (EPSPs) originating in brainstem and mediated through N-methyl-D-aspartate (NMDA) excitatory synapses. IPSPs can be suppressed by diffusion with strychnine, suggesting the inhibitory role of glycine.

The above data explains why the *tendon reflexes* in NonREM sleep are diminished and why during REM sleep they are abolished. It was suggested that the beneficial effect of sleep on extrapyramidal diseases may be explained by an inhibited thalamus in the basal ganglia-thalamo-cortical circuit. *During sleep* the autonomic homeostatic equilibrium is replaced by a predominantly parasympathetic activity during NonREM sleep and a predominantly sympathetic activity during REM sleep. Through microneurographic methods the muscle sympathetic nerve activity (MSNA) and the sensitive sympathetic nerve activity (SSNA) are decreased in NonREM sleep, and increased in REM sleep. In SWS the classic pulse synchronization of the MSNA and SSNA

is absent. Translated into neurotransmitter terms during NonREM cholinergic activity is predominant while during REM sleep noradrenergic activity is predominant. Movements during sleep are not accompanied by a homeostatic response from the autonomic nervous system (ANS). This is why a more prolonged muscle activity lacking the ANS support provokes arousal. PD patients with autonomic failure are at high risk of hypoxia due to the diminished arousal associated with sleep events demanding an energetic effort.

Basal ganglia during wakefulness are involved in routine and automatic behavior according to cognitive, limbic and hippocampic information, while during sleep behavior is the result of peripheral stimuli.

The poet and philosopher Lucretius pronounced 2000 years ago a sentence which became notorious at that time: "Sleep is the absence of wakefulness". If Lucretius meant by wakefulness consciousness he was right and is right still today. Today we have to add to this universal truth that there is no wakefulness without sleep, and sleep without wakefulness, because sleep/wakefulness is a continuum. The two states have been artificially separated. During two thirds of our life we are awake and one third we are asleep, health is the result of a harmonious wakefulness daily strengthened by a restorative sleep. Illnesses means the alteration of the physiologic continuum, either in its wake period or in its sleep period.

Sleep disturbances in Parkinson's Disease

The approach to disturbed sleep-arousal in Parkinson's Disease (PD) is based on personal experience and the review of selected articles (see references).

Idiopathic PD is a disorder characterized by a nigrostriatal dopaminergic terminal degeneration, associated with degeneration of the cortex, brainstem and intermedio-lateral column. The few remaining nigrostriatal terminals have difficulty in taking up exogenous L-dopa and converting it to dopamine for subsequent storage and release. These remaining neurons and terminals display an enhanced sensitivity to small changes in plasma dopaminergic (DA) drugs, producing many adverse reactions. The neuro-degenerative process and the side effects of the drugs are the two major causes, responsible for sleep-arousal disturbances (Lees et al., 1988; Nausidea et al., 1982; Menza and Rosen, 1995; Zweig et al., 1989; Comella et al., 1998; Plazzi et al., 1997). The neurodegenrative process imply its direct consequences, such as bradikinesia-rigidity, psychiatric complications, circadian disruption and REM disturbances (Lees et al., 1988; Nausidea et al., 1982; Menza and Rosen, 1995; Zweig et al., 1989; Comella et al., 1998; Plazzi et al., 1997). The side-effects of drugs consequences imply dyskinetic – dystonic movements.

The prevalence of disturbed sleep in PD varies from an objectively rated percentage of 60–90% (Trenkwalder, 1998), 74–98% (Partinen, 1997). Determinations of the quality of life (QoL) in PD patients are emphasizing the important role of sleep (Smith et al., 1997; Martinez-Martin, 1998; Karlson et al., 1999). Karlson et al. by using the Nottingham Health Profile test on 233 PD patients showed that the most predictable variables for the QoL of PD

patients are depression, sleep disturbances (SD) and dependence (Karlson et al., 1999).

According to a self-rated methodology the prevalence of disturbed sleep varies from a percentage of 25% in males to 41% in females (Damiano et al., 1999). Two health related quality of life tests were elaborated for PD patients Parkinson's Disease Questionnaire – PDQ-39- and Parkinson's Disease Quality of Life Questionnaire –PDQL-. Both of them include sleep and rest measurements, despite the lack of these data in the UPDRS (Damiano et al., 1999). The Keyston Colorado consensus conference on an algorithm for the management of PD held in February 1994 marked the introduction of sleep disorders in PD patients as a current topic for an adequate approach (Koller et al., 1994).

We suggest the following approach to guidelines for the treatment of disturbed sleep in PD patients. This approach is meant to postpone the institutionalization of PD patients, allowing the spouse or the caregiver a quiet sleep at night. This approach consists in 3 steps, each one of major importance.

1. FIRST STEP consists in: 1.1. correct diagnosis of sleep disturbances based on detailed anamnesis of the patient and of the spouse or of the caregiver; 1.2. recording for one week a symptom diary (log) by the patient or the caregiver; 1.3. correct diagnosis of sleep disturbances due to co morbidities (a sleep disorder not related to the PD); 1.4. choosing the most appropriate test or group of tests, for the specific type of sleep disturbance among: polysomnography (PSG), multiple sleep latency test (MSLT), multiple wake latency test (MWLT), Epworth sleepiness scale (ESS) (Table 1) (Johns, 1991), actigraphy (Katayama, 2000) or video-PSG.

PSG is useful in LFS, AMADS, RBD, and SRBD; MSLT, MWLT or ESS is useful in EDS, SA, SRBD; Ac is useful in AMADS; and Video-PSG is useful in SRH and SRPB.

Table 1. How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? Even if you have not been in such situations try to work out how they would have affected you

Choose the most appropriate number for dozing:	0 = never 1 = slight chance 2 = moderate chance 3 = high chance
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place	_____
As a passenger in a car for an hour	_____
Lying down to rest in the afternoon	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped a few minutes in the traffic	_____

2. SECOND STEP or the nonspecific therapy, is effective for all the types of sleep-arousal disturbances and consists on 2.1. checking the effect of sleep on motor performance; 2.2. psycho-physical assistance; 2.3. adjustment of the therapy.

2.1. Checking the effect of sleep on the motor performance in PD patients. This information, gives us an important clue to the interrelationship sleep/PD. Three possible effects of sleep on the motor performance were described in PD patients: sleep benefit (SB), sleep worse (SW) and sleep neutral (SN). The beneficial effect of sleep on motor performance manifested itself from half an hour to 3 hours. SB was found to be present in 10–55% of the PD patients (Hogl et al., 1998; Tandberg et al., 1999; Bateman et al., 1999; Factor and Weiner, 1998; Takahashi et al., 1968; Weitman and Hellman, 1974; Adam and Oswald, 1983; Ramm and Smith, 1990). A group of authors have described SB as a frequent phenomenon among the late PD patients of older age, lengthy disease duration, high doses of dopaminergic agonists, long duration of dopaminergic therapy and with more hallucinations and vocalization during sleep (Merello et al., 1997; Curie et al., 1997; Clark and Feinstein, 1977). Others did not find any difference in age stage, duration of the disease, symptomatology and duration of treatment (Factor et al., 1990). Sleep disorders were found in an equal proportion in the SB patients called also "morning better" and SW called also "morning worse" patients. The third group of SN called also "morning same" who are less frequent than the other 2 groups, displays less severe disease, shorter duration and low doses of DA drugs (Factor et al., 1990). The morning motor function is probably more related to the fluctuation of the dopaminergic receptor and to "off" phenomena during sleep than to an impaired sleep mechanism (Factor et al., 1990). Sleep benefit may be also present in PD of early onset (Merello et al., 1997; Curie et al., 1997; Clark and Feinstein, 1977). By checking the effect of sleep on motor performance one may establish the subset of SB and SW which can offer a hint to the development of severe fluctuations at the dopaminergic receptor site in the future and bring light in this controversy.

2.2. Psyco-physical assistance. The obvious tendency of PD patients to lead a sedentary life is directly related to the progress of the disease which favors daily somnolence. In order to avoid the daily somnolence the following 10 hygiene commandments are recommended: 1) An afternoon nap has to be allowed only in PD patients with a longstanding habit of napping; 2) PD patients have to avoid day dozing, alcohol, coffee and heavy meals before bedtime; 3) Maintenance of a regime of regular day activity with physical work; 4) Exercise may provide benefits through its effect on the cardiovascular system, on the muscle mass, on postural comples and cognition; 5) Limit fluid intake after 17:00; 6) A warm bath before bedtime; 7) Instrumental aids for getting out of and into bed; 8) Easy accessibility to water, bathroom and alarm clock at night; 9) A PD nurse has an important role in avoiding sleep disturbances of the PD patient; 10) chronotherapy fulfills psychophysical assistance in PD patients with biological clock disorders (Butler et al., 1998; Mac Mahon, 1999; Hauri, 1981; Zarcone, 1987; Spielman et al., 1987; Lichstein and Fischer, 1985; Weitzman et al., 1981).

2.3. Adjustment therapy has to be performed before any specific therapeutic approach. The rationale of the adjustment is imposed by the evolution of the disease. The progression of nigrostriatal degeneration and the increased sensitivity of the terminals alter the normal modulator mechanisms of motor centers in PD patients. Among the many neuro-transmitters of the nigrostriatal pathway one can distinguish two, with a major influence on REM and NonREM sleep. REM sleep corresponds to an increased cholinergic receptor activity and a decreased dopaminergic activity. This is the reason why REM sleep deprivation by suppressing cholinergic receptor activity improves PD motor symptoms. L-Dopa and its agonists by suppressing cholinergic receptors suppress REM sleep. L-Dopa may have also an arousal or suppressing effect on NonREM sleep, potentiating wakefulness and enhancing the fragmentation due to involuntary movements, or deepening sleep and enhancing imobility. Using the above mentioned sleep effects of anticholinergic drugs and dopaminergic agonists one can improve the sleep of the PD patient, simply by dose adjustment (Askenasy and Yahr, 1985). The evaluation of the dosage and of the timetable or the use of new dopaminergic agonists (ropinorole, pramipexole) with fewer motor side-effects improve sleep disturbance. The dopaminergic adjustment, by using a slow release therapy like Sinemet CR (Stocchi et al., 1998), or a selective and reversible COMT inhibitor like Tolcapone (Micek and Ernst, 1999), or Domperidone or Cisapride (Pfeiffer, 1998) for dopaminergic failure due to a severe reduction of gastric movement, may improve sleep disturbances significantly. Gabapentin (a GABA analogue) may be an important adjuvant in the treatment of sleep disturbances in PD patients, by increasing slow wave sleep, with simultaneous improvement of tremor, rigidity, bradykinesia and motor fluctuations (Chana et al., 1997; Rao et al., 1988).

The night motor activity recorded by means of a wrist-worn monitor in 84 PD and 83 normal controls age-sex matched, showed a significant improvement of sleep disturbances in severe forms of PD, following dopaminergic adjustment (van Hilton et al., 1994).

3. THIRD STEP: or the specific therapy. Is directed specifically to each sleep syndrome, and each therapeutic approach has to be tailored to each individual PD patient. Due to the complex etiology of sleep disturbance in PD, frequently more than one type of sleep disturbance is found. By improving one type of sleep disturbance, a clear improvement can be reached with another type.

For example treating successfully restless legs and periodic leg movements or sleep behavior disorders, excessive daytime sleepiness may be resolved.

Light fragmented sleep (LFS)

LFS was first described as a characteristic sleep disturbance entity of PD patients in 1981 (Askenasy, 1981). It consists of difficulties in the initiation and maintenance of sleep, causing insomnia (Askenasy, 1981). It is by far the most frequent type of sleep disturbance among PD patients (Tandberg et al., 1998). Up to 80% of PD patients complain of LFS (Factor et al., 1990).

Light and fragmented sleep is of multifactorial origin (Lees, 1988; Factor et al., 1990; Tandberg et al., 1998; van Hilten, 1993). The factors implicated are of 1.1.1. motor origin: either due to hyper mobility expressed by resting tremor, eye blinking, dyskinesia, limb-facial dystonia, jerks, painful leg cramps and fragmentary myoclonus, or due to immobility with an inability to turn around in bed and stiffness (Rao et al., 1988; van Hilten et al., 1994); 1.1.2. of disturbed breathing origin, 1.1.3. vivid dreams or nightmares, 1.1.4. nocturia (van Hilten et al., 1994; Askenasy, 1981; Tandberg et al., 1998; Horiguchi et al., 1990) which may also expose the PD patient to frequent falls, resulting in hip fractures, 1.1.5. anxiety and depression may frequently aggravate the insomnia, 1.1.6. screaming while sleeping is able to wake up 50% of the cases displaying this phenomenon (Nakamuro et al., 1998). The arousal due to screaming is the result of a dysfunction of the lower brainstem, Locus Ceruleus and pedunculo-pontine nuclei, related to REM muscle atonia (Nakamuro et al., 1998). On the PSG test a parasympathetic deceleration of the heart rate is frequently observed (Laihinen et al., 1987). At the receptor level a disequilibrium of its sensitivity is considered to be the cause of LFS (Trenkwalder, 1998; Partinen, 1997; Butler et al., 1998; MacMahon, 1999; van Hilten, 1994; Askenasy, 1981; Tandberg et al., 1998; Apps et al., 1985; Feinsilver et al., 1986). A direct consequence of LFS is daytime dozing.

Treatment

The possibilities offered by dopaminergic adjustment and psycho-physical nonpharmacologic therapy has to be the first of all approach in every case. Inspite of the fact that the dominant complaint of the LFS PD patient is the severe insomnia, the prescription of a sleeping pill has to be largely avoided because of the chronic nature of sleep disturbance and the risk of developing dependence. If it has to be used in some cases, the duration of the treatment has to be of maximum one month and the hypnotic has to be changed every night to avoid dependence. Nondiazepines short acting are imidazopyridine, used at a dose of 5–10 mg., and cyclopyrrolone at a dose of 7.5 mg. (Schatzberg et al., 1997; Fairweather et al., 1992; Ganzoni et al., 1995; Monti et al., 1994; Lader, 1997; Goa and Heel, 1986). The tricyclic antidepressant amitriptyline at a dose of 10–40 mg., as well as the antihistaminic diphenhydramine at a dose of 25–50 mg. have good hypnotic results, even in nondepressive and nonallergic PD patients. Benzodiazepines remain attached to the neuroreceptor during the next morning, provoking daytime sedation, dozing, memory deficit and discoordination of perceptual skills. This is why short acting benzodiazepines like triazolam, zolpidem and brotizolam, with a half-life of 3.5 hours, are preferred, and not flurazepam with a half-life of 84 hours (Hoehns and Perry, 1993; Scharf et al., 1994; Shaw et al., 1992). The consuming of hypnotics may be also a source of sleep fragmentation at withdrawal (Partinen, 1997; Fish et al., 1991; Rubio et al., 1995; Linsen et al., 1995). The association of Zopiclon with Aniracetam was found to be effective (Katsunuma et al., 1998). Intranasal Desmopressin was

observed to be a useful tool in LFS due to nocturia of PD patients (Partinen, 1997).

In intractable LFS, with persistent sleep rest tremor and severe sleep muscle hyperactivity, a neurosurgical approach may be the solution. Chronic subthalamic nucleus stimulation (Moro et al., 1999), continuous high frequency stimulation of the ventral intermediate nucleus of thalamus (Arnulf et al., 2000) or unilateral/bilateral pallidotomy (Favre et al., 2000) were shown to improve sleep in operated PD patients. When LFS was caused by night pain, pallidotomy was observed to be the best neurosurgical choice (Honey et al., 1999).

Abnormal motor activity during sleep (AMADS)

Periodic Leg Movements during sleep and Restless Legs Syndrome (PLM-RLS). PLM wakes up the patient, while RLS occur as a post-effect of the PLM. PLMS appears during sleep, while RLSS raise the patient during wakefulness making him walk due to the irresistible urge to move. They may exist separately but more often they are coexisting. This is the perfect example of the sleep/wake continuum disturbance or of a "sleep/wake disorder".

PLMS consists in 1–6 per minute rhythmic segmental movements of the muscles of the legs, mainly anterior tibial, during sleep (Chesson et al., 1999). The positive diagnosis of PLM is through PSG with two leads for the anterior tibial muscles of both sides. RLS consists in an irresistible urge to move affected limbs (lower and upper limbs) during sleep, which oblige the sleeper to wake up and take some steps (Chabli et al., 2000; Wetter et al., 2000). PD patients displaying PLM/RLS may benefit from its positive response to DA drugs (Askenasy et al., 1985; Lang, 1987; Linazasoro et al., 1993; Montplaisir et al., 2000). Up to 80% of PLM-RLS respond to DA drugs (Montplaisir et al., 1997). PLM-RLS was described to be higher in some populations either by population survey (Lavigne and Montplaisir, 1994; Phillips et al., 2000) or by clinical ascertainment (Rothdach et al., 2000). The segmental movements are usually extension of the big toe, ankle, knee or hip, depending on the amplitude of the neuronal discharge (Chesson et al., 1999; Rye and Bliwise, 1997) When compared with the RLS, PLM are more often unilateral (Askenasy and Yahr, 1990). PLM-RLS are more evident in the first part of the night sleep (Askenasy et al., 1985). They may coexist in PD patients with sleep apnea syndrome and REM behavior disorder. Electromyographic (EMG) studies of PLM showed that movements appear in association with bursts lasting 0–5 seconds when the amplitudes of potentials are above 130 microvolt (Rye and Bliwise, 1997). EMG and PSG studies revealed an interesting phenomena which is more evident in late PD: the presence of burst-tremor (see Fig. 1) (Rye and Bliwise, 1997; Askenasy and Yahr, 1983, 1990).

The etiology of PLM syndrome is unknown. It was suggested based on neurophysiological data and functional MRI that a suprasegmental disinhibition during sleep may provoke PLM (Trenkwalder et al., 1996; Bucher et al., 1997; Yokota et al., 1991; Watanabe et al., 1987). The efficacy of levodopa and dopamine agonists in reducing PLM is also an argument favoring this theory

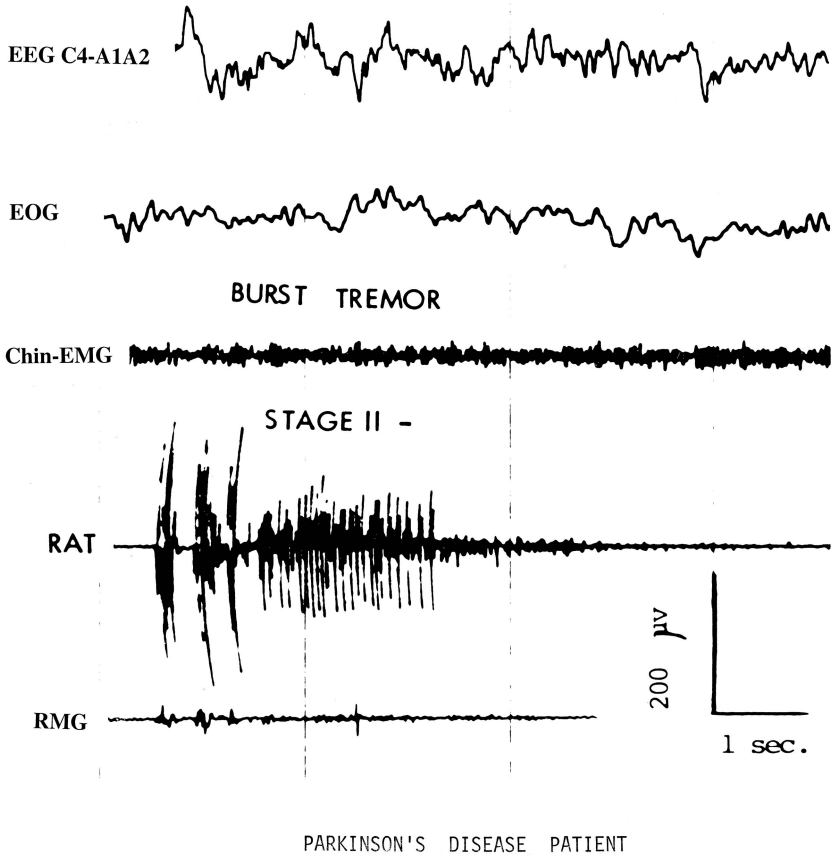

Fig. 1. Burst-tremor of the right anterior tibial muscle during nonREM sleep stage II in a 67 years old patient suffering of idiopathic Parkinson's disease stage III

(Brodeur et al., 1988; Wetter et al., 1999). A PSG study recorded during two nights of sleep of 10 PD patients, 10 multiple system atrophy patients and 10 Huntington's chorea patients, age/sex matched and free of drugs for 2 weeks, showed that the PLM index is significantly higher in naive PD patients, suggesting that it is the neurodegenerative process the cause of PLM (Wetter and Pollmacher, 1997). It was suggested that in PD patients movements in limbs may be favored by the presence of an "off" nocturnal phenomenon as a result of more severe BG neuronal degeneration (Askenasy et al., 1985; Reuter et al., 1999). It was argued that the prevalence of PLM in the general population above 65 years and in PD patients is similar (Ancoli-Israel et al., 1991).

In PD patients PLM was found to appear almost exclusively in sleep stage II (Askenasy et al., 1985; Montplaisir et al., 1997). The absence of slow wave sleep in aged PD patients may explain the lack of PLM in stage III and IV and their presence almost in stage II. The lack of PLM in REM sleep, suggest that the inhibition of the skeletal muscles is very strong in this stage, and that different laws govern motor activity in sleep and in wakefulness and their physiology is different (Rye and Bliwise, 1997; Ancoli-Israel et al., 1991;

Chase and Morales, 1982; Siegel, 1985; Morrison and Bowker, 1975; Askenasy and Yahr, 1990). The etiology of RLS syndrome is unknown.

Studies on the PLM-RLS frequency in PD patients are still inconclusive and this issue needs further well elaborated studies (Wetter and Pollmacher, 1997; Montplaisir et al., 1986).

Treatment

Therapy of syndromes of unknown ethiology have an empirical basis. In the case of PLMS-RLSS, a consensus conferences have elaborated the standards of treatment (Chesson et al., 1999). As the first step, the Practice Parameters Standards (PPS) (Chesson et al., 1999) recommend, preliminary to the therapy, a) analytic anamnesis from the patient and bed partener, b) evaluation for comorbid conditions, c) follow-up for side-effects and tolerance. Second preliminary step consist in avoiding the exacerbating effect on PLM of drugs such as tricyclic agents, monoaminoxidase inhibitors (MAOI) AB (phenelzine) or MAOI B (selegiline) in the evening (Koller et al., 1994; Askenasy and Yahr, 1988). The third preliminary to the therapy step is the drug adjustment consisting in the association of DA slow release drugs with physical assistance, like stretching or passive movements (Trenkwalder, 1998; Koller et al., 1994; Chesson et al., 1999). Only then PPS recommend starting of the drug therapy per se. As efficient drugs for PLM it was recommended: Pergolide, Bromocriptine or Clonazepam and for RLS Clonidine, Gapapentin, Clonazepam, Iron. Low doses of clonazepam (0.5–2 mg), temazepam, nitrazepam, carbamazepine, clonidine or lioresal, may be helpful and in recalcitrant cases opiates like oxycodone or propoxyphene nightly are useful (Trenkwalder, 1998; Koller et al., 1994; Wetter and Pollmacher, 1997; Montplaisir et al., 1986; Rye and Bliwise, 1997; Askenasy and Yahr, 1983, 1988, 1990; Trenkwalder et al., 1996; Bucher et al., 1997; Yokota et al., 1991; Watanabe et al., 1987; Brodeur et al., 1988; Wetter et al., 1999; Reuter et al., 1999; Ancoli-Israel et al., 1991; Montagna et al., 1997; Matthewa, 1979; Boghen, 1980; Oshorty and Vijayan, 1980; Trzepacz et al., 1984; Hanwerker and Palmer, 1985; Mitler et al., 1986; Moldofsky et al., 1986; Henning et al., 1986; Bastani and Westervell, 1987; Zucconi et al., 1989; Bonnet and Arand, 1990; Guilleminault and Flagg, 1984). In very refractory cases nocturnal continuous subcutaneous overnight apomorphine infusions of 1% were shown to produce a dramatic reduction of nocturnal awakenings, nocturnal off periods, pain, dystonia and nocturia, which are related to PLM (Reuter et al., 1999; Ancoli-Israel et al., 1991; Askenasy and Yahr, 1988; Montagna et al., 1997; Matthewa, 1979; Boghen, 1980; Oshorty and Vijayan, 1980; Trzepacz et al., 1984; Hanwerker and Palmer, 1985; Mitler et al., 1986; Moldofsky et al., 1986; Henning et al., 1986; Bastani and Westervell, 1987; Zucconi et al., 1989; Bonnet and Arand, 1990; Guilleminault and Flagg, 1984; Frankel et al., 1990). The infusions with apomorphine have a short action of 34 minutes equivalent to the short half life time (Reuter et al., 1999; Ancoli-Israel et al., 1991; Askenasy and Yahr, 1988; Montagna et al., 1997; Matthewa, 1979; Boghen, 1980; Oshorty and Vijayan, 1980; Trzepacz et al., 1984; Hanwerker and Palmer, 1985; Mitler et al., 1986; Moldofsky et al., 1986; Henning et al., 1986).

A special attention was attributed by PPS to the treatment of PLM-RLS in pregnant women. The medication was classified according to the degree of risk from least to highest in the categories ABC and X. In category B was included pergolide, in category C: L-dopa-carbidopa, clonazepam, propoxyphene, codeine, carbamazepine, gapapentin, and clonidine, and and in category X temazepam (Chesson et al., 1999).

Tremor During Sleep (TDS). In PD patients tremor may reappear in all the NONREM sleep stages, with an amplitude up to 150 microvolt (Askenasy, 1981; Askenasy and Yahr, 1990). Its frequency of appearance decreases with the deepening of sleep (Askenasy, 1981; Askenasy and Yahr, 1990). Its appearance during REM sleep is exceptional, but may be associated with the movements preceding or succeeding the REM (Askenasy, 1981; Stern et al., 1968; April, 1966; Tassinari et al., 1965; Aldrich, 2000). It was shown to be rarely associated with sleep spindles or K complexes (Hening et al., 1995). The alternating pattern of tremor disappears during sleep, and both agonist and antagonist muscles are activated independently in a non-alternating pattern (Askenasy and Yahr, 1990).

Fragmentary Nocturnal Myoclonus (FNM). Irregular myoclonic jerks of random appearance during sleep, are a frequent phenomena in PD patients, and more evident during light sleep (Montplaisir et al., 2000; Askenasy and Yahr, 1983; Hening et al., 1995).

– *TREATMENT OF TREMOR AND FNM.* DA agonists adjustment by avoiding monoaminoxidase inhibitors (MAOI) AB (phenelzine) or MAOI B (selegiline) in the evening, and use of low doses of clonazepam (0,5–2 mg) are the most useful therapeutic approach.

REM behavior disorder (RBD)

RBD is a REM violent dream associated with automatic motor behavior related to the dream content, resulting in self-injury or the injury of bed partner (Schenck et al., 1986, 1987). The injuries are the direct result of executing the defense act, imposed by the violent dream, in the absence of muscle atonia. The lack of muscle atonia, or the presence of phasic muscle activity, which characterize the disorder, has to be confirmed by the EMG channel on PSG. In rare cases RBD can be asymptomatic and revealed by a routine PSG. The prevalence of RBD in PD patients was found to be very high, between 50–75% (Schenck et al., 1996; Comella et al., 1993). The relationship between self-injury and the assault of spouses is of 32/64% (Olsen et al., 2000). The result of self injuries and assault attacks described up till now consists of wounds, fractures, haematomas and subdural haematomas (Olsen et al., 2000; Schenck and Mahowald, 1990). This aggressive behavior according to law is an "actus reus" not associated with a "mens rea" and hence is not punishable. When woken up the explanation in 87% of the RBD patients is of defense against attack (Olsen et al., 2000). Interestingly it can be found in PD as well as preceding the appearance of PD (Olsen et al., 2000; Schenck and Mahowald, 1990; Tan et al., 1996). Out of 100 PD patients; 15 displayed RBD (Comella et al., 1998), out of

100 RBD patients 38 developed PD (Boeve et al., 1998). A more frequent association of RBD than with PD was found in Lewy body dementia (LBD) with a significant male predominance (Comella et al., 1998; Trenkwalder, 1998). Interestingly RBD was described as a premonitory syndrome in various neurodegenerative extrapyramidal disorders such as PD, LBD and Multiple System Atrophy (MSA) (Schenck et al., 1996; Comella et al., 1993; Olsen et al., 2000; Schenck and Mahowald, 1990; Tan et al., 1996; Boeve et al., 1998; Negro and Faber, 1996; Turner et al., 1997; Uchiyama et al., 1995).

Treatment

The specific therapeutic approach of RBD has to be applied at once with the nonspecific approach. Levodopa and dopaminergic agonists suppressing REM may improve RBD severity or reverse it (Olsen et al., 2000; Schenck and Mahowald, 1990). Clonazepam (Rivotril) is by far the most efficient drug in RBD at a dose of 0.5–2.0 mg. before bedtime, with a range of positive results between 87% to 89,5% (Schenck and Mahowald, 1990).

Sleep related breathing disorders (SRBD)

SRBD are frequent among PD patients, especially in late PD patients (Trenkwalder, 1998; Tandberg et al., 1999; Micek and Ernst, 1999). Even during wakefulness late PD patients have a tendency to a Kussmaul or Cheyne-Stokes type of breathing in the supine position. Upper airway resistance syndrome –UARS– and the 3 forms of sleep apnea syndrome –SAS– obstructive, central and mixed, may be present among PD patients. It is interesting to note that in late PD patients, central sleep apnea is more often present than obstructive sleep apnea (Apps et al., 1985). Overweight is rare among PD patients, but when present is frequently associated with SRBD. Congenital Central Hypoventilation syndrome or Ondine's Curse consists of failure of autonomic control of ventilation during NonREM sleep, resulting in hypercapnia and hypoxemia. Congenital central hypoventilation syndrome was described among PD with autonomic disturbances (Apps et al., 1985; Feinsilver et al., 1986). Tachypnea may also appear during REM sleep. Perry et al. published in 1979 a Parkinsonian syndrome with severe alveolar hypoventilation in two identical twins whose autopsies showed PD with brainstem damage (Perry et al., 1990). Genetical predisposition was observed in cases of ventilatory disturbances in PD patients (Feinsilver et al., 1986). They received strong support from recent genetic studies describing a subset of dopaminergic neurons in the petrosal ganglia of the glossopharyngeal nerve, which convey sensory information on hypoxemia from the carotid body to the central nervous system. These dopaminergic neurons are controlled by a gene named "brain derived neurotrophic gene" (BDNF) (Balkowiec and Katz, 1998; Katz and Balkowiec, 1997). The dopaminergic treatment hyperactivating alternatively this subset of petrosal neurons may determine the ventilatory disequilibrium. PSG is the ideal method for the correct diagnosis of SRBD, but the electronic sleep strip recently approved by the FDA can be

also a simple and efficient method for the detection of the SRBD, as well as night oximetry.

Treatment

Hypoxia due to SRBD has to be avoided in PD patients by using CPAP or BIPAP for night sleep. According to the severity of the sleep apnea syndrome and to the biological state of the patient partial/total UPPP or nasal interventions may be considered. The use of oxygen in PD patients suffering from SRBD must be avoided because it aggravates sleep apnea and the consequent hypoxia owing to the elevated threshold of the response to decreased O2 and increased CO2 during sleep.

Sleep related hallucinations (SRH)

Hallucinations in PD patients are mainly visual and rarely auditory, they may appear in minor forms, as the sensation of a person or an animal either present or in a side passage or in an illusion. In major forms like complex hallucinations with relatively stereotyped content of bright colors and dramatic settings (Fenelon et al., 2000; Manford and Anderman, 1998). The relationship between hallucinations and sleep may appear in one or more of the following four aspects: hypnagogic (at sleep onset), hypnapompic (at sleep end), REM incorporated or WASO (wake after sleep onset) dependent. The association between altered dreams and hallucinations in PD patients was forcefully shown, suggesting a common underlying pathogenetic mechanism (Factor et al., 1990; Fenelon et al., 2000; Manford and Anderman, 1998; Sanchez-Ramos et al., 1996; Moscovitz et al., 1978). SRH prevalence in PD patients with altered dreams is considered to be 21.8–29.5% (Factor et al., 1990; Sharf et al., 1978). Being one of the common causes for nursing home placement, a correct diagnosis and therapeutic approach is very important (Sanchez-Ramos et al., 1996). Using a logistic regression analysis in 216 PD patients, 3 predictive factors were identified: cognitive degradation, excessive daytime sleepiness and long duration of PD (Fenelon et al., 2000). One may add to these 3 predictive factors, that of advanced age (Manford and Anderman, 1998), and of longstanding treatment with agonistic dopaminergic drugs (Nausidea et al., 1982; Moskovitz et al., 1978). SRH are suggested to be the consequence of brainstem lesions affecting cholinergic and serotoninergic pathways in Parkinson's disease (Manford and Anderman, 1998), or due to the stimulation of mesolimbic dopamine receptors by dopaminergic treatment (Comella et al., 1993). In PD patients under dialysis for renal insufficiency, SRH appeared close to the end of the dialysis (Askenasy). Another argument for the highly statistically significant relationship between hallucinations and altered dreams in PD patients is the presence of REM aberrations among PD hallucinators compared with PD nonhallucinators (Pappert et al., 1999; Comella et al., 1993).

Treatment

The therapeutic approach has to be started in SRH only after exhausting the benefit of drug adjustment. The adjustment will start with the discontinuation of selegiline and amantadine, followed by discontinuation of anticholinergic agents and dopamine agonists. One has to start diminishing progressively the doses at bedtime, in the late evening and then in the afternoon (Comella et al., 1993). Dehydration, constipation, interactions with recent drugs or dose changes of the chronic drugs, urinary or pulmonary infections have to be taken into consideration (Factor et al., 1995). Psycho-physical assistance will be directed to illuminating the bedroom at night. Only when SRH persists despite adjustment of the maximally tolerated reduction of dopaminergic agents, clozapine may be started. Clozapine (Leponex) is the most efficient drug (starting with 6.25 mg. up to 12.5) despite side effects (agranulocytosis) which imposes monthly haematologic tests, excessive somnolence and orthostatic hypotension (Friedman and Lannon, 1989). Clozapine is a less potent blocker of striatal dopamine receptors and a more potent blocker of the mesolimbic dopamine receptors (Koller et al., 1994). A starting dose of 12.5 mg. at bedtime may be increased to 50 mg. Risperidone at a dose of 0.5 to 1.0 mg., Olanzepine at a dose of 5–15 mg., or Ondansetron at a dose of 4–12 mg., can replace the clozapine in case of contraindication or to an exacerbation of the parkinsonism (Koller et al., 1994; Wolters et al., 1996; Zoldan et al., 1996; Wong et al., 1993; Rich et al., 1995; Zoldan et al., 1993).

Sleep related psychotic behavior (SRPB)

SRPB consists in a) nocturnal wandering, panic, anxiety, depression and paranoid delusions during WASO (wake after sleep onset) periods; b) agitation uncontrolled behavior with vocalization and screaming during NonREM and REM sleep (Juncus, 1999; Friedman, 1998; Stoppe et al., 1999). SRPB has become increasingly common with PD owing to a greater longevity and improved therapy (Valldeoriola and Molinuevo, 1999). The most frequent SRPB is due to depression. The low motor level of PD patients may mask the characteristic depressive features (Valldeoriola and Molinuevo, 1999). Depression and anxiety were evaluated in 99 PD patients and 47-control age/sex matched subjects. PD patients were found to have significantly higher scores of disturbed sleep variables. The disturbed sleep variables in depressed PD patients were directly related to on-off phenomena, levodopa dose and age (Menza and Rosen, 1995). The depression score accounted for most of the variance in a stepwise regression analysis of the effect of clinical variables; showed that depression is the most important factor associated with sleep disorder (Starkstein et al., 1991). The prevalence of depression in PD patients is of 47% (Dooneief et al., 1992). The incidence of depression in PD patients was found to increase 1.86%/year when compared with aged subjects (0,14%/year in men and 0.19%/year in women) (Dooneief et al., 1992). Depressive PD patients display RLS more frequently. Interestingly PD with depressive illness often experienced mood, tremor and rigidity improvements with fatigue (Demet et al., 1999). Sleep deprivation may activate mechanisms, which

are typical of suppressing cholinergic activity, which is thought to be excessive in relation to monoaminergic transmission in depressed and PD patients (Demet et al., 1999). When comparing the depressed PD patients with the nondepressed a significantly shorter REM latency was found in the depressed PD group (Kostic et al., 1989). A REM latency of 65 minutes was found in 69% of 39 PD patients (Kostic et al., 1989). Anxiety is common in PD and causes insomnia, fatigability and daytime sleepiness (Henderson et al., 1992; Mayeux, 1987). Following depression and anxiety the third risk factor for PD patients to develop SRPB is dementia (Juncus, 1999; Valldeoriola and Molinuevo, 1999; Stoppe et al., 1999).

Treatment

The therapeutic approach is meant to improve the QoL owing to a correct analysis of the underlying causes of the SRPB. It is wise to start antidepressants after discontinuation of selegiline (Cote, 1999). Most current antidepressive drugs could be administered in PD patients such as: tricyclic antidepressants, MAO inhibitors and selective serotonin reuptake inhibitors with two amendments: a) in the presence of confusion and hallucinations it is best to avoid tricyclics; b) in cases of very severe motor conditions serotonin reuptake blockers and MAO inhibitors have to be avoided (Cote, 1999; Vallderiola et al., 1997; Treves et al., 1995; Cohen, 1997). In very severe cases of depression electroconvulsive therapy can be useful (Factor et al., 1995). Except in depression and dementia the drug of choice in SRPB is Clozapine in low doses (up to 50 mg/day) (Valldeoriola and Molinuevo, 1999; Stoppe et al., 1999; Vallderiola et al., 1997; Trosch et al., 1998; Musser and Akil, 1996). When dementia is obviously dominant risperidone at a dose of 0,5 to 2 mg/day is useful (Stoppe et al., 1999). Ondansteron at a dose of 12–24 mg. is effective in paranoid delusions (Rich et al., 1995; Lesser et al., 1979). Olanzepine was recommended in SRPB patients at a dose of 5–15 mg/day (Wolters et al., 1996). The drug of choice for anxiety is a benzodiazepine, such as alprazolam before bedtime. In more severe anxiety clorazepam or prazepam may be useful. In cases the anxiolitic effect was not obtained by means of diazepines one can try Buspiron 10–40 mg. which is a serotoninergic anxyolitic, or imipramine 50 mg.daily (Feldman et al., 1997).

Arousal disturbances

Sleep attacks (SA)

SA have been observed in PD patients. The phenomenon was described mainly during car driving. It consists in sudden irresistible attacks of sleep during wakefulness, occurring in PD patients treated with antiparkinsonian drugs. The dopaminergic drugs published in the medical literature as causing SA are Promipexole, Ropinorole, Pergolide, Bromocriptine, Lisuride, and Piribedil (Frucht et al., 1999; Schapira, 2000; Ferreira et al., 2000). Frucht who published a study of 9 PD patients causing accidents by falling asleep while driving, mentioned that 5 of them experienced no warning signs before falling asleep (Frucht et al., 1999). Ferreira who published 3 PD patients suffering

from sleep attacks, while treated with ergot alkaloids and piribedil a DA agonist with vasodilator effect, believe that all dopamine agonists can induce sleep attacks, despite the well-known arousal effect of levodopa and pergolide (Ferreira et al., 2000).

Treatment

The therapeutic approach in these cases is stopping and progressively changing the drug.

Excessive daytime somnolence (EDS)

EDS consists in inappropriate short periods of sleep or somnolence, appearing during wakefulness, any time the PD patient is in a passive state (not performing an activity), alone or in the presence of others. They may appear at any hour of the day, even during the major arousal periods, such as early morning or early evening, in a sitting or supine position. The circadian rhythm of PD patients, usually aged around 65 years, has a physiologic tendency to become biphasic, being inclined to falling asleep at siesta time (0,5 to 20% of the nonPD elderly population has this tendency). When 90 nondepressive PD patients were compared with 71 aged matched healthy controls, on a detailed questionnaire method, the incidence of EDS was found significantly high in PD patients (van Hilten et al., 1993). When comparing the presence of EDS in 3 groups, the results showed 15,5% in PD group, 4% in the diabetic group and 1% in the healthy control group (Whitney et al., 1998). Others denied the prevalence of EDS in PD patients (Askenasy and Yahr, 1984; Morewitz, 1988; Carskaden, 1989). It may be suggested that PD patients lose the capacity of separating the wake period from the sleep period, and the two states are intermingled. The PD patients displaying EDS had significant advanced stages of the disorder, were more disabled and showed a higher frequency of cognitive decline (Tandberg et al., 1999). When analyzing the frequency of EDS and sleep benefit (SB) on motor performance it was found that PD with EDS and SB has the longest duration of levodopa treatment, and significantly more fluctuations and dyskinesias than EDS without SB (Tandberg et al., 1999). It can be stipulated that EDS is frequently observed in late PD patients, contrary to the sleep attacks syndrome. One has to differentiate the EDS from excessive daytime fatigue (EDF) consisting in physical tiredness and lack of energy. EDF was reported to be present in 43% of the PD patients (Smith et al., 1997). The permanent excessive fatigue of these patients was found to be related more to motor deficits than to circadian factors (van Hilten et al., 1993). EDF expresses the impairment of the complex arousal mechanism of the central nervous system (Rye et al., 2000; El-Ad and Korczin,1998). Depression is frequently present among EDF PD patients, this is the reason why antidepressants may improve it. Multiple sleep latency test is the exam of choice in EDS. When performed in 27 PD patients EDS was obviously less associated with impaired quality and quantity of prior sleep but more primary impairment of waking and REM sleep (Tandberg et al., 1999; Rye et al., 2000). Because MSLT is time-

consuming Epworth Sleepiness Scale is preferred (Johns, 1993, 1994) (Table 1).

Treatment

The therapeutic approach in EDS is first of all nonspecific (see psycho-physical assistance recommendations) with emphasis on psycho-physical assistance by avoiding sleep periods during the day, in order to strengthen sleep at night. One has to take into consideration that, the total number of sleep hours is the same as before the PD onset, but diffusely distributed along the 24 hours. Arousal drugs like caffeine have to be used with great caution, in order to avoid increasing hyperactivity at night. In extreme cases of very severe EDS, clinically difficult to differentiate from hypersomnia, one can try Modafinil (Modiodal, Provigil 10 mg/day).

Conclusion

We suggest the following types of sleep disturbances to be considered in each PD patient and to be scored according to the following scheme:

V. Sleep-arousal disturbances:

– Sleep disturbances

- Light Fragmented Sleep (LFS)
- Abnormal Motor Activity During Sleep (AMADS)
- REM Behavior Disorders (RBD)
- Sleep Related Breathing Disorders (SRBD)
- Sleep Related Hallucinations (SRH)
- Sleep Related Psychotic Behavior (SRPB)

– Arousal disturbances

- Sleep Attacks (SA)
- Excessive Daytime Sleepiness (EDS).

Each syndrome has to receive a score between: 0 = absent; 1 = mild; 2 = moderate; 3 = severe.

References

Adam K, Oswald I (1983) Protein synthesis, bodily renewal and the sleep-wake cycle. Clin Sci 65: 561–567

Aldrich MS (2000) Parkinsonism. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. WB Saunders, Philadelphia

Ancoli-Israel S, Kripke D, Klauber M, Mason WJ, et al (1991) Periodic leg movements in sleep in community dwelling elderly. Sleep 14: 496–500

Apps MC, Sheaff PC, Ingram DA, Kennard C, et al (1985) Respiration and sleep in Parkinson's disease. J Neurol Neurosurg Psychiatry 48: 1240–1245

April RS (1996) Observations on Parkinsonian tremor in all-night sleep. Neurology 16: 720–724

Arnulf I, Bejjani BP, Garma L, Bonnet AM, et al (2000) Effect of low and high frequency thalamic stimulation on sleep of patients with Parkinson's disease and essential tremor. J Sleep Res 9: 55–62.
Askenasy JJM (unpublished case report)
Askenasy JJM (1981) Sleep patterns in extrapyramidal disorders. Int J Neurol 15: 62–76
Askenasy JJM, Yahr MD (1983) Correlation of sleep patterns with muscle activity in patients with Parkinson's disease. In: Yahr MD (ed) Current concepts of Parkinson disease and related disorders. Excerpta Medica, Amsterdam, pp 172–194
Askenasy JJM, Yahr MD (1984) Suppression of REM rebound by pergolide. J Neural Transm 59: 151–159
Askenasy JJ, Yahr MD (1985) Reversal of sleep disturbance in Parkinson's disease by antiparkinsonian therapy: a preliminary study. Neurology 35: 527–32
Askenasy JJM, Yahr MD (1988) Is monoaminoxidase inhibitor induced myoclonus serotoninergically mediated? J Neural Transm 72: 67–76
Askenasy JJM, Yahr MD (1990) Different laws govern motor activity in sleep than in wakefulness. J Neural Transm 79: 103–111
Askenasy JJM, Yahr MD (1990) Parkinsonian tremor loses its alternating aspect during non-REM sleep and is inhibited by REM sleep. J Neurol Neurosurg Psychiatry 53: 749–753
Askenasy JJM, Weitzman ED, Yahr MD (1985) Are periodic movements in sleep a basal ganglia dysfunction? J Neural Transm 70: 337–348
Balkowiec A, Katz DM (1998) Brain-derived neurotrophic factor is required for normal development of the central respiratory rhythm in mice. J Physiol 510: 527–533
Bastani B, Westervell FB (1987) Effectiveness of clonidine in alleviating the symptoms of restless legs. Am J Kidney Dis 10: 326
Bateman DE, Levett K, Marsden CD (1999) Sleep benefit in Parkinson's disease. J Neurol Neurosurg Psychiatry 67: 384–385
Boeve BF, Silber MH, Ferman TJ, Kokmen E, et al (1998) REM sleep behavior disorder and degenerative dementia: an association likely reflecting Lewy body disease. Neurology 51: 363–370
Boghen D (1980) Successful treatment of restless legs with clonazepam. Ann Neurol 8: 341
Bonnet MH, Arand DL (1990) The use of triazolam in older patients with periodic leg movements, fragmented sleep and daytime sleepiness. J Gerontol 45: 139–144
Brodeur C, Montplaisir J, Godbout R, et al (1988) Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind, controlled study. Neurology 38: 1845–1848
Bucher SF, Seelos KC, Oertel WH, Reiser M, Trenkwalder C (1997) Cerebral generators involved in the pathogenesis of the restless legs syndrome. Ann Neurol 41: 639–645
Butler RN, Davis R, Lewis CB, Nelson ME, et al (1998) Physical fitness: benefits of exercise for the older patient. Geriatrics 53: 46–49
Carskaden MA (1989) Sleep and alertness. Raven Press, New York, pp 53–69
Chabli A, Michaud M, Montplaisir J (2000) Peridic arm movements in patients with restless legs syndrome. Eur Neurol 4: 133–138
Chana P, de Marins A, Barrientos N (1997) Gabapentin and motor fluctuations in Parkinson's disease. Mov Disord 12: 608
Chase MH, Morales FR (1982) Phasic changes in motoneuron membrane potential during REM periods of active sleep. Neurosci Lett 34: 177–182
Chesson AL Jr, Wise M, Davila D, Johnson S, et al (1999) Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Report. Standards of Practice Committee of the American Academy of Sleep Medicine. Sleep 22: 961–968
Clark EC, Feinstein B (1977) The on/off effect in Parkinson's disease treated with levodopa with remarks concerning the effect of sleep. Adv Exp Med Biol 90: 175–182

Cohen LJ (1997) Rational drug use in the treatment of depression. Pharmacotherapy 17: 45–61
Comella CL, Ristanovic R, Goetz CG (1993) Parkinson's disease patients with and without REM behavior disorder (RBD): a polysomno-graphic and clinical comparison. Neurology 43 [Suppl 2]: A 301
Comella CL, Tanner CM, Ristanovic RK (1993) Polysomnographic sleep measures in Parkinson's disease patients with treatment-induced hallucinations. Ann Neurol 34: 710–714
Comella CL, Nardine TM, Diederich NJ, Stebbins GT (1998) Sleep related violence, injury, and REM sleep behavior disorders in multiple system atrophy. Neurology 51: 526–529
Cote L (1999) Depression: impact and management by the patient and family. Neurology 52 [Suppl 3]: S7–S9
Curie LJ, Bennett JP Jr, Harrison MB, Trugman JM, et al (1997) Clinical correlates of sleep benefit in Parkinson's disease. Neurology 48: 1115–1117
Damiano AM, Snyder C, Strausser B, Willian MK (1999) A review of health-related quality-of-life concepts and measures for Parkinson's disease. Qual Life Res 8: 235–243
Demet EM, Chicz-Demet A, Fallon JH, Sokolski KN (1999) Sleep deprivation therapy in depressive illness and Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 23: 753–784
Dooneief G, Mirabello E, Bell K, Marder K, et al (1992) An estimate of the incidence of depression in idiopathic Parkinson's disease. Arch Neurol 49: 305–307
El-Ad B, Korczyn AD (1998) Disorders of excessive daytime sleepiness-an update. J Neural Sci 153: 192–202
Factor SA, Weiner WJ (1998) "Sleep benefit" in Parkinson's disease. Neurology 50: 1514–1515
Factor SA, McAlarney T, Sanchez-Ramos JR, Weiner WJ (1990) Sleep disorders and sleep effect in Parkinson's disease. Mov Disord 5: 280–285
Factor SA, Molho ES, Podskalny GD, Brown D (1995) Parkinson's disease: drug-induced psychiatric states. In:Weiner WJ, Lang AE (eds) Advances in neurology: behavioral neurology of movement disorders. Lippincot-Raven, Philadelphia
Fairweather DB, Kerr JS, Hindmarch I (1992) The effects of acute and repeated doses of zolpidem on subjective sleep, psychomotor performance and cognitive function in elderly volunteers. Eur J Clin Pharmacol 43: 597–601
Favre J, Burchiel KJ, Taha JM, Hammerstad J (2000) Outcome of unilateral and bilateral pallidotomy for Parkinson's disease: patient assessment. Neurosurgery 46: 344–353
Feinsilver SH, Friedman JH, Rosen JM (1986) Respiration and sleep in Parkinson's disease. J Neurol Neurosurg Psychiatry 49: 964
Feldman RS, Meyer JS, Quenzer LF (1997) Sedative hypnotic and anxyolitic drugs. Principles of neueropsychopharmacology. Sinauer Associates, Sunderland
Fenelon G, Mahieux F, Huon R, Ziegler M (2000) Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 123: 733–745
Ferreira JJ, Galitzky M, Montastruc JL, Rascol O (2000) Sleep attacks and Parkinson's disease treatment. Lancet 355: 1333–1334
Fish DR, Sawyers D, Allen PJ, Blakie JD, et al (1991) The effect of sleep on the dyskinetic movements of Parkinson's disease, Gilles de la Tourette syndrome, Huntington's disease and torsion dystonia. Arch Neurol 48: 210–214
Frankel JP, Lees AJ, Kempster PA, Stern GM (1990) Subcutaneous apomorphine treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 53: 96–101
Friedman JH (1998) Behavioral dysfunction in Parkinson's disease. Clin Neurosci 5: 87–93
Friedman JH, Lannon MC (1989) Clozapine in the treatment of psychosis in Parkinson's disease. Neurology 39: 1219–1221

Friedman JH, Goetz CC, Stebbins GT (1997) Psychotic symptoms in Parkinson's disease. J Am Geriatr Soc 45: 252–253
Frucht S, Rogers JD, Greene PE, Gordon MF, et al (1999) Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 52: 1908–1910
Ganzoni E, Santoni JP, Chevillard V, Sebille M, et al (1995) Zolpidem in insomnia: a 3 year post-marketing surveillance study in Switzerland. J Int Med Res 23: 61–73
Goa KL, Heel RC (1986) Zopiclone: a review of its pharmacodinamic and pharmacokinetic properties and therapeutic efficacy as an hypnotic. Drugs 32: 48–65
Guilleminault C, Flagg W (984) Effect of baclofen on sleep-related periodic leg movements. Ann Neurol 15: 234–239
Hanwerker J, Palmer RF (1985) Clonidine in the treatment of "restless leg" syndrome. N Engl J Med 313: 1228–1220
Hauri P (1981) Treating psychophysiologic insomnia with biofeedback. Arch Gen Psychiatry 38: 752–758
Henderson R, Kurlan R, Kersum JM, Como P (1992) Preliminary examination of the co-morbidity of anxiety and depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci 4: 257–264
Hening WA, Walters AS, Chokroverty S (1995) Motor functions and dysfunctions of sleep. In: Chokroverty S (ed) Sleep disorders medicine. Butterworth – Heinemann, pp 265–266
Henning WA, Walters A, Kavey (1986) Dyskinesias while awake and periodic leg movements in sleep in restless leg syndrome: treatment with opioids. Neurology 36: 1363–1366
Hoehns JD, Perry PJ (1993) Zolpidem: a nonbenzodiazepine hypnotic for treatment of insomnia. Clin Pharmacy 12: 814–828
Hogl BE, Gomez-Arevalo G, Garcia S, Scipioni O, et al (1998) A clinical, pharmacologic, and polysomnographic study of sleep benefit in Parkinson's disease. Neurology 50: 1332–1339
Honey CR, Stoessl AJ, Tsui JK, Schulzer M, et al (1999) Unilateral pallidotomy for reduction of parkinsonian pain. J Neurosurg 91: 198–201
Horiguchi J, Inami Y, Nishimatsu O, Innami T, et al (1990) Sleep-wake complaints in Parkinson's disease. Rinsho Shinkeigaku 30: 214–216
Johns MW (1991) A new method for measuring day time sleepiness: the Epworth Sleepiness scale. Sleep 14: 540–545
Johns MW (1993) Daytime sleepiness, snoring, and obstructive sleep apnea: the Epworth sleepiness scale. Chest 103: 30–36
Johns MW (1994) Sleepiness in different situations measurd by the Epworth Sleepiness scale. Sleep 17: 703–710
Juncus JL (1999) Management of psychotic aspects of Parkinson's disease. J Clin Psychiatry 60 [Suppl 8]: 42–53
Karlson KH, Larsen JP, Tandberg E, Maeland JG (1999) Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 66: 431–435
Katayama S (2000) Actigraphic analysis of diurnal motor fluctuations during dopamine agonist therapy. Proceedings, 3d ASRS Congress, Bangkok
Katsunuma H, Shimizu T,Ogawa K, Kubo H, et al (1998) Treatment of insomnia by concomitent therapy with Zopiclon and Aniracetam in patients with cerebral infarction, cerebroatrophy, Alzheimer's disease and Parkinson's disease. Psychiatry Clin Neurosci 52: 198–200
Katz DM, Balkowiec A (1997) New insights into the ontogeny of breathing from genetically engineered mice. Curr Opin Pulm Med 3: 433–439
Koller WC, Silver DE, Lieberman A (1994) An algorithm for the management of Parkinson's disease. Neurology 44 [Suppl 10]: 1–52

Kostic VS, Susic V, Covickovic-Sternic N, Marinkovic Z, et al (1989) Reduced rapid eye movements sleep latency in patients with Parkinson's disease. J Neurol 236: 421–423

Lader M (1997) Zopiclone: is there any dependence and abuse potential? J Neurol 244 [Suppl]: S18–S22

Laihinen A, Alihanka J, Raitasuo S, Rinne UK (1987) Sleep movements and associated autonomic nervous activities in patients with Parkinson's disease. Acta Neurol Scand 76: 64–68

Lang AE (1987) Restless leg syndrome and Parkinson's disease: insights into pathophysiology. Clin Neuropharmacol 10 [Suppl 5]: 476–478

Lavigne GJ, Montplaisir JY (1994) Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep 17: 739–743

Lees AJ, Blackburn NA, Campbell V (1988) The nighttime problems of Parkinson's disease. Clin Neuropharmacol 11512–11519

Lesser RP, Fahn S, Snider SR, Cote LJ, et al (1979) Analysis of the clinical problems in parkinsonian and the complications of long-term levodopa therapy. Neurology 29: 1253–1260

Lichstein KL, Fischer SM (1985) Insomnia. In: Hersen M, Bellak AS (eds) Handbook of clinical behavior therapy with adults. Plenum Press, New York

Linazasoro G, Masso JFM, Suarez JA (1993) Nocturnal akathisia in Parkinson's disease: treatment with clozapine. Mov Disord 8: 171–174

Linazasoro G, Grandas F, Martinez Martin P, et al (1999) Controlled release levodopa in Parkinson's disease: influence on selection criteria and conversion recommendations in the clinical outcome of 450 patients. STAR Study Group. Clin Neuropharmacol 22: 74–79

Linsen SM, Zitman FG, Breteler MH (1995) Defining benzodiazepine dependence: the confusion persists. Eur Psychiatry 10: 306–311

Menza MA, Rosen RC (1995) Sleep in Parkinson's disease. The role of depression and anxiety. Psychosomatics 36: 262–266

Merello M, Hughes A, Colosimo C, Hoffman M, Starkstein S, Leiguarda R (1997) Sleep benefit in Parkinson's disease. Mov Disord 12: 506–508

MacMahon DG (1999) Parkinson's disease nurse specialists: an important role in disease management. Neurology 52: S21–S25

Manford M, Andermann F (1998) Complex visual hallucinations. Clinical and neurobiological insights. Brain 121: 1819–1840

Martinez-Martin P (1998) An introduction to the concept of "quality of life in Parkinson's disease". J Neurol 245 [Suppl 1]: S2–S6

Matthews WB (1979) Treatment of the restless legs syndrome with clonazepam. Br Med J 281: 751

Mayeux R (1987) Mental state. In: Koller WC (ed) Handbook of Parkinson's disease. Marcel Dekker, New York

Micek ST, Ernst ME (1999) Tolcapone: a novel approach to Parkinson's disease. Am J Health Syst Pharm 56: 2195–2205

Mitler MM, Browman CP, Menn SJ (1986) Nocturnal myoclonus: treatment efficacy of clonazepam and temazepam. Sleep 9: 385–392

Moldofsky H, Tullis C, Quance G, Lue FA (1986) Nitrazepam for periodic movements in sleep (sleep-related myoclonus). Can J Neurol Sci 13: 52–54

Montagna P, Lugaresi E, Plazzi G (1997) Motor disorders in sleep. Eur Neurol 38: 190–197

Monti JM, Attali P, Monti D, Zipfel A, et al (1994) Zolpidem and rebound insomnia, a double-blind, controlled polysomnographic study in chronic insomniac patients. Pharmacopsychiatry 27: 166–175

Montplaisir J, Godbout R, Poirier G, Bedard MA (1986) Restless legs syndrome and periodic movements in sleep: physiopathology and treatment with L-dopa. Clin Neuropharmacol 9: 456–463

Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P (1997) Clinical, polysomnographic, and generic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 12: 61–65

Montplaisir J, Godbout R, Pelletier G, Warnes H (2000) Restless leg syndrome and periodic leg movements during sleep. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. WB Sauders, Philadelphia

Morewitz JH (1988) Evaluation of excessive daytime sleepiness in the elderly. J Am Geriatr Soc 36: 324–339

Morrison AR, Bowker RM (1975) The biological significance of PGO spikes in the sleeping cat. Acta Neurobiol Exp 35: 821–840

Moro E, Scerrati M, Romito LM, Roselli R, et al (1999) Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. Neurology 53: 85–90

Moskovitz C, Moses K, Klawans HL (1978) Levodopa-induced psychosis: a kindling phenomenon. Am J Psychiatry 135: 669–675

Musser WS, Akil M (1996) Clozapine as a treatment for psychosis in Parkinson's disease: a review. J Neuropsychiatry Clin Neurosci 8: 1–9

Nakamuro T, Futamura N, Murata K, Suzumara A, et al (1998) Screaming during sleep in Parkinson's disease. Rinsho Shinkeigaku 38: 457–460

Nausidea PA, Weiner WJ, Kaplan LR, Weber S, Klawans HL (1982) Sleep disruption in the course of chronic levodopa therapy; an early feature of the levodopa psychosis. Clin Neuropharmacol 5: 183–194

Negro PJJ, Faber R (1996) Lewy body disease in a patient with REM sleep disorder. Neurology 46: 1493

Olsen EJ, Boewe BF, Silber MH (2000) Rapid eye movements sleep behavior disorder: demographic, clinical and laboratory findings in 93 cases. Brain 123: 331–339

Olson WL, Gruenthal M, Mueller ME, Olson WH (1997) Gabapentin for parkinsonism: a double blind, placebo-controlled crossover trial. Am J Med 102: 60–66

Oshtory MA, Vijayan N (1980) Clonazepam treatment of insomnia due to sleep myoclonus. Arch Neurol 37: 119–120

Pappert EJ, Goetz CG, Niedermann FG, Raman R, et al (1999) Hallucinations, sleep fragmentation, and altered drem phenomena in Parkinson's disease. Mov Disord 14: 117–121

Partinen M (1997) Sleep disorder related to Parkinson's disease. J Neurol 244: S3–S6

Perry TL, Wright JM, Berry K, Hansen S, et al (1990) Dominantly inherited apathy, central hypoventilation, and Parkinson's syndrome: clinical, biochemical, and neuropathological studies of 2 new cases. Neurology 40: 1882–1887

Pfeiffer RF (1998) Gastrointestinal dysfunction in Parkinson's disease. Clin Neurosci 5: 136–146

Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C (2000) Epidemiology of restless legs syndromes in adults. Arch Intern Med 160: 2137–2140

Plazzi G, Corsini R, Provini F, Pierangeli G, Martinelli P, Montagna P, Lugaresi E, Cortelli P (1997) REM sleep behavior disorders in multiple system atrophy. Neurology 48: 1094–1097

Ramm P, Smith CT (1990) Rates of cerebral protein synthesis are linked to slow wave sleep in the rat. Physiol Behav 48: 749–753

Rao ML, Clarenbach P, Vahlensieck M, Kratzschmar S (1988) Gabapentin augments whole blood serotonin in healthy young man. J Neural Transm 73: 129–134

Reuter I, Ellis CM, Ray Chaudhuri K (1999) Nocturnal subcutaneous apomorphine infusion in Parkinson's disease and restless legs syndrome. Acta Neurol Scand 100: 163–167

Rich SS, Friedman JH, Ott BR (1995) Risperidone versus Clozapine in the treatment of psychosis in six patients with Parkinson's disease and other akinetic-rigid syndromes. J Clin Psych 56: 556–559

Rothdach AJ, Trenkwalder C, Haberstock J, Keil U, Berger K (2000) Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. Neurology 54: 1064–1068

Rubio P, Burguera JA, Sobrino R, Ameabe Y, et al (1995) Sleep disorders and Parkinson's disease: study of series. Rev Neurol 23: 265–268

Rye DB, Bliwise DL (1997) Movement disorders specific to sleep and the nocturnal manifestations of waking movement disorders. In: Watts RL, Koller WC (eds) Movement disorders: neurologic principles and practice. Mc Graw-Hill, New York

Rye DB, Bliwise DL, Dihenia B, Gurecki P (2000) Daytime sleepiness in Parkinson's disease. J Sleep Res 9: 63–69

Siegel JM (1985) Pontomedullary interactions in the generation of REM sleep. In: Mc Ginty DJ, Drucker-Collin R, Morrison A, Parmeggiani PL (eds) Brain mechanisms of sleep. Raven Press, New York, pp 157–174

Sanchez-Ramos JR, Ortoll R, Paulson GW (1996) Visual hallucinations associated with Parkinson's disease. Arch Neurol 53: 1265–1268

Schapira AH (2000) Sleep attacks (sleep episodes) with pergolide. Lancet 355: 1332–1333

Scharf MB, Roth T, Vogel GW, Walsh JKA (1994) Multicenter, placebo controlled study evaluating Zolpidem in the treatment of chronic insomnia. J Clin Psychiatry 55: 192–199

Schatzberg AF, Cole JO, De Battista C (1997) Hypnotoics. Manual of clinical psychopharmacology. American Psychiatric Press, Washington, DC

Schenck CH, Mahowald MW (1990) Polysomnographic, neurologic, psychiatric, and clinical outcome report on 70 consecutive cases with REM sleep behavior disorder (RBD): sustained clonazepam efficacy in 89, 5 of 57 cases. Cleve Clin J Med 57 [Suppl]: S9–S23

Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW (1986) Chronic behavioral disorders of human REM sleep: a category of parasomnia. Sleep 9: 203–308

Schenck CH, Bundlie SR, Patterson AL, Mahowald MW (1987) Rapid eye movement sleep behavior disorder: a treatable parasomnia affecting older adults. J Au Med Assoc 257: 1786–1789

Schenck CH, Bundlie SR, Mahowald MW (1996) Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behavior disorder. Neurology 46: 388–393

Sharf B, Moskovitz C, Lupton MD, Klawans HL (1978) Dream phenomena induced by chronic levodopa therapy. J Neural Transm 43: 143–151

Shaw SH, Curson H, Coquelin JP (1968) A double-blind, comparative study of zolpidem and placebo in treatment of insomnia in elderly insomnia in elderly psychiatric inpatients. J Nerv Ment Dis 147: 202–210

Smith MC, Ellgring H, Oertel WH (1997) Sleep disturbances on Parkinson's disease patients and spouses. J Am Geriatr Soc 45: 194–199

Spielman AJ, Saskin P, Thorpy MJ (1987) Treatment of chronic insomnia by restriction of time in bed. Sleep 10: 45–46

Starkstein SE, Preziosi TJ, Robinson RG (1991) Sleep disorders, pain, and depression in Parkinson's disease. Eur Neurol 31: 352–355

Stern M, Roffwarg H, Duvoisin R (1997) The Parkinsonian tremor in sleep spouses. J Am Geriatr Soc 45: 194–199

Stocchi F, Barbato L, Nordera G, Berardelli A, et al (1998) S. Sleep disoders in Parkinson's disease. J Neurol 245 [Suppl 1]: S15–S18

Stoppe G, Brandt CA, Staedt JH (1999) Behavioural problems associated with dementia: the role of newer antipsychotics. Drug Aging 14: 4154

Takahashi Y, Kipnis D, Daughaday W (1968) Growth hormon secretion during sleep. J Clin Invest 47: 2079–2090

Tandberg E, Larsen JP, Karlsen K (1998) A community-based study of sleep disorders in patients with Parkinson's disease. Mov Disord 13: 895–899

Tandberg E, Larsen JP, Karlsen K (1999) Excessive daytime sleepiness and sleep benefit in Parkinson's disease: a community-based study. Mov Disord 14: 922–927
Tan A, Salgado M, Fahn S (1996) Rapid eye movement sleep behavior disorder preceding Parkinson's disease with therapeutic response to levodopa. Mov Disord 11: 214–216
Tassinari CA, Broughton R, Poire R (1965) An electro-clinical study of nocturnal sleep in patients presenting abnormal movements. Electroencephalogr Clin Neurophysiol 18: 95
Trenkwalder C (1998) Sleep dysfunction in Parkinson's disease. Clin Neurosci 5: 107–114
Trenkwalder C, Bucher SF, Oertel WH (1996) Electrophysiological pattern of involuntary limb movements in the restless legs syndrome. Muscle Nerve 19: 155–162
Treves TA, Paleacu D, Korczin AD (1995) Treatment of depression in Parkinson's disease. In: Koller WC, Paulson G (eds) Therapy of Parkinson's disease. Marcel Dekker, New York
Trosch RM, Friedman JH, Lannon MC, Pahwa R, et al (1998) Clozapine use in Parkinson's disease:a retrospective analysis in a large multicentered clinical experience. Mov Disord 13: 377–382
Trzepacz PT, Violette EJ, Sateia MJ (1984) Response to opioids in three patients with restless leg syndrome. Am J Psychiatry 141: 993–995
Turner RS, Chervin RD, Frey KA, Minoshima S, et al (1997) Probable diffuse Lewy body disease presenting as REM sleep behavior disorder. Neurology 49: 523–527
Uchiyama M, Isse K, Tanaka K (1995) Incidental Lewy body disease in a patient with REM sleep behavior disorder. Neurology 45: 709–712
Valldeoriola F, Molinuevo J (1999) Therapy of behavioral disorders in Parkinson's disease. Biomed Pharmacother 53: 149–153
Vallderiola F, Nobbe FA, Tolosa E (1997) Treatment of behavioural disturbances in Parkinson's disease. J Neural Transm 51 [Suppl]: 175–204
van Hilten JJ, Weggeman M, van der Velde EA, Kerkhof GA, et al (1993) Sleep, excessive daytime sleepiness and fatigue in Parkinson's disease. J Neural Transm [PD Sect] 5: 235–244
van Hilten B, Hoff JI, Middelkoop HA, van der Velde EA, et al (1994) Sleep disruption in Parkinson's disease. Assessment by continuous activity monitoring. Arch Neurol 51: 922–928
Watanabe S, Sakai K, Ono Y, Seino H, Naito H (1987) Alternating periodic leg movements induced by spinal anesthesia in an elderly male. Anaesth Analg 66: 1031–1032
Weitzman ED, Hellman L (1974) Temporal organization of the 24 h pattern of the hypothalamic-pituitary axis. In: Ferin M, Halberg F, Richart RM (eds) Biorhythms and human reproduction. Wiley, New York
Weitzman ED, Czeisler CA, Coleman RM (1981) Delayed sleep phase syndrome. A chronobiological disorder with sleep onset insomnia. Arch Gen Psychiatry 38: 737–746
Wetter TC, Pollmacher T (1997) Restless legs and periodic leg movements in sleep syndromes. J Neurol 244 [Suppl 1]: S37–S45
Wetter TC, Stiansky K, Winkelmann J, et al (1999) A randomized, controlled study of pergolide in patients with restless legs syndrome. Neurology 52: 944–950
Wetter TC, Collado-Seidel V, Pollmacher T, Yassouridis A, Trenkwalder C (2000) Sleep and periodic leg movement patterns in drug-free patients with Parkinson's disease and multiple system atrophy. Sleep 23: 361–367
Whitney CW, Enright PL, Newman AB, Bonekat W, et al (1998) Correlates of daytime sleepiness in 4578 elderly persons: the cardiovascular health study. Sleep 21: 27–36
Wolters EC, Jansen ENH, Tuynman-Qua HG, Bergmans PLM (1996) Olanzepine in the treatment of dopaminomimetic psychosis in patients with Parkinson's disease. Neurology 47: 1085–1087
Wong DT, Calligaro DO, Bymaster FP, Moore NA, et al (1993) Preclinical pharmacology of olanzepine: a novel antipsychotic agent. Proceedings, 9th World Congress of Psychiatry, Rio de Janeiro, Brazil

Zarcone VPJ (2000) Sleep hygiene. In: Kryger MH, Roth T, Dement WC (eds) Principles and practice of sleep medicine. WB Saunders, Philadelphia
Zoldan J, Friedburg G, Goldenberg-Stern H, Melamed E (1993) Ondansteron in hallucinations in advanced Parkinson's disease. Lancet 341: 562–563
Zoldan J, Friedburg G, Weitzman A, Melamed E (1996) Ondansteron, a 5HT3 antagonist for visual hallucinations and paranoid delusional disorder associated with chronic l-dopa therapy in advenaced Parkinson's disease. In: Battisin L, Scarlato G, Caraceni T, Rugieri S (eds) Advances in neurology: Parkinson's disease. Lippincot-Raven, Philadelphia
Zucconi M, Cocagna G, Petronelli R (1989) Nocturnal myoclonus in restless legs syndrome: effect of carbamazepine treatment. Funct Neurol 4: 263–271
Zweig RM, Jankel WR, Hedreen JC (1989) The pedunculopontine nucleus in Parkinson's disease. Ann Neurol 26: 41–46
Yokota T, Hirose K, Tanabe H, et al (1991) Sleep related periodic leg movements (nocturnal myoclonus) due to spinal cord lesion. J Neurol Sci 104: 13–18

Author's address: Prof. J.J.M. Askenasy, Ben Yehuda 79, Herzlya 46403, Israel, e-mail: ajean@post.tau.ac.il