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Excessive Daytime Sleepiness and Sleep Disturbances in Patients with Neurological Diseases

Epidemiology and Management

Svenja Happe

Department of Clinical Neurophysiology, University of Göttingen, Göttingen, Germany

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Abstract

Up to 12% of the general population experience excessive daytime sleepiness (EDS), with increasing prevalence in the elderly. EDS may lead to cognitive impairment, resulting in inattentiveness, poor memory, mood disorders and an increased risk of accidents. As a result, quality of life is reduced in most patients with EDS as well as in their caregiving spouses. There are a variety of causes leading to EDS, including CNS pathology, neurological dysfunction, associated sleep disorders with insufficient or fragmented sleep, and drug therapy. Since EDS accompanies many neurological disorders, such as neurodegenerative and neuromuscular diseases, neurologists should be familiar with the diagnosis, its major causes and with treatment options.

The main focus of this article is on movement disorders, neuromuscular diseases, multiple sclerosis, dementia, cerebrovascular diseases, head and brain trauma, pain and epilepsy. General managment strategies for EDS in all these neurological diseases include sleep hygiene aspects such as extensions of noctural time in bed and frequent naps during the day. Pharmacological treatment is generally achieved with stimulants such as amphetamine, methylphenidate and pemoline, or newer compounds such as modafinil.

Excessive daytime sleepiness (EDS) is a frequent symptom that may lead to an impaired quality of life and an increased risk of accidents.[1] Large population-based studies reported that up to 30% of the elderly experience daytime sleepiness.[2] It is important to differentiate normal sleepiness that is a product of circadian rhythm variation in vigilance from pathological sleepiness, also called EDS. EDS is defined as a subjective feeling of an imperious need of sleep in unusual time and environmental conditions.[3] There are a variety of causes leading to EDS, including CNS pathology, neurological dysfunction, associated sleep disorders with insufficient or fragmented sleep, or drug therapy. EDS may lead to cognitive impairment, resulting in inattentiveness, poor memory, mood disorders and chronic accident proneness. For example, each year more than 50 000 motor vehicle accidents in the US are attributed to driving while sleepy.[4] To date, EDS is still under diagnosed and frequently misdiagnosed. Since it accompanies many neurological disorders, such as neurodegenerative and neuromuscular diseases, neurologists should be familiar with the diagnosis, its major causes and with treatment options.

The aim of the present paper is to review EDS as a symptom in neurological diseases, with epidemiological and treatment aspects. Although primary sleep disorders such as sleep apnoea syndrome (SAS), narcolepsy and periodic limb movement disorder during sleep (PLMS) are also frequently associated with EDS, they are not reviewed in detail in this manuscript. For further information on these sleep disorders, please see the reviews by El-Ad and Korczyn[5] and Guilleminault and Brooks.[6] Since EDS and sleep disturbances are best investigated in movement disorders, a main focus of this review is this group of neurological disorders.

1. Definition and Assessment of Excessive Daytime Sleepiness

As discussed, EDS is a subjective feeling of an imperious need of sleep in unusual time and environmental conditions, meaning falling asleep unintentionally or at inappropriate times and locations.[3] It affects up to 12% of the general population.[7] The differential diagnosis of EDS requires objective and subjective assessments. EDS can subjectively be assessed by visual analogue scales[8] and questionnaires, the best known being the Epworth Sleepiness Scale (ESS),[9] and others such as the Stanford Sleepiness Scale.[10] An instrument to measure functional status outcomes for disorders of EDS was developed by Weaver et al.[11] Objective tests assess the sleep-wake balance disturbances. The most widely used tests are the Multiple Sleep Latency Test (MSLT),[12] the Maintenance of Wakefulness Test (MWT)[13] and the Oxford Sleep Resistance Test.[14] These tests measure the time to sleep emergence in different conditions. Others are pupillometry[15] and performance tasks, such as the vigilance test 'Quatember and Maly'[16] (a computerised version of the Mackworth Clock Test[17]), measuring the state of alertness as shown by pupillary distress index, reaction time and mistakes in different tasks. However, differences have been observed between behavioural and physiological measures of sleepiness, suggesting that these techniques may assess different aspects of sleepiness.[18] It is important to take a precise history. The combination of both objective and subjective information allows the clinician to diagnose EDS and its severity.

There are four major causes of EDS: (i) qualitative and quantitative sleep deficiencies such as insufficient sleep and fragmented sleep, as in SAS and

somatic and psychiatric diseases; (ii) CNS pathological abnormalities such as neurological disorders, narcolepsy and idiopathic CNS hypersomnia; (iii) circadian rhythm disorders such as misalignments of the body's circadian pacemaker with the environment (e.g. jet lag or shift work); and (iv) drugs.[7]

General management strategies for EDS include sleep hygiene aspects such as extensions of time in bed and frequent naps. Improving sleep in general should be the aim. Various medical devices such as nasal masks for continuous positive airway pressure (CPAP) ventilation, oral appliances and, in some cases, surgery, are successfully used in SAS. Pharmacotherapy is generally achieved with stimulants such as amphetamine, methylphenidate and pemoline, or newer compounds like modafinil (table I).[7] Where available, specific management strategies of EDS in the diverse neurological diseases are discussed in the following sections.

2. Movement Disorders

In patients with movement disorders, an increasing number of sleep abnormalities have been recognised. Parkinson's disease and restless legs syndrome (RLS) are the most frequent and best investigated movement (and neurological) disorders concerning nocturnal motor patterns and sleep characteristics.[26] During sleep, movement characteristics of the wake condition and specific motor patterns seem to appear in most patients with movement disorders such as Parkinson's disease, Gilles de la Tourette syndrome (GTS), Huntington's disease and torsion dystonia.[27-29] Tremor, chorea, dystonic spasms and tics were all found to reappear during sleep, often associated with arousal phenomena.[28] In addition, disturbances of rapid eye movement (REM) sleep with increased muscle tone are common in neurodegenerative diseases and may already precede the clinically apparent motor dysfunction of Parkinson's disease.[30,31] Therefore, movement disorders may disturb sleep quality and quantity, and are often associated with daytime sleepiness and reduced sleep quality and should be investigated thoroughly. Treatment of the underlying neurological disease may improve the sleep disturbance and the EDS. Certain general principles such as elimination of medications that may contribute to sleep disturbances, treatment of associated depression or anxiety, institution of regular sleep times and sleep hygiene, and specific treatment of sleep-related respiratory disorders or PLMS should be considered carefully for each individual to improve sleep quality.[27]

2.1 Parkinson's Disease

In a community-based study in Norway, 15.5% of patients with Parkinson's disease but only 1% of healthy elderly and 4% of older patients with diabetes mellitus reported experiencing EDS, whereas the frequency of mild daytime sleepiness was similar.[32] Factor and co-workers[33] also found that EDS and dozing, but not napping, are more frequent in patients with Parkinson's disease than in elderly controls. The prevalence of 'sleep attacks' was about seven times higher in patients with Parkinson's disease than in healthy controls, and associated with a higher dose of levodopa and longer duration of disease.[34] Another study reported similar results showing that somnolence in patients with Parkinson's disease is, on average, 25% higher than in other neurological diseases, and is related to Parkinson's disease stage, levodopa dose and the use of dopamine agonists.[35] The neurodegenerative process itself, with disturbances of elements of the reticular activating system, sleep disorders such as SAS and narcolepsy, REM sleep behaviour disorder (RBD), mood disorders as well as various drugs, can be responsible for EDS.[27]

Recent reports that dopaminergic medication, in particular the dopamine D_2 and D_3 receptor agonists pramipexole and ropinirole, precipitate daytime sleepiness with sudden sleep episodes in patients with Parkinson's disease, have received widespread attention. It was suggested that the sedating effect of ropinirole and pramipexole may be due to their stronger D_3 receptor activity compared with other dopamine receptor agonists.[36,37] However, reports from two more recent studies[38,39] suggested that sedation may be a class effect of dopamine receptor agonists in general, since EDS was generally more

Table I. Management of excessive daytime sleepiness (EDS) in neurological diseases with stimulating and wakefulness-promoting drugs[a]

Drug	Daily dose	Common adverse effects	Neurological disease (reference)	Remarks
Modafinil	50–400mg	Headache, nausea, nervousness, palpitations, gastrointestinal symptoms	Parkinson's disease,[19,20] myotonic dystrophy,[21] multiple sclerosis[22]	Fewer adverse effects than amphetamines, widely used in narcolepsy
Amphetamines				
levoamphetamine dextroamphetamine	50mg (5–60mg) 15mg (5–60mg)	Tremor, palpitations, headache, restlessness, sweating, anorexia, hypertension, cardiac arrhythmia	Parkinson's disease[23]	Potential for abuse and dependency
Methylphenidate	5–40mg	Similar to amphetamines	Myotonic dystrophy[24,25]	Most often used stimulant worldwide, potential for abuse and dependency
Amantadine	100–600mg	Livido reticularis, sleeplessness, psychosis, dizziness, blurred vision	Parkinson's disease	Caveat in renal insufficiency
Selegiline	5–40mg	Dry mouth, dizziness, headache, restlessness	Parkinson's disease	Known to reduce EDS in narcolepsy
Caffeine	Up to 200mg	Palpitation, tachycardia, restlessness, headache, tremor, hypertonus	Can be tried in nonspecific EDS	Readily available, inexpensive
Antidepressants				
SSRIs (e.g. paroxetine) MAO inhibitors (moclobemid) noradrenergic inhibitor (e.g. reboxetine)	10–40mg 150–600mg 4–12mg	Sleeplessness, agitation, palpitation, orthostatic hypotonia	Can be tried in nonspecific EDS	Particularly useful in disorders associated with depression
γ-Hydroxybutyrate	3–9g (twice nightly)	Nausea, vomiting, weight loss, occasional residual sedation	Can be tried in nonspecific EDS	Fewer adverse effects than amphetamines, used in narcolepsy

a Caveat = no use of stimulating drugs in epilepsy syndromes because of increased cerebral excitability.

MAO = monoamine oxidase; **SSRI** = selective serotonin reuptake inhibitors.

frequent in patients taking a dopamine receptor agonist. In patients with Parkinson's disease with EDS, diagnostic testing including polysomnography is warranted to exclude secondary causes of EDS as the basis for therapeutic interventions. A recently developed Parkinson's disease sleep scale[40] may help to differentiate between various sleep disorders and optimise treatment strategies in this patient group. It should be kept in mind that sleep-related problems, depressive symptoms and EDS have an important impact on quality of life, not only in patients with neurodegenerative diseases such as Parkinson's disease[41,42] but also in their caregivers.[41]

If medication adjustments such as giving of amantadine or discontinuation of selegiline, benzodiazepines and dopamine receptor agonists are ineffectual, agents specifically designed to promote daytime alertness may be beneficial. RBD can be treated with benzodiazepines, clonazepam at a dose of 0.5–2mg at bedtime markedly reduces all symptoms in about 90% of patients.[43,44] Previous reports have shown that amphetamines increased daytime alertness in patients with Parkinson's disease.[23] Recently, it was shown that EDS improved under treatment with modafinil, a psychostimulant drug acting on postsynaptic α_1-adrenergic receptors; however, the exact mode(s) of action of modafinil are still being debated.[19,20] Therefore, modafinil may be considered as an optional therapy for EDS in patients with Parkinson's disease. However, other treatable sleep disturbances associated with EDS and other causes, such as drug-induced EDS, should be ruled out and treated first.

2.2 Gilles de la Tourette Syndrome

Forty-four to eighty percent of patients with GTS report sleep disturbances, including parasomnias and respiratory disturbances. Insomnia with difficulties falling asleep and early awakening are most frequently reported. There are some studies to date investigating sleep in patients with GTS by means of polysomnography. However, results on the amount of sleep are controversial.[26] There are increased motor phenomena in comparison with healthy controls during sleep such as PLMS,[45] RBD[46] and tics,[28,47-49] with less complexity during sleep than during wakefulness. These increased rates of motor phenomena and arousals during the night might be the result of a reduced intracortical inhibition of motor pathways in GTS during wakefulness[29,50] and can lead to EDS during the day. Other possible causes are alterations of dopamine, serotonin or norepinephrine (noradrenaline) metabolism.[27,45,51]

Since it is known that medication (e.g. tetrabenazine) that reduces tics during the waking stage also lead to a reduction of tics during sleep,[49,52] an efficacious daytime treatment and a special treatment of PLM and RBD may help to improve sleep in patients with GTS. This may secondarily lead to a reduced EDS during the day.

2.3 Huntington's Disease

Disturbed sleep is a frequent finding in many patients with Huntington's disease; it increases with progression of the disease and is associated with atrophy of the caudate nuclei. In addition, choreiform movements during sleep may lead to arousals and cause fragmentation of sleep profile. Therefore, degenerative changes affecting structures regulating sleep-wakefulness, presence of chorea and dystonia, medication and depression may be responsible for sleep disturbances in patients with Huntington's disease.[27] However, EDS was not reported to be increased in Huntington's disease.[53-55]

An optimised symptomatic treatment of hyperkinesia, depression and other psychiatric problems should be considered to improve sleep. Next to physio- and psychotherapy, symptomatic drug therapy, for example with antidepressants and benzodiazepines, can also be tried to reduce sleep disturbances.[56]

2.4 Dystonia

Sleep disturbances are common in dystonia and deteriorate with progression of the disease.[27] To date, however, only a few studies have investigated sleep by means of polysomnography.[27,57-59] Dystonic movements may persist during sleep with partial reactivation during REM sleep but with reduced

frequency,[27] which may lead to a fragmented sleep profile and result in EDS. Reduced amounts of serotonin in the dorsal raphe nucleus and norepinephrine in the locus coeruleus in addition to motor abnormalities, as described previously by Chokroverty,[27] may be related to sleep disturbances in torsion dystonia.

The abnormal movements can be altered by certain drugs such as trihexyphenidyl, profenamine, benzodiazepines and levodopa, by stereotactic lesions in the ventrolateral nuclei of the thalamus and pallidum, and by periodic injections of botulinum toxin into the affected muscles.[60] An optimised treatment of motor symptoms may also improve sleep quality and EDS during the day.

Other movement disorders are primarily classified as sleep disorders and listed under 'dyssomnias' within the classification of the American Sleep Disorders Association.[3] RLS is the most common of these, closely related to PLMS, often culminating in daytime sleepiness.[61]

2.5 Restless Legs Syndrome and Periodic Limb Movement Disorder During Sleep

Adult prevalence of RLS ranges from 5% to 15%,[62-64] increasing with age.[61,65,66] RLS often leads to sleep disturbances with prolonged sleep latency, reduced total sleep time, decreased slow-wave sleep and decreased sleep efficiency, often culminating in daytime sleepiness. In 63–92% of patients with idiopathic RLS a positive family history is present.[67] A metabolic basis of secondary RLS has also been postulated, since RLS is commonly associated with iron-deficiency anaemia,[68] hypothyroidism,[69] diabetes,[63,70] rheumatoid arthritis and Sjögren's syndrome.[71] Abnormal involuntary movements during sleep, such as PLMS, have been reported to be associated with RLS in up to 88% of patients with RLS.[61,72,73] However, the relationship between RLS and PLMS is still unclear. It is known that the prevalence of PLMS increases with increasing age[65] and that about one-third of patients with Parkinson's disease also have PLMS.[27] PLMS also occurs in patients with idiopathic RBD, narcolepsy and SAS.[74] As a result of intensive movements, PLMS can lead to sleep onset difficulty, arousals with fragmentation of the sleep profile, nocturnal awakenings and associated daytime sleepiness.[74] The frequency of polysomnographically detected PLMS correlates strongly with the severity of RLS, and can be used for diagnosis of RLS and monitoring of treatment.[61] Other objective assessments to measure PLMS include actigraphy[75] and suggested immobilisation tests.[76] Diagnostic criteria and phenomenology are described elsewhere in more detail.[26,77]

In isolation, PLMS does not necessarily require treatment and does not primarily have any pathological impact. If EDS is the major complaint, PLMS should be suspected and ruled out if not present.[78] Before pharmacological treatment is started, non-pharmacological treatment strategies should be tried first, including sleep hygiene and avoidance of stimulants or aggravating drugs (e.g. caffeine, alcohol, antihistamines, antipsychotics, antidepressants). In iron-deficiency anaemia, iron supplementation should be given first. In physiological conditions such as pregnancy, symptoms may resolve after delivery. Pharmacological treatment strategies for RLS and PLMS are diverse, and mainly focus on dopaminergic therapy.[79-81] Opioids,[82-84] clonazepam,[85] anticonvulsants (such as carbamazepine)[86] and gabapentin[87,88] are drugs of second choice if dopaminergic agents are not effective or if contraindications do not allow dopaminergic treatment. They should be considered when pharmacotherapy is indicated and patients cannot tolerate first-line agents.

3. Neuromuscular Diseases

Physiologically, muscle tone is reduced during sleep with a maximum reduction during REM sleep, the so-called REM sleep atonia. However, in contrast with the activity of the intercostal muscles, the diaphragmatic muscle function remains normal during REM sleep. A disturbed function of the diaphragm may be the result of a paresis of the phrenic nerve or of neuromuscular diseases such as myasthenia gravis and myopathies.[89] A disturbed diaphragmatic ventilation is usually compensated

during wake and non-REM sleep by the activity of the intercostal muscles and the accessory muscles of ventilation. During REM sleep, on the one hand, central apnoeas and hypopneas may be increased; on the other hand, a secondary hypoventilation may occur. The hypoventilation, caused by a neuromuscular insufficiency, can usually be distinguished as intermittent flat ventilation with intact respiratory drive and increasing respiratory acidosis from central apnoeas and hypopneas with missing respiratory drive and eu- or hypocapnia. However, an association of central apnoeas and hypopneas with alveolar hypoventilation is possible.[90] Obstructive apnoeas and hypopneas occur mainly during REM sleep in neuromuscular disorders.[90] An increased reduction of muscle tone is the main pathomechanism for obstructive breathing disorders, leading to a collapse of upper airways. An additional factor is an adipositas, provoked by reduced physical activity due to the neuromuscular disease[91,92] or by therapy with corticosteroids.[93] Adipositas may lead to obstructive apnoeas on the one hand and to reduced function of the diaphragm and, therefore, to hypoventilation on the other hand.[94]

Therefore, respiratory insufficiency may occur during sleep despite nearly normal daytime pulmonary function. Measurement of nocturnal blood oxygen and carbon monoxide is useful to establish respiratory insufficiency, the results of which may be sleep disturbances and daytime sleepiness. However, polysomnographic data in neuromuscular diseases are sparse.

3.1 Myotonic Dystrophy

Daytime sleepiness is common in myotonic dystrophy and might be attributed to disturbed nocturnal breathing. In polysomnographical studies, 50-77% of patients with myotonic dystrophy were found to have pathological EDS. These patients did not show significantly different quantitative sleep variables or sleep apnoeas compared with the patients not experiencing EDS.[24,95] However, there was evidence that EDS in this patient group may be the result of a dysfunction of central sleep regulation rather than disturbed nocturnal breathing.[24,25] The ultradian rhythm characteristics of nocturnal sleep indicated a prolonged mean cycle duration and decreased stability of non-REM/REM cycle and the temporal structure of REM sleep was changed, suggesting that EDS in myotonic dystrophy reflects a malfunction of the circadian and ultradian timing system.[96]

The central stimulants methylphenidate[24,25] and modafinil[21] produced sustained benefit in patients with myotonic dystrophy who experienced EDS.

3.2 Amyotrophic Lateral Sclerosis

Polysomnographic findings in two patients with clinically and electrophysiologically confirmed amyotrophic lateral sclerosis with minimal weakness showed profound oxygen desaturations and prolonged periods of hypoventilation during sleep. This led to severe sleep maintenance insomnia and frequent arousals. CPAP or bilevel positive airway pressure (PAP) [bilevel PAP] may restore nocturnal ventilation and blood oxygen, and sleep parameters and daytime sleepiness may improve.[97]

3.3 Myasthenia Gravis

Polysomnographic studies in clinically stable patients with myasthenia gravis showed a prevalence of sleep apnoea of 60%[98,99] to 75%,[93] showing mainly central apnoeas and hypopneas, almost exclusively during REM sleep.[98,99] REM sleep and slow-wave sleep were reduced, sleep profile was fragmented, light sleep stages were increased as usually seen in patients with SAS.[98,99] Duration and severity of the disease, and antibodies against acetylcholine receptors, were not associated with the occurrence of sleep apnoeas, whereas an increased body mass index and a pathological respiratory function during daytime was correlated with sleep apnoeas.[99] Only a few patients in these studies experienced EDS. To date, nocturnal respiratory problems are still underdiagnosed in patients with myasthenia gravis. Nonspecific symptoms such as sleepiness, fatigue, concentration and memory problems could well be symptoms of a sleep-related breathing disorder in patients with myasthenia gravis.

Additional to a sufficient treatment of the disorder itself with thymectomy and weight loss, nocturnal ventilation therapy with CPAP or bilevel PAP may be effective. The number of apnoeas were reduced by thymectomy in one study.[93] Drug therapy with pyridostigmine slow release to improve muscle strength during the night is also recommended.[91]

3.4 Other Neuromuscular Diseases

Patients with post-polio syndrome may develop additional neuromuscular and respiratory symptoms decades after the acute attack, with additional nocturnal obstructive and mixed apnoea syndromes or hypoventilation and sleep apnoea attributable to respiratory muscle weakness. These patients may experience EDS and may be treated either with nasal CPAP or with nasal mask ventilation.[100]

4. Multiple Sclerosis

Fatigue as one of the differential diagnoses of EDS is one of the most frequent symptoms in patients with multiple sclerosis (MS). However, its pathogenesis is poorly understood. A functional magnetic resonance imaging study could show that fatigue in MS is related to impaired interactions between functionally related cortical and subcortical areas.[101] Management of fatigue in patients with MS often entails both pharmacological and behavioural components. Recently, both fampridine 32mg[102] and modafinil 200mg[22] have been shown to improve fatigue in patients with MS and showed good tolerability.

5. Dementia

Alzheimer's disease and dementia with Lewy bodies (DLB) are progressive dementing diseases associated with sleep changes. Sleep disturbance adds to carer burden and leads to additional prescription of medication in many patients.[103] Sleep disruptions and sundowning (characterised by twilight and nocturnal agitation and confusion), probably related to disturbances of circadian rhythms, are common and troublesome in about 45% of patients with Alzheimer's disease.[5,104,105] As a result, daytime sleepiness with daytime napping is increased. The severity of sleep disturbances is known to worsen with increasing memory impairment.[106] Sleep apnoea as another reason for daytime sleepiness is also reported to be more common in demented patients.[107] The decreased proportion of REM sleep and the fluctuating level of consciousness in about 80% of patients with DLB may be a predictable consequence of the marked loss of cholinergic neurons. Patients with DLB show an increased rate of sleep disturbances compared with patients with Alzheimer's disease with more confusion on waking and abnormal control of movement such as RBD.[108] A new form of progressive dementia associated with hypersomnolence, RBD with oneiric behaviour and total loss of slow-wave sleep has recently been introduced as 'oneiric dementia'.[109] Another study provides evidence that EDS in older adults may be an early indicator of decline in cognitive functioning and onset of dementia.[110] Thorough assessment of associated psychopathology, daytime behaviour, medical disorders, drugs, pain and environmental conditions is needed for optimal management.

Differential diagnosis of a sleep problem in dementia is the basis of rational pharmacotherapy. If caused by illness, effective treatment of a specific medical or psychiatric problem should help alleviate the sleep problem as well. Changes in the timing of drug administration may improve sleep and daytime sleepiness. For the treatment of chronic insomnia, behaviour techniques should always be tried in combination with pharmacological therapy with sedative-hypnotic drugs. The treatment of choice for obstructive SAS (OSAS) is CPAP. For PLMS, dopaminergic agents are therapy of first choice. RBD can best be controlled with clonazepam,[111] and treatment with rivastigmine may correct some of the sleep disturbances seen in DLB.[108,112] Recently, positive treatment effects of melatonin[105] and light treatment[113] on sleep disturbances[105] and sundowning[105,113] in patients with dementia have been reported.

6. Cerebrovascular Diseases

Patients with acute cerebrovascular diseases have a 5-fold risk increased risk of experiencing OSAS and related EDS than healthy controls. Frequency and severity of OSAS seem to be similar in stroke and transient ischaemic attacks. OSAS in stroke patients should early be treated with CPAP or bilevel PAP since it may have implications for prevention, acute treatment and rehabilitation.[114] In particular, paramedian thalamic stroke may lead to EDS since the thalamus is involved in maintenance of wakefulness and promotion of non-REM sleep.[115] It is known that daytime sleepiness and length of nocturnal sleep (>8 hours per night) are independent risk factors for stroke. Persons who report both >8 hours of sleep and daytime sleepiness seem to have a greatly increased risk for stroke.[116]

7. Head and Brain Trauma

EDS occurs in about one-third of patients with brain injuries, with a relatively high prevalence of SAS (12%).[117] Sleep-disordered breathing was also a common finding in patients with whiplash injury.[118] In patients with head-neck trauma, post-traumatic complaint of somnolence, associated with variable degree of daytime functioning, was reported in >98% of patients. Patients who were in a coma for 24 hours, who had a skull fracture or who had immediate neurosurgical interventions were likely to have EDS.[118,119] To date, no specific treatment strategies are reported.

8. Pain

Pain in general is an important factor in nocturnal sleep disruption and daytime sleepiness. Headaches, as the most frequent painful neurological diagnoses, are often associated with sleep disorders; some headache syndromes are even related to certain sleep phases or circadian rhythms. These so-called sleep-related headache syndromes are specific migraine types, cluster headache, chronic paroxysmal hemicrania and the hypnic headache syndrome.[120] To date, no data about frequency and aetiology of EDS in painful diseases exist. To avoid EDS in headache syndromes and other pain syndromes as a result of chronification of sleep disorders, pain should be treated as soon as it occurs with analgesic drugs and conservative methods such as physiotherapy and application of warmth.

9. Epilepsy

Seizures and antiepileptic drugs affect sleep and may lead to EDS. EDS often complicates the clinical picture of epilepsy, facilitating the occurrence of seizures and aggravating cognition and behaviour. Patients with epilepsy who are taking antiepileptic drugs are known to frequently report daytime sleepiness.[121] However, EDS has been documented in patients with epilepsy before starting any drug treatment or after its discontinuation.[122] Other studies could potentially show that the degree of EDS in patients with epilepsy did not differ significantly from that of patients affected with other neurological disorders, and that coexisting symptoms such as OSAS and RLS are stronger predictors of subjective EDS than antiepileptic drugs or type and frequency of epileptic seizures.[123,124] A more recent study[125] prospectively evaluated sleepiness by means of the ESS in a series of 244 patients with epilepsy and 205 healthy individuals. Patients with epilepsy did not show a significant difference in the ESS score, but suspected OSAS and recurrence of seizures were associated with EDS. Nocturnal sleep fragmentation and EDS have been reported in temporal lobe and frontal lobe epilepsy, namely nocturnal lobe epilepsy.[122] Therefore, epilepsy patients with persistent daytime sleepiness should be investigated by means of neurophysiological testing such as polysomnography, MSLT and MWT.

Treatment options in patients with epilepsy who have EDS depend on its origin and might be optimisation of antiepileptic drug therapy, preferably with monotherapy and treatment of an underlying primary sleep disorder such as OSAS or PLMS. Sleep hygiene with regular sleep times of sufficient length is an important factor in patients with epilepsy in order to prevent EDS and seizures. However, it must be kept in mind that sleep is also a potent activator of seizures and epileptiform discharges,

since in some patients seizures occur exclusively or predominantly in sleep.[126] If so, antiepileptic treatment may improve clinical and polysomnographic sleep pattern and EDS. Pharmacotherapy for sleepiness in epilepsy should be a last resort.

10. Conclusion

Controlling the symptom of EDS is an important responsibility of sleep medicine. In many patients, EDS is the result of non-restorative sleep, and the treatment with hypnosedatives at night may help to improve sleep and daytime symptoms. The most important aspect for treatment is to diagnose sleep disturbances leading to EDS thoroughly and to treat them according to the specific aetiology. Stimulant drugs such as amphetamines and modafinil may allow patients with persistent EDS to function throughout the day at normal levels of sleep tendency and psychomotor functioning, if restful nighttime sleep is not enough. The following principles should be applied in the therapeutic use of stimulant drugs.[127]

- EDS warrants aggressive treatment when sustained alertness is necessary for individual or public safety.
- Stimulant drugs are important in the therapeutic approach to patients with EDS.
- The prime goal, although sometimes unachievable, should be symptom-free daytime functioning. It is important that, during therapy, a period of symptom-free daytime functioning is achieved for a frame of reference for evaluating future treatments.
- Treatment efficacy should be assessed periodically with subjective and objective techniques such as the MSLT or the MWT.
- In some patients, stimulant doses may exceed the manufacturer's recommendations.

In summary, neurologists should be awake to identifying EDS in their patients and are responsible for helping their patients to improve individual daytime functioning.

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References

1. Connor J, Whitlock G, Norton R, et al. The role of driver sleepiness in car crashes: a systematic review of epidemiological studies. Accid Anal Prev 2001; 33: 31-41
2. Asplund R. Daytime sleepiness and napping amongst the elderly in relation to somatic health and medical treatment. J Intern Med 1996; 239: 261-7
3. American Sleep Disorders Association. International classification of sleep disorders, revised: diagnostic and coding manual. Rochester (NY): American Sleep Disorders Association, 1997
4. Mahowald MW. Eyes wide shut: the dangers of sleepy driving. Minn Med 2000; 83: 25-30
5. El-Ad B, Korczyn AD. Disorders of excessive daytime sleepiness: an update. J Neurol Sci 1998; 153: 192-202
6. Guilleminault C, Brooks SN. Excessive daytime sleepiness: a challenge for the practising neurologist. Brain 2001; 124: 1482-91
7. Roth T, Roehrs TA. Etiologies and sequelae of excessive daytime sleepiness. Clin Ther 1996; 18: 562-76
8. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. Psychiatry Res 1991; 36: 291-8
9. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991; 14: 540-5
10. Hoddes E, Zarcone V, Smythe H, et al. Quantification of sleepiness: a new approach. Psychophysiology 1973; 10: 431-6
11. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep 1997; 20: 835-43
12. Richardson GS, Carskadon MA, Flagg W, et al. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalogr Clin Neurophysiol 1978; 45: 621-7
13. Mitler MM, Krishnareddy SG, Browman CP. Maintenance of wakefulness test: a polysomnographic technique for evaluating treatment efficacy in patients with excessive somnolence. Electroencephalogr Clin Neurophysiol 1982; 53: 658-61
14. Bennett LS, Stradling JR, Davies RJ. A behavioural test to assess daytime sleepiness in obstructive sleep apnea. J Sleep Res 1997; 16: 142-5
15. Wilhelm B, Wilhelm H, Lüdtke H, et al. Pupillographic assessment of sleepiness in sleep-deprived healthy subjects. Sleep 1998; 21: 258-65
16. Meier-Ewert K. Abnorme Tagesschläfrigkeit: Ansätze zu einer Typologie. Ther Umsch 1991; 48: 746-50
17. Mackworth NH. Vigilance. Advancement Sci 1957; 53: 389-93
18. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the Epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res 2000; 9: 5-11
19. Happe S, Pirker W, Sauter C, et al. Successful treatment of excessive daytime sleepiness in Parkinson's disease with modafinil. J Neurol 2001; 248: 632-4
20. Nieves AV, Lang AE. Treatment of excessive daytime sleepiness in patients with Parkinson's disease with modafinil. Clin Neuropharmacol 2002; 25: 111-4

21. Damian MS, Gerlach A, Schmidt F, et al. Modafinil for excessive daytime sleepiness in myotonic dystrophy. Neurology 2001; 56: 794-6
22. Rammohan KW, Rosenberg JH, Lynn DJ, et al. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. J Neurol Neurosurg Psychiatry 2002; 72 (2): 179-83
23. Parkes JD, Tarsy D, Marsden CD, et al. Amphetamines in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry 1975; 38: 232-7
24. Van der Meche FG, Bogaard JM, van der Sluys JC, et al. Daytime sleep in myotonic dystrophy is not caused by sleep apnoea. J Neurol Neurosurg Psychiatry 1994; 57: 626-8
25. Miyamoto T, Miyamoto M, Suga T, et al. Methylphenidate hydrochloride for excessive daytime sleepiness in a patient with myotonic dystrophy. Psychiatry Clin Neurosci 2002; 56: 271-2
26. Happe S, Trenkwalder C. Movement disorders in sleep: Parkinson's disease and restless legs syndrome. Biomed Tech (Berl) 2003 Mar; 48 (3): 62-7
27. Chokroverty S. Sleep and degenerative neurologic disorders. Neurol Clin 1996; 4: 807-26
28. Fish DR, Sawyers D, Allen PJ, et al. 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 1991; 48: 210-4
29. Rothenberger A, Kostanecka T, Kinkelbur J, et al. Sleep and Tourette syndrome. In: Cohen DJ, Goetz CG, Jankovic J, editors. Tourette syndrome. Philadelphia (PA): Lippincott Williams and Wilkins, 2001: 245-59
30. Boeve BF, Silber MH, Ferman TJ, et al. Association of REM sleep behavior disorder and neurodegenerative disease may reflect an underlying synucleinopathy. Mov Disord 2001; 16: 622-30
31. Eisensehr I, Lindeiner H, Jäger M, et al. REM sleep behavior disorder in sleep-disordered patients with versus without Parkinson's disease: is there a need for polysomnography? J Neurol Sci 2001; 186: 7-11
32. Tandberg E, Larsen JP, Karlsen K. Excessive daytime sleepiness and sleep benefit in Parkinson's disease: a community based study. Mov Disord 1999; 14: 922-7
33. Factor SA, McAlarney T, Sanchez-Ramoz JR, et al. Sleep disorders and sleep effect in Parkinson's disease. Mov Disord 1990; 5: 280-5
34. Tan EK, Lum SY, Fook-Chong SM, et al. Evaluation of somnolence in Parkinson's disease: comparison with age- and sex-matched controls. Neurology 2002; 58: 465-8
35. O'Suilleabhain PE, Dewey Jr RB. Contributions of dopaminergic drugs and disease severity to daytime sleepiness in Parkinson disease. Arch Neurol 2002; 59: 986-9
36. Frucht S, Rogers J, Greene P, et al. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999; 52: 1908-10
37. Ryan M, Slevin JD, Wells A. Non-ergot dopamine agonist-induced sleep attacks. Pharmacotherapy 2000; 20: 724-6
38. Pal S, Bhattacharya KF, Agapito C, et al. A study of excessive daytime sleepiness and its clinical significance in three groups of Parkinson's disease patients taking pramipexole, cabergoline and levodopa mono and combination therapy. J Neural Transm 2001; 108: 71-7
39. Happe S, Berger K. The association of dopamine agonists with daytime sleepiness, sleep problems and quality of life in patients with Parkinson's disease: a prospective study. J Neurol 2001; 248: 1062-7
40. Chaudhuri KR, Pal S, Bridgman K, et al. Achieving 24-hour control of Parkinson's disease symptoms: use of objective measures to improve nocturnal disability. Eur Neurol 2001; 46 Suppl. 1: 3-10
41. Happe S, Berger K. The association between caregiver burden and sleep disturbances in partners of patients with Parkinson's disease. Age Ageing 2002; 31: 349-54
42. Karlsen KH, Larsen JP, Tandberg E, et al. Influence of clinical and demographic variables on quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1999; 66: 431-5
43. Schenck C, Hurwitz T, Mahowald M. REM sleep behavior disorder: an update on a series of 96 patients and a review of the world literature. J Sleep Res 1993; 2: 224-31
44. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behavior disorder: demographic, clinical and laboratory findings in 93 cases. Brain 2000; 123: 331-9
45. Voderholzer U, Müller N, Haag C, et al. Periodic limb movements during sleep are a frequent finding in patients with Gilles de la Tourette's syndrome. J Neurol 1997; 244: 521-6
46. Tarajanovic NN, Shapiro CM, Sandor P. REM sleep behaviour disorder in patients with Tourette's syndrome [abstract]. Sleep Res 1997; 26: 524
47. Cohrs S, Rasch T, Altmeyer S, et al. Decreased sleep quality and increased sleep related movements in patients with Tourette's syndrome. J Neurol Neurosurg Psychiatry 2001; 70: 192-7
48. Glaze DG, Frost Jr JD, Jankovic J. Sleep in Gilles de la Tourette's syndrome: disorder of arousal. Neurology 1983; 33: 586-92
49. Jankovic J, Rohaidy H. Motor, behavioral and pharmacologic findings in Tourette's syndrome. Can J Neurol Sci 1987; 14: 541-6
50. Ziemann U, Paulus W, Rothenberger A. Decreased motor inhibition in Tourette's disorder: evidence from transcranial magnetic stimulation. Am J Psychiatry 1997; 154: 1277-84
51. Butler IJ, Doslow SH, Sieger WE, et al. Biogenic amine metabolism in Tourette syndrome. Ann Neurol 1979; 6: 37-9
52. Mendelson WB, Caine ED, Goyer P, et al. Sleep in Gilles de la Tourette syndrome. Biol Psychiatry 1980; 15: 339-43
53. Bollen EL, den Heijer JC, Ponsioen C, et al. Respiration during sleep in Huntington's chorea. J Neurol Sci 1988; 84: 63-8
54. Hansotia P, Wall R, Berendes J. Sleep disturbances and severity of Huntington's disease. Neurology 1985; 34: 1672-4
55. Wiegand M, Möller AA, Lauer CJ, et al. Nocturnal sleep in Huntington's disease. J Neurol 1991; 238: 203-8
56. Feigin A, Kiebertz K, Shoulson I. Treatment of Huntington's disease and other choreic disorders. In: Kurlan R, editor. Treatment of movement disorders. Philadelphia (PA): JB Lippincott, 1994: 337-64
57. Fish DR, Allen PJ, Sawyers D. Sleep spindles in torsion dystonia. Arch Neurol 1990; 47: 216-8
58. Fish DR, Sawyers D, Smith SJ, et al. Motor inhibition from the brainstem is normal in torsion dystonia during REM sleep. J Neurol Neurosurg Psychiatry 1991; 54: 140-4
59. Jankel WR, Niedermeyer E, Graf M, et al. Polysomnography of torsion dystonia. Arch Neurol 1984; 41: 1081-3
60. Bressman SB. Dystonia update. Clin Neuropharmacol 2000; 23: 239-51
61. Montplaisir J, Boucher S, Poirier G, et al. Clinical, polysomnographic, and genetic characteristics of restless legs

syndrome: a study of 133 patients diagnosed with new standard criteria. Mov Disord 1997; 12: 61-5
62. Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep 1994; 17: 739-43
63. Phillips B, Young T, Finn L, et al. Epidemiology of restless legs symptoms in adults. Arch Intern Med 2000; 160: 2137-41
64. Rothdach AJ, Trenkwalder C, Haberstock J, et al. Prevalence and risk factors of RLS in an elderly population: the MEMO Study. Neurology 2000; 54: 1064-8
65. Ancoli-Israel S, Kripke DM, Klauber MR, et al. Periodic limb movements in sleep in community dwelling elderly. Sleep 1991; 14: 496-500
66. Walters AS, Hickey K, Maltzman J, et al. A questionnaire study of 138 patients with restless legs syndrome: the 'night walkers' survey. Neurology 1996; 46: 92-5
67. Hening W, Allen R, Earley C, et al. The treatment of restless legs syndrome and periodic limb movement disorder. Sleep 1999; 22: 970-99
68. Earley CJ, Connor JR, Beard JL, et al. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. Neurology 2000; 54: 1698-700
69. Banno K, Delaive K, Walld R, et al. Restless legs syndrome in 218 patients: associated disorders. Sleep Med 2000; 1: 221-9
70. Machtey I, Tiqwa P. Restless legs syndrome: a metabolic disorder [letter]? Arch Intern Med 1996; 156: 2386
71. Ondo W, Tan EK, Mansoor J. Rheumatologic serologies in secondary restless legs syndrome. Mov Disord 2000; 15: 321-3
72. Lugaresi E, Coccagna G, Tassinari CA, et al. Polygraphic data on motor phenomena in the restless legs syndrome. Riv Neurol 1965; 35: 550-61
73. Atlas Task Force of the American Sleep Disorders Association. Recording and scoring of leg movements. Sleep 1993; 16: 748-59
74. Montplaisir J, Nicolas A, Godbout R, et al. Restless legs syndrome and periodic limb movement disorder. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia (PA): WB Saunders, 2000: 742-52
75. Kazenwadel J, Pollmacher T, Trenkwalder C, et al. New actigraphic assessment method for periodic leg movements (PLM). Sleep 1995; 18: 689-97
76. Michaud M, Lavigne G, Desautels A, et al. Effects of immobility on sensory and motor symptoms of restless legs syndrome. Mov Disord 2002; 17: 112-5
77. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institute of Health. Sleep Med 2003; 4 (2): 101-19
78. Hornyak M, Kotterba S, Trenkwalder C. Indications for performing polysomnography in the diagnosis and treatment of restless legs syndrome. Somnologie 2001; 5: 159-62
79. Becker PM, Jamieson AO, Brown WD. Dopaminergic agents in restless legs syndrome and periodic limb movements of sleep: response and complications of extended treatment in 49 cases. Sleep 1993; 16: 713-6
80. Chesson AL, Wise M, Davila D, et al. 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 Academy of Sleep Medicine. Sleep 1999; 22: 961-8
81. Walters AS. Toward a better definition of restless legs syndrome: the International Restless Legs Syndrome Study Group. Mov Disord 1995; 10: 634-42
82. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. J Clin Psychiatry 1999; 60: 241-4
83. Walters AS, Wagner ML, Hening WA, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. Sleep 1993; 16: 327-32
84. Walters AS, Winkelmann J, Trenkwalder C, et al. Long-term follow-up on restless legs syndrome patients treated with opioids. Mov Disord 2001; 16: 1105-9
85. Montagna P, Sassoli de Bianchi L, Zucconi M, et al. Clonazepam and vibration in restless legs syndrome. Acta Neurol Scand 1984; 69: 428-30
86. Telstad W, Sorensen O, Larsen S, et al. Treatment of the restless legs syndrome with carbamazepine: a double blind study. BMJ 1984; 288: 444-6
87. Happe S, Klösch G, Saletu B, et al. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. Neurology 2001; 57: 1717-9
88. Garcia-Borruguero D, Larrosa O, de la Llave Y, et al. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002; 59: 1573-9
89. Guilleminault C, Stoohs R, Quera-Salva MA. Sleep-related obstructive and nonobstructive apneas and neurologic disorders. Neurology 1992; 42 (6 Suppl.): 53-60
90. George CF. Neuromuscular disorders. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 2nd ed. Philadelphia (PA): WB Saunders Company, 1994: 776-81
91. Barthlen GM. Nocturnal respiratory failure as an indication of non-invasive ventilation in the patient with neuromuscular disease. Respiration 1997; 64 (1 Suppl.): 35-8
92. Culebras A. Sleep and neuromuscular disorders. Neurol Clin 1996; 1: 791-805
93. Amino A, Shiozawa Z, Nagasaka T, et al. Sleep apnoea in well-controlled myasthenia gravis and the effect of thymectomy. J Neurol 1998; 245: 77-80
94. Kryger MH. Restrictive lung diseases. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 2nd ed. Philadelphia (PA): WB Saunders Company, 1994: 769-75
95. Giubilei F, Antonini G, Bastianello S, et al. Excessive daytime sleepiness in myotonic dystrophy. J Neurol Sci 1999; 164: 60-3
96. Van Hilten JJ, Weggeman M, van der Velde EA, et al. Sleep, excessive daytime sleepiness and fatigue in Parkinson's disease. J Neural Transm 1993; 5: 235-44
97. Barthlen GM, Lange DJ. Unexpectedly severe sleep and respiratory pathology in patients with amyotrophic lateral sclerosis. Eur J Neurol 2000; 7: 299-302
98. Quera-Salva MA, Guilleminault C, Chevret S, et al. Breathing disorders during sleep in myasthenia gravis. Ann Neurol 1992; 31: 86-92
99. Stepansky R, Weber G, Zeitlhofer J. Sleep apnea and cognitive dysfunction in myasthenia gravis. Acta Med Austriaca 1997; 24: 128-31
100. Steljes DG, Kryger MH, Kirk BW, et al. Sleep in postpolio syndrome. Chest 1990; 98 (1): 133-40

101. Filippi M, Rocca MA, Colombo B, et al. Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. Neuroimage 2002; 15: 559-67

102. Rossini PM, Pasqualetti P, Pozzilli C, et al. Fatigue in progressive multiple sclerosis: results of a randomized, double-blind, placebo-controlled, crossover trial of oral 4-aminopyridine. Mult Scler 2001; 7: 354-8

103. McGaffigan S, Bliwise DL. The treatment of sundowning: a selective review of pharmacological and nonpharmacological studies. Drugs Aging 1997; 10: 10-7

104. Ancoli-Israel S, Klauber MR, Gillin JC, et al. Sleep in non-institutionalised Alzheimer's patients. Aging (Milano) 1994; 6: 451-8

105. Cardinali DP, Brusco LI, Liberczuk C, et al. The use of melatonin in Alzheimer's disease. Neuroendocrinol Lett 2002; 23 Suppl. 1: 20-3

106. Pollack CP, Stokes PE. Circadian rest-activity in demented and non-demented older community residents and their caregivers. J Am Geriatr Soc 1997; 45: 446-52

107. Bader GG, Turesson K, Wallin A. Sleep related breathing and movement disorders in healthy elderly and demented subjects. Dementia 1996; 7: 279-87

108. Grace JB, Walker MP, McKeith IG. A comparison of sleep profiles in patients with dementia with Lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry 2000; 15: 1028-33

109. Cibula JE, Eisenschenk S, Gold M, et al. Progressive dementia and hypersomnolence with dream-enacting behavior: oneiric dementia. Arch Neurol 2002; 59: 630-4

110. Foley D, Monjan A, Masaki K, et al. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in Japanese-American men. J Am Geriatr Soc 2001; 49: 1628-32

111. Shochat T, Loredo J, Ancoli-Israel S. Sleep disorders in the elderly. Curr Treat Options Neurol 2001; 3: 19-36

112. Boeve BF, Silber MH, Ferman TJ, et al. REM sleep behavior disorder and degenerative dementia. Neurology 1998; 51: 363-70

113. Ancoli-Israel S, Martin JL, Kripke DF, et al. Effect of light treatment on sleep and circadian rhythms in demented nursing home patients. J Am Geriatr Soc 2002; 50: 282-9

114. Bassetti C, Aldrich MS. Sleep apnea in acute cerebrovascular diseases: final report on 128 patients. Sleep 1999; 22: 217-23

115. Bassetti Mathis J, Gugger M, et al. Hypersomnia following paramedian thalamic stroke. A report of 12 patients. Ann Neurol 1996; 39: 471-80

116. Qureshi AI, Giles WH, Croft JB, et al. Habitual sleep patterns and risk for stroke and coronary heart disease: a 10-year follow-up from NHANES I. Neurology 1997; 48: 904-11

117. Masel BE, Scheibel RS, Kimbark T, et al. Excessive daytime sleepiness in adults with brain injuries. Arch Phys Med Rehabil 2001; 82: 1526-32

118. Guilleminault C, Yuen KM, Gulevich MG, et al. Hypersomnia after head-neck trauma: a medicolegal dilemma. Neurology 2000; 54: 653-9

119. Guilleminault C, Faull KF, Miles L, et al. Posttraumatic excessive daytime sleepiness: a review of 20 patients. Neurology 1983; 33: 1584-9

120. Happe S, Zeitlhofer J, Evers S. Schlafgebundene Kopfschmerzen. Wien Klin Wochenschr 2001; 113: 259-65

121. Beghi E. Adverse reactions to antiepileptic drugs: a multicenter survey of clinical practice. Epilepsia 1996; 27: 323-30

122. Manni R, Tartara A. Evaluation of sleepiness in epilepsy. Clin Neurophysiol 2000; 111 (2 Suppl.): 111-4

123. Malow BA, Bowes RJ, Lin X. Predictors of sleepiness in epilepsy patients. Sleep 1997; 20: 1105-10

124. Vaughan BV, D'Cruz OF, Beech R, et al. Prevalence of sleep complaints in patients with epilepsy: application of the Epworth sleepiness scale [abstract]. J Sleep Res 1997; 25: 453

125. Manni R, Politini L, Sartori I, et al. Daytime sleepiness in epilepsy patients: evaluation by means of the Epworth sleepiness scale. J Neurol 2000; 247: 716-7

126. Foldvary N. Sleep and epilepsy. Curr Treat Options Neurol 2002; 4: 129-35

127. Mitler MM, Erman M, Hajdukovic R. The treatment of excessive somnolence with stimulant drugs. Sleep 1993; 16: 203-6

Correspondence and offprints: Dr *Svenja Happe*, Department of Clinical Neurophysiology, University of Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany.
E-mail: shappe@gwdg.de