Sleep Disorders in Neurology

A practical approach

EDITED BY

Sebastiaan Overeem MD, PhD

Centre for Sleep Medicine "Kempenhaeghe"
Heeze, the Netherlands; and
Department of Neurology
Radboud University Medical Centre
Nijmegen, the Netherlands

Paul Reading MA, FRCP, PhD

Department of Neurology
The James Cook University Hospital
Middlesbrough, UK

WILEY-BLACKWELL

A John Wiley & Sons, Ltd., Publication

This page intentionally left blank

Sleep Disorders in Neurology

This page intentionally left blank

Sleep Disorders in Neurology

A practical approach

EDITED BY

Sebastiaan Overeem MD, PhD

Centre for Sleep Medicine "Kempenhaeghe"
Heeze, the Netherlands; and
Department of Neurology
Radboud University Medical Centre
Nijmegen, the Netherlands

Paul Reading MA, FRCP, PhD

Department of Neurology
The James Cook University Hospital
Middlesbrough, UK

WILEY-BLACKWELL

A John Wiley & Sons, Ltd., Publication

This edition first published 2010, © 2010 by Blackwell Publishing Ltd

Blackwell Publishing was acquired by John Wiley & Sons in February 2007. Blackwell's publishing program has been merged with Wiley's global Scientific, Technical and Medical business to form Wiley-Blackwell.

Registered office: John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell

Library of Congress Cataloging-in-Publication Data
Sleep disorders in neurology : a practical approach / [edited by] Sebastiaan Overeem, Paul Reading.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4051-8843-2
1. Sleep disorders. 2. Nervous system—Diseases—Complications. I. Overeem, Sebastiaan. II. Reading, Paul.
[DNLM: 1. Sleep Disorders—complications. 2. Nervous System Diseases—complications. WM 188 S63225 2009]
RC547.S527 2009
616.8'498—dc22

2009020429

ISBN: 978-1-4051-8843-2

A catalogue record for this book is available from the British Library.

Set in 9.5/13pt Meridien by MPS Limited, A Macmillan Company

Printed in Singapore

1 2010

Contents

Contributors

Isabelle Arnulf PhD, MD
Sleep Disorders Unit
Pitié-Salpêtrière Hospital (APHP) and
Pierre and Marie Curie University
Paris, France

Claudio L. Bassetti
Department of Neurology
University Hospital Zürich
Zürich, Switzerland

Christian R. Baumann
Department of Neurology
University Hospital Zurich
Zurich, Switzerland

Valérie Cochen De Cock MD, PhD
Sleep Disorders Unit and
National Reference French Center for
Multiple System Atrophy
Hôpitaux de Toulouse
Toulouse, France

Luigi Ferini-Strambi MD, PhD
Associate Professor
Head of Sleep Disorders
Center University Vita-Salute San Raffaele
Milan, Italy

G. John Gibson BSc, MD, FRCP, FRCPE
Emeritus professor of Respiratory Medicine
Newcastle university
Newcastle upon Tyne, UK

Francesc Graus MD
Neurology Service
Hospital Clínic de Barcelona &
Institut d'Investigació Biomèdiques
August Pi i Sunyer (IDIBAPS)
Barcelona, Spain

Dirk M. Hermann MD
Professor of Neurology
University Hospital Essen
Essen, Germany

Alex Iranzo MD, PhD
Neurology Service
Hospital Clínic de Barcelona;
Institut d'Investigació Biomèdiques August Pi i Sunyer (IDIBAPS) &
Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED)
Barcelona, Spain

Takashi Kanbayashi MD, PhD
Department of Neuropsychiatry
Akita University School of Medicine
Akita, Japan

Gert Jan Lammers
Department of Neurology and Clinical Neurophysiology
Leiden University Medical Center
Leiden, the Netherlands

Margaret D. Lineberger PhD
Department of Psychiatry and Behavioral Sciences
Duke University Medical Center
Durham, NC, USA

Elio Lugaresi
Department of Neurological Sciences
University of Bologna Medical School
Bologna, Italy

José Enrique Martínez-Rodríguez MD, PhD
Neurology Service, Hospital del Mar
IMAS, IMIM, Barcelona, Spain

Geert Mayer MD
Sleep Disorder Unit, Hephata Klinik
Schwalmstadt-Treysa, Germany

Melanie K. Means PhD
Department of Veterans Affairs Medical Center and Department of Psychiatry and Behavioral Sciences
Duke University Medical Center
Durham, NC, USA

Seiji Nishino MD, PhD
Department of Psychiatry and Behavioral Sciences
Sleep and Circadian Neurobiology Laboratory
Stanford University School of Medicine
Stanford CA, USA

David J. Nutt DM FRCP FRCPsych FMedSci
The Edmond J Safra Chair
Neuropsychopharmacology Unit
Centre for Pharmacology and Therapeutics
Division of Experimental Medicine
Imperial College London
London, UK

Dirk Pevernagie
Centre for Sleep Medicine "Kempenhaeghe,"
Heeze, The Netherlands

J. Steven Poceta MD
Scripps Clinic Sleep Center
Division of Neurology
Scripps Clinic
La Jolla, CA, USA

Federica Provini
Department of Neurological Sciences
University of Bologna Medical School
Bologna, Italy

Jeanetta C. Rains PhD
Center for Sleep Evaluation at Elliot Hospital
Manchester, NH, USA

Gé S.F. Ruigt MD
Department of Translational Medicine
Merck Research Laboratories
Oss, the Netherlands

John Shneerson MD, FRCP
Respiratory Support and Sleep Centre (RSSC)
Papworth Hospital
Cambridge, UK

Karel Šonka
Charles University, 1st Medical Faculty and General Teaching Hospital
Department of Neurology
Prague, Czech Republic

J. Gert van Dijk PhD
Department of Neurology and Clinical Neurophysiology
Leiden University Medical Center
Leiden, the Netherlands

Joop van Gerven
Centre for Human Drug Research
Leiden, The Netherlands

Marie Vidailhet MD
Movement Disorders Unit
Department of Neurology;
CRICM UMR-S UPMC/Inserm 975
Pitié-Salpêtrière Hospital (APHP) &
University Pierre Marie Curie Paris-6
Paris, France

Thomas C. Wetter MD MA
Professor of Psychiatry
Head, Department of Sleep Medicine and Clinical Sleep Research
Psychiatric University Hospital Zurich
Zurich, Switzerland

Sue Wilson PhD
Psychopharmacology Unit
University of Bristol
Bristol, UK

Foreword

When I was a medical student, then a junior hospital doctor, then a trainee neurologist and even when I was a young consultant neurologist I did not take a sleep history from patients if the problem was neither insomnia nor excessive daytime sleepiness. In practice – back then – insomnia did not come to neurologists anyway and still mostly doesn't unless maybe restless legs are an issue, and excessive daytime sleepiness was all but synonymous with the narcolepsy syndrome in the days before sleep apnoea and other sleep-related breathing disorders were popularised and we all were alerted to how common they were. 'How do you sleep?' and 'do you snore?' were just not amongst the routine questions one asked of neurology patients, but of course we always enquired about blackouts, headache, double vision and so on. Also neurologists were perhaps more than a little unwilling to sit up all night with patients in the days before video and all the other sophisticated monitoring equipment became available (paradoxically though it is still the history from the patients and any bed partner that counts more than the tests, at least for neurology rather than sleep-related breathing disorders). And maybe sleep problems were regarded as more of an amusing foible than needing proper attention.

But these days sleep, the lack of it, and too much of it, is everywhere in neurology. And parasomnias are now recognised as an important differential diagnosis for nocturnal epilepsy. Indeed, if difficult parasomnias are not sent to a neurologist who else is going to sort them out? I don't think this new found interest is 'disease mongering' stirred up by the pharmaceutical industry but a reflection of important and frequent symptoms that we missed – or simply ignored – in past times.

Sleep problems do hover slightly uneasily between neurologists and respiratory physicians who clearly have to work together to provide a specialised service; their skills and knowledge are complementary. But this book's focus is on the needs of neurologists and neurological rather than respiratory problems, edited by a sleep physician and a general neurologist with a sub specialist interest in sleep.

It is extraordinary how common sleep problems are in neurology patients, and how we just did not recognise them until relatively recently – maybe

we just 'switched off' when patients and their relatives tried to tell us about symptoms which we were unfamiliar with and so didn't make a lot of sense, either for diagnosis or management. I hope this book will help neurologists deal better with sleep problems as well as the other more traditional symptoms that their patients may have.

Charles Warlow
Emeritus Professor of Medical Neurology
University of Edinburgh, UK
January 2010

Preface

There are those who predict that medical textbooks will shortly become the extinct "dinosaurs" of information transfer and education. Indeed, the global availability of knowledge and thirst for brand-new data, the inevitable delays in producing written multi-authored texts, the expense of books together with the demise of traditional libraries would all appear to support this contention. In a rapidly changing environment, therefore, books, like dinosaurs, need to evolve in parallel and certainly be clearer in their aims than previously. Edited by a sleep physician and a general neurologist with a subspecialist interest in sleep, this book was conceived as a counterpoint to the established large encyclopedic reference volumes currently available. The intentions were to cover areas not always addressed by standard sleep medicine or, indeed, neurology textbooks, at least from a practical perspective. The book is aimed at clinicians and healthcare professionals not specifically trained or experienced in sleep medicine who nevertheless need to manage neurologically damaged patients with increasingly recognized sleep-wake disturbances. As such, we envisage the book will serve as an easily digested and practical handy companion, rather than as an exhaustive and fully referenced factual tome.

Largely for historical reasons, most neurologists receive little formal training in academic and clinical aspects of sleep medicine. Most sleep units are run solely by physicians primarily interested in breathing-related sleep disorders and patients under their care may have little access to neurological expertise. This may seem paradoxical given conditions such as narcolepsy that are clearly "neurological" with recently defined specific neuropathology and neurochemistry. The lack of exposure to sleep medicine naturally tends to produce neurologists with an unconfident, at best, or nihilistic, at worst, approach to sleep-related symptoms in the clinic. By necessity, the situation is changing, especially given the increasingly recognized relevance of poor sleep or impaired wakefulness to the quality of life for chronic neurological patients. Furthermore, it is clear to most clinicians that deterioration in sleep often coincides with or even causes worsening control of many chronic neurological conditions such as epilepsy.

Most neurologists are not referred cases of primary insomnia or obvious obstructive sleep apnea but may well encounter them incidentally. Despite their high prevalence, there is little emphasis on these common sleep disorders in this book and the focus is on those specific symptoms commonly experienced by neurological patients, assuming they are asked about them.

When sleep "goes wrong" it impacts highly on all aspects of a subject's well-being and often their carer's. As a result, increasing attention to patient choice has appropriately led to a higher expectation that such symptoms should be taken seriously. However, many neurologists with traditional approaches might feel that sleep problems are not disabling enough to warrant detailed attention. We would counter-argue that "sleep is for the brain" and without enough of it, the brain suffers. It is perhaps worthwhile recalling somewhat distasteful experiments from the late nineteenth century demonstrating that puppies could survive longer without water than without sleep.

The reputation that neurology is a discipline in which successful therapeutic options play second fiddle to diagnostic acumen is only partly true. Perhaps counterintuitively, treating sleep symptoms in neurology is often particularly rewarding, patients and carers appreciating even partial improvements in controlling their sleep-wake cycle. A recurrent theme in the book is that drugs to improve sleep are often selected using "medicine-based" evidence and personal experience rather than the gold standard of evidence-based medicine. Despite this, together with the relative limited armamentarium of drugs available to the sleep physician, we believe the majority of patients can be helped with a flexible and pragmatic approach. When drugs are mentioned, their proposed use is often "off license" and any prescriber will need to take responsibility for monitoring and progress. Similarly, doses of drugs are often approximate recommendations and it is not intended to provide strict or didactic guidelines. In many of the sleep-disordered populations covered in the book, it is appropriate to suggest long-term therapy on the assumption that spontaneous improvement is unlikely. This often needs to be emphasized to primary care physicians who are more accustomed to providing short-term prescriptions for sleep-related problems.

The point or threshold at which a general neurologist should engage the help of a sleep specialist clearly depends on a number of factors. However, an exchange of views and expertise in a multidisciplinary setting, if possible at an early stage, would seem to be the best approach if facilities allow. We would encourage neurologists to forge stronger links with physicians more dedicated to sleep medicine in the firm belief any "cross fertilization" will benefit both sides.

By necessity, there is some overlap in the topics covered by some chapters. However, given the personal and practical approach we have espoused throughout the book, we hope different perspectives will improve rather than hinder understanding and effective symptom management in sleep-disordered neurological patients.

Sebastiaan Overeem MD, PhD
Centre for Sleep Medicine "Kempenhaeghe"
Heeze, the Netherlands; and
Department of Neurology
Radboud University Medical Centre
Nijmegen, the Netherlands

and

Paul Reading MA, FRCP, PhD
Department of Neurology
The James Cook University Hospital
Middlesbrough, UK

This page intentionally left blank

PART I
Diagnosis of Sleep Disorders

This page intentionally left blank

CHAPTER 1
The sleep history

Paul Reading[1] *and Sebastiaan Overeem*[2]

[1] Department of Neurology, James Cook University Hospital, Middlesbrough, UK
[2] Centre for Sleep Medicine "Kempenhaeghe", Heeze, The Netherlands; and Department of Neurology, Donders Institute for Neuroscience, Radboud University Medical Centre, Nijmegen, The Netherlands

Introduction

It is a commonly held misperception that practitioners of sleep medicine are highly dependent on sophisticated investigative techniques to diagnose and treat sleep-disordered patients. To the contrary, with the possible exception of sleep-related breathing disorders, it is relatively rare for tests to add significant diagnostic information, provided a detailed and accurate 24-hour sleep-wake history is available. In fact, there can be few areas of medicine where a good, directed history is of more diagnostic importance. In some situations, this can be extremely complex due to potentially relevant and interacting social, environmental, medical, and psychological factors. Furthermore, obtaining an accurate sleep history often requires collateral or corroborative information from bed partners or close relatives, especially in the assessment of parasomnias.

In sleep medicine, neurological patients can present particular diagnostic challenges. It can often be difficult to determine whether a given sleep-wake symptom arises from the underlying neurological disorder and perhaps its treatment or whether an additional primary sleep disorder is the main contributor. The problem is compounded by the relative lack of formal training in sleep medicine received by the majority of neurology trainees that often results in reduced confidence when faced with sleep-related symptoms. However, it is difficult to underestimate the potential importance of disordered sleep in many chronic neurological conditions such as epilepsy, migraine, and parkinsonism.

The following framework is a personal view on how to approach sleep-wake complaints from a neurological perspective. Although the focus is on individual or particular symptoms, it should be realized that several conditions can produce a variety of symptoms across the full 24-hour sleep-wake

Sleep Disorders in Neurology. Edited by S. Overeem and P. Reading.

period. In chapters 2 and 3, the various ways in which sleep can be recorded are discussed. Finally, in chapter 4, an "integrative" approach to diagnosis is outlined, illustrated by case examples.

Excessive daytime sleepiness

Excessive daytime sleepiness (EDS) is an increasingly recognized symptom deemed worthy of assessment. It is relatively prevalent and disabling both in general and neurological populations [1]. A not uncommon question posed to general neurologists is whether a sleepy patient might have narcolepsy or a similar primary sleep disorder. Furthermore, "secondary" or "symptomatic" narcolepsy is evolving as a valid concept given recent major advances in unraveling the neurobiology of sleep regulation. In particular, a variety of pathologies predominantly affecting the hypothalamus can mimic elements of idiopathic or primary narcolepsy [2].

In the initial assessment of EDS, it is essential to gain an impression of the severity of symptoms and how they are impacting on the subject. It is also crucial to confirm that the complaint is that of true excessive somnolence rather than simple fatigue or lethargy. Although sleepiness questionnaires are widely used and can act as an effective screening tool in this respect, they rarely help with actual diagnosis. Asking a subject about particularly unusual or inappropriate sleep episodes can therefore provide valuable insight. Habitual mid-afternoon or late evening naps when unoccupied could be considered normal phenomena, whereas regularly dropping to sleep mid-morning or in public places usually indicates a problem. A history of invariably napping as a car passenger for journeys of over an hour may suggest pathological levels of sleepiness. In narcolepsy, the subject may describe sleep onset even while engaged in physical activities such as writing or standing. Furthermore, in severe EDS, the subject may report awakening from naps unaware of any prior imperative to sleep. So-called "sleep attacks" are recognized in narcolepsy and have been widely reported in sleepy parkinsonian patients. Regarding the latter population, recent evidence suggests that they may be particularly poor at monitoring their levels of subjective sleepiness, making the history from relatives particularly important [3].

The commonest causes of mild and severe EDS are probably insufficient sleep and poor-quality overnight sleep, respectively (see chapter 19). A directed history, perhaps backed by a sleep diary, usually helps in diagnosing the former and can indicate causes of the latter. If a subject regularly reports at least 7 or 8 hours of continuous sleep yet remains significantly somnolent during the day, it is most likely that there is a disturbance of sleep architecture and, usually, that insufficient deep or restorative sleep is

being obtained. An overabundance of light (stage 2) sleep compared to deep non-REM sleep (stages 3 and 4) is frequently seen in sleep-related breathing disorders and periodic limb movement disorder. These diagnoses can easily be missed from the history if the subject is not a typical phenotype for the former or if they sleep alone. However, leading questions such as "do you invariably awake with a dry mouth?" or "are the bed clothes usually disrupted on waking?" can provide diagnostic clues. Morning headaches or general sensations of "heaviness" are traditionally associated with obstructive sleep apnea although are equally common in a variety of sleep disorders.

A drug history including alcohol habit is also clearly relevant in assessing EDS as numerous agents given before bed may appear to induce drowsiness and aid sleep onset but actually worsen nocturnal sleep quality overall. Tricyclic preparations and benzodiazepines are frequently associated with unrefreshing sleep yet are frequently given primarily as hypnotic agents. It is worth noting that most antidepressants will potentially worsen restless legs syndrome or periodic limb movement disorder (see chapter 8).

Less recognized causes of disturbed nocturnal sleep may be picked up by a focussed history. Nocturnal pain, frequent nocturia, persistent wheeze, and acid reflux are usually fairly obvious "toxins" to sleep and are generally readily reported. However, more subtle phenomena such as teeth grinding (bruxism) may not be recognized by the subject and only suspected if direct questions are asked about teeth wear, temporomandibular joint dysfunction, or jaw pain, especially on waking.

A number of primary neurological disorders, including narcolepsy, disrupt the continuity of nocturnal sleep most likely as a result of pathology in various brain regions intimately involved in sleep-wake control. A new symptom of sleep fragmentation and daytime somnolence in a patient with inflammatory brain disease such as multiple sclerosis, for example, might sometimes suggest inflammatory pathology in the pontomedullary area [4] or around the hypothalamus [5]. Idiopathic Parkinson's disease is strongly associated with EDS, especially in the advanced stages. Although there are many potential causes, including dopaminergic medication, primary Lewy body brainstem pathology itself is a likely substrate for most of the sleep-wake dysregulation, especially with regard to REM sleep [6]. If a neurological patient complains of significant EDS and no obvious cause such as Parkinson's disease is determined after a detailed history and subsequent sleep investigations, magnetic resonance brain imaging can be justified to exclude unexpected inflammatory or even structural pathology. This may particularly apply to sleepy, overweight children, for example [7].

There are usually sufficient clues from a patient's history to suggest a specific diagnosis of narcolepsy, the quintessential primary disorder of sleep-wake dysregulation (chapter 19). Typically, narcolepsy causes

symptoms from early adolescence and profound delays in receiving a diagnosis are still commonplace. A detailed history, therefore, exploring issues of excessive sleepiness around schooling can be illuminating. Apart from its severity, the nature of sleepiness is not particularly exceptional or unique in narcolepsy. However, even short naps, planned or unplanned, tend to be restorative, allowing a "refractory" wakeful period of 3–4 hours. Given that REM sleep is particularly dysregulated in narcolepsy, it is also useful to enquire about the presence of dreams, dream-like experiences, or sleep paralysis during short naps. Even when alert, the majority of narcoleptics will be prone to automatic behaviors and reduced powers of concentration or vigilance, potentially reflecting brief "micro-sleeps." These can be explored from a full history. Losing objects around the house or placing inappropriate objects in the fridge are particularly common examples of this phenomenon.

Cataplexy is present in two-thirds of narcoleptics and is very rarely seen in other situations. It is therefore an extremely specific phenomenon and important to recognize with confidence. Full-blown episodes of temporary paralysis triggered by positive emotions or their anticipation are generally easy to pick up from the history. Subtle or atypical variants may be missed, however, especially since "going weak" with laughter or other strong emotions is probably a normal phenomenon. Typically, cataplexy occurs in a relaxed or intimate environment in the company of friends or family. It is usually manifested by descending paralysis in a rostrocaudal direction over 2 or 3 seconds, preceded by head bobbing or facial twitching. Subjects often learn to anticipate the situations in which they are at risk of attacks and may even develop social phobias as a result. Common precipitants include positive emotions such as surprise at meeting an old acquaintance or watching comedy on television. Some report that the anticipation of a positive emotion, perhaps as a punch-line is approaching, acts as the most potent stimulus. Negative emotions such as frustration, particularly that induced by children or pets, can also induce episodes in many. Partial attacks can be missed or hidden. Indeed, minor facial twitching, head bobbing, mild neck weakness, or a stuttering dysarthria when telling a joke may reflect the only observable manifestations of cataplexy. On the other hand, cataplexy is a doubtful explanation if episodes are very sudden or prolonged. Similarly, if consciousness levels are significantly impaired or if injuries frequently incurred during attacks, alternative diagnoses need consideration.

Nocturnal symptoms in narcolepsy are extremely varied but frequently significant. Often to the surprise of physicians inexperienced with narcolepsy, restless sleep with impaired sleep maintenance and even sleep-onset insomnia is common, as are excessive limb movements during sleep. The latter may reflect simple restlessness or periodic limb movements.

Many narcoleptics also exhibit dream enactment during REM sleep although it generally appears as a more benign phenomenon than that commonly seen in neurodegenerative disease [8]. In particular, the movements tend to be less explosive or violent in narcolepsy and there is not the striking male predominance as observed in Parkinson's disease, for example.

Unpleasant dreams that are particularly vivid and difficult to distinguish from reality are commonplace in narcolepsy. Indeed, narcoleptic children often become fearful of sleep as a result, so-called "clinophobia." Frank hallucinatory experiences in a variety of modalities including tactile may not be mentioned spontaneously through fear of being labeled mentally ill. These experiences are commonest around the sleep-wake transition periods or in states of drowsiness. A full history should therefore actively explore dream-like experiences in detail.

A less common sleep disorder, idiopathic hypersomnolence (IH), can often mimic narcolepsy although certain historical pointers may help with the differential diagnosis [9]. Idiopathic hypersomnolence in its classical form is characterized by long yet unrefreshing overnight sleep with prolonged napping during the day and continual sensations of reduced alertness. Difficulty in morning waking or prolonged confusion on forced waking are typical symptoms as are frequent acts of automatic behavior during the day. Important negative historical features might include the lack of REM sleep-related phenomena. Overnight sleep is also usually undisturbed by arousals or excessive movement. It is recognized that mood disorders may be particularly common in idiopathic hypersomnolence although it is not clear whether they are simply a consequence of the sleep disorder [10].

Although not a symptom routinely presented to neurologists, difficulty with morning waking is not uncommon and can lead to significant problems either with education or maintaining employment. If the sleep history indicates that the most likely cause is an abnormally late time of nocturnal sleep onset, the possibility of delayed sleep phase syndrome should be considered. This primarily affects adolescents and is often assumed simply to reflect socio-behavioral factors. However, although bad habits may worsen the situation, it is often a defined disorder of circadian timing such that subjects are "hard wired" to sleep and rise later than average, acting as extreme "night owls" [11]. The diagnosis, if suspected, can be deduced from the history and subsequently supported by investigations.

Insomnia

Chronic insomnia either at sleep onset or through the night is undoubtedly common and most often reflects a combination of psychological and

poorly defined constitutional factors. Although a patient's history might indicate severe symptoms, it should be noted that a minority will have so-called "paradoxical insomnia" and will actually sleep fairly well when objectively investigated.

Many chronic insomniacs are able to identify a significant event or lifestyle change that seemed to trigger their sleep disturbance. Despite seemingly severe symptoms of poor nocturnal sleep and reported lethargy, most primary insomniacs are unable to nap during the day. The diagnosis of primary insomnia should therefore be questioned and secondary causes sought in the presence of significant daytime somnolence. This is particularly relevant to neurological populations as insomnia symptoms are common and frequently adversely affect long-term conditions such as epilepsy.

One of the commonest and most under-recognized contributors to delayed sleep onset, sleep fragmentation and, indeed, daytime somnolence is restless legs syndrome (RLS) and associated periodic limb movement disorder (PLMD) (chapter 8). Restless legs syndrome is defined solely from a positive history [12]. There should be restlessness, usually, but not always, in the lower limbs, most often associated with ill-defined sensory symptoms that worsen in the late evening. Symptoms are triggered by rest or immobility and eased, at least temporarily, by movement or rubbing the affected limb or limbs. Associated involuntary jerks can be significant and intrude during wakefulness or light sleep, often adversely affecting sleep quality and causing daytime somnolence. The condition may not be suspected if the upper limbs are predominantly involved or if the symptoms are mistakenly attributed to arthritis or poor circulation, for example. In patients with underlying neuropathies, radiculopathies, or demyelinating disease, restless legs syndrome may be secondary to the primary diagnosis and should not be overlooked. Particularly in younger patients, a positive family history is common and should be actively sought from the history.

Discrete or identifiable brain pathology rarely leads to insomnia as an isolated phenomenon. However, it is relatively common both in neurodegenerative diseases and inflammatory disorders such as multiple sclerosis in the context of more obvious physical neuro-disability [13]. Furthermore, insomnia can also be an apparent direct consequence of head injuries or strokes, particularly those producing subcortical pathology and potentially involving the paramedian thalamic region [14]. Insomnia and severely disturbed sleep are also increasingly recognized accompanying features of limbic encephalitis, a rare disorder in which fluctuating confusion, seizures, and autonomic symptomology usually predominate [15]. Finally, delayed sleep phase syndrome sometimes presents as insomnia although, unlike the typical case of primary

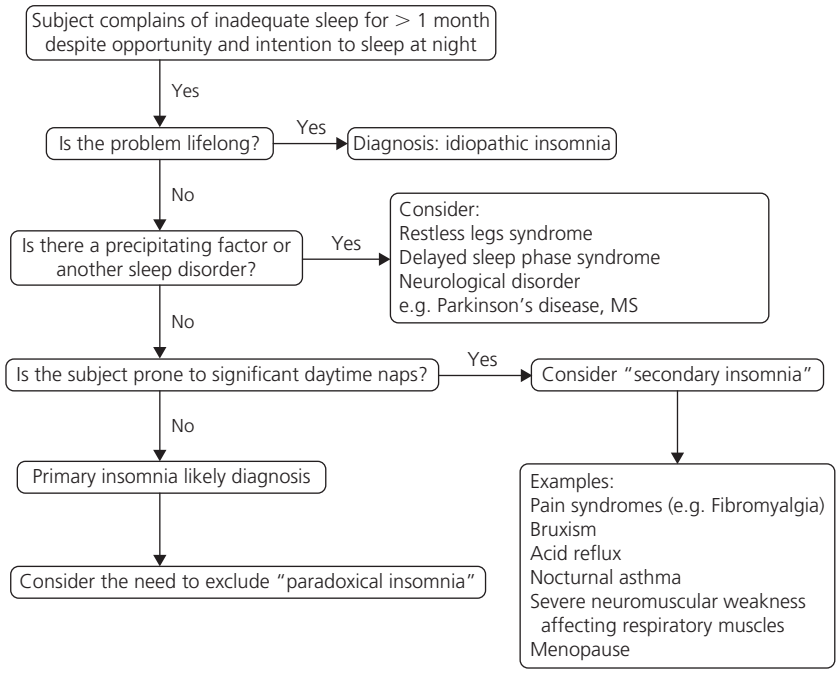

Figure 1.1 This algorithm outlines a diagnostic approach to some of the common causes of primary and secondary insomnia that might present to neurologists.

insomnia, by definition, there are also major problems in waking at a conventional hour.

A simple algorithm to assess insomnia presenting to a neurologist is shown in figure 1.1.

Nocturnal disturbances

Neurologists are frequently asked to assess patients with abnormal nocturnal behaviors or experiences, often with the query, implicit or explicit, as to whether there is an epileptic explanation. Distinguishing parasomnias from epileptic or psychiatric phenomena can clearly be difficult, especially given the practical issues of investigating nocturnal symptoms that are invariably intermittent (see chapter 16). However, a full history supported by spouses and family members together with a detailed background knowledge of parasomnias and their spectrum usually allow for a confident diagnosis.

Sleep-wake transition disorders are poorly studied but often alarming phenomena that may require reassurance if not treatment. They are relatively easy to recognize from the history. Most people are familiar with

an occasional and slightly unpleasant sensation of sudden falling through space at the point of sleep onset. In sleep-wake transition disorders this phenomenon is amplified, more frequent, and often accompanied by a variety of unusual and disturbing sensory or experiential symptoms such as loud auditory or intense visual stimuli. At the more severe end of the spectrum, the so-called "exploding head syndrome" has been described [16]. If frequent or recurrent, significant insomnia at sleep onset and through the night may result.

Parasomnias arising from non-REM sleep are not rare in young adults and probably affect around 1%. They usually reflect incomplete and abnormal arousals from deep non-REM or slow-wave sleep that can lead to a variety of complex and occasionally disturbing nocturnal behaviors. The events themselves usually have relatively little impact on daytime functioning or levels of sleepiness. For a confident diagnosis, it is important to ask about sleep-related phenomena in early childhood as the majority will have a positive history for night terrors, confusional arousals, sleep walking, or all three. Given the likely genetic component to non-REM parasomnias, a family history of nocturnal disturbances, including sleep talking, can also be insightful. In adults, a frequency of one or two events a month is typical, often with identifiable precipitants. These include sleep deprivation, alcohol intake before bed, or sleeping in an unfamiliar or uncomfortable environment. Coinciding with the first period of deep non-REM sleep, the nocturnal disturbance will generally occur within an hour or two of sleep onset and will rarely recur through the night. Subsequent recollection of the event by the subject is at best hazy although agitated events may produce vague memories of nonspecific threats or frightening situations. Detailed or bizarre dream narratives are rare. Events can be prolonged and the subject may appear superficially awake, responding in a limited way to questions and commands. Relatively complex motor tasks such as eating, performing housework and driving are certainly possible.

Distinguishing adult non-REM parasomnias from nocturnal complex partial seizures can be difficult as both may produce complicated behaviors and confusion (see chapter 16). Epileptic episodes are often of frontal lobe origin and can occur several or many times a night from any sleep stage, except REM sleep. If detailed descriptions or, ideally, video clips of several events demonstrate strictly stereotyped episodes, especially with fixed or dystonic limb posturing, a diagnosis of epilepsy is likely. Alternatively, if episodes are long-lasting with an indistinct termination or if they appear to wax and wane, a parasomnia is favored. Strongly expressed emotions or leaving the bed are not particularly discriminatory features.

In a neurological setting, it is commoner to see parasomnias arising from REM sleep, particularly in the context of parkinsonian neurodegenerative

disease. In particular, REM sleep behavior disorder (RBD) typically affects men in late middle age, often many years in advance of any motor or, indeed, cognitive symptomology [17]. The nocturnal disturbances are usually of more concern to the bed partner who may incur injuries from violent dream enactment. The episodes themselves are generally more frequent and prolonged at the end of the night when REM sleep is more prevalent. Movements are often associated with vocalisation and tend to be defensive, brief and undirected, typically involving the upper limbs with eyes generally closed. The subject is usually fairly easy to arouse and will often recall a vivid dream, perhaps involving previous acquaintances or occupations. In certain conditions such as multiple system atrophy and narcolepsy, REM sleep behavior disorder seems to affect females equally [18]. Moreover, in narcolepsy, the dreams and movements may be relatively banal and probably reflect differing underlying pathogenetic mechanisms to those seen in parkinsonism.

The generally restless sleeper can be difficult to diagnose from history alone even if detailed witnessed accounts and videos are available. Periodic limb movement disorder can exist in the absence of restless legs syndrome and is relatively common. Persistent rocking or stereotyped rolling movements involving virtually any body part may reflect a so-called rhythmic movement disorder. This often evolves from childhood "head banging" at sleep onset although can occur in any sleep stage, even REM sleep, in adults [19]. As with many parasomnias, the bed partner is usually the main complainant.

Conclusions

As within many areas of neurology, a detailed and directed history is paramount when trying to diagnose sleep disorders. The need for a full 24-hour sleep-wake history should be emphasized, corroborated where possible by observers. At the very least, a good history usually provides a credible differential diagnosis which investigations may subsequently further refine. However, if significant diagnostic doubt remains after obtaining a full sleep history, it is relatively rare for sleep investigations to fully elucidate the problem. Furthermore, given the expense and patchy distribution of specialist sleep centers, the sleep history assumes particular diagnostic importance.

Disordered sleep is undoubtedly prevalent in neurological disease and may exacerbate underlying conditions such as migraine and epilepsy. Aside from their direct deleterious effects on daily and nightly functioning, there is therefore ample justification for taking sleep-related symptoms seriously in a neurological setting.

Key points

- The patient history is the single most important diagnostic tool in neurological sleep medicine.
- In neurological patients, it can sometimes be difficult to determine whether a sleep-wake symptom is due to an underlying neurological disorder, its treatment or a coexisting primary sleep disorder.
- Excessive daytime sleepiness is not uncommon, and may easily be missed or mistaken for fatigue.
- Additional symptoms not directly related to the sleep-wake cycle may be crucial for the diagnosis (e.g. cataplexy in the case of narcolepsy).
- Sleep onset or sleep maintenance insomnia can reflect an idiopathic or primary phenomenon but is more often secondary to a variety of disorders, including other primary sleep disorders (e.g. restless legs syndrome), psychiatric (e.g. depression) or neurological disease (e.g. multiple sclerosis, neurodegenerative diseases or stroke).
- A knowledge of the typical pattern and spectrum of the various parasomnias normally allows a confident history from history alone and helps exclude epilepsy as a diagnosis.

References

1 Bixler EO, Kales A, Soldatos CR, Kales JD, Healey S. Prevalence of sleep disorders in the Los Angeles metropolitan area. Am J Psychiatry 1979; 136(10):1257–1262.
2 Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. Sleep Med Rev 2005; 9(4):269–310.
3 Merino-Andreu M, Arnulf I, Konofal E, Derenne JP, Agid Y. Unawareness of naps in Parkinson's disease and in disorders with excessive daytime sleepiness. Neurology 2003; 60(9):1553–1554.
4 Mathis J, Hess CW, Bassetti C. Isolated mediotegmental lesion causing narcolepsy and rapid eye movement sleep behaviour disorder: a case evidencing a common pathway in narcolepsy and rapid eye movement sleep behaviour disorder. J Neurol Neurosurg Psychiatry 2007; 78(4):427–429.
5 Oka Y, Kanbayashi T, Mezaki T, Iseki K, Matsubayashi J, Murakami G et al. Low CSF hypocretin-1/orexin-A associated with hypersomnia secondary to hypothalamic lesion in a case of multiple sclerosis. J Neurol 2004; 251(7):885–886.
6 Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML et al. Parkinson's disease and sleepiness: an integral part of PD. Neurology 2002; 58(7): 1019–1024.
7 Marcus CL, Trescher WH, Halbower AC, Lutz J. Secondary narcolepsy in children with brain tumors. Sleep 2002; 25(4):435–439.
8 Nightingale S, Orgill JC, Ebrahim IO, de Lacy SF, Agrawal S, Williams AJ. The association between narcolepsy and REM behavior disorder (RBD). Sleep Med 2005; 6(3):253–258.
9 Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. Sleep 2007; 30(10):1274–1281.
10 Bassetti C, Aldrich MS. Idiopathic hypersomnia. A series of 42 patients. Brain 1997; 120 (Pt 8):1423–1435.

11 Archer SN, Robilliard DL, Skene DJ, Smits M, Williams A, Arendt J et al. A length polymorphism in the circadian clock gene Per3 is linked to delayed sleep phase syndrome and extreme diurnal preference. Sleep 2003; 26(4):413–415.
12 Benes H, Walters AS, Allen RP, Hening WA, Kohnen R. Definition of restless legs syndrome, how to diagnose it, and how to differentiate it from RLS mimics. Mov Disord 2007; 22 Suppl 18:S401–S408.
13 Tachibana N, Howard RS, Hirsch NP, Miller DH, Moseley IF, Fish D. Sleep problems in multiple sclerosis. Eur Neurol 1994; 34(6):320–323.
14 Bassetti CL. Sleep and stroke. Semin Neurol 2005; 25(1):19–32.
15 Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004; 127(Pt 3):701–712.
16 Sachs C, Svanborg E. The exploding head syndrome: polysomnographic recordings and therapeutic suggestions. Sleep 1991; 14(3):263–266.
17 Schenck CH, Bundlie SR, Ettinger MG, Mahowald MW. Chronic behavioral disorders of human REM sleep: a new category of parasomnia. 1986 [classical article]. Sleep 2002; 25(2):293–308.
18 Iranzo A, Santamaria J, Rye DB, Valldeoriola F, Marti MJ, Munoz E et al. Characteristics of idiopathic REM sleep behavior disorder and that associated with MSA and PD. Neurology 2005; 65(2):247–252.
19 Stepanova I, Nevsimalova S, Hanusova J. Rhythmic movement disorder in sleep persisting into childhood and adulthood. Sleep 2005; 28(7):851–857.

CHAPTER 2

Polysomnography: indications, interpretation, and pitfalls

John Shneerson
Respiratory Support and Sleep Centre, Papworth Hospital, Cambridge, UK

What is polysomnography?

Electroencephalogram (EEG) monitoring in sleep was carried out as long ago as 1937 [1], but it was only after the discovery of rapid eye movement (REM) sleep in 1953 that this type of recording was combined with other physiological measurements [2]. Polysomnography is the simultaneous acquisition and analysis of data used to assess the sleep state and stage together with a variety of physiological measurements. The latter may include monitoring of respiration, heart rate, leg movements, body position, oesophageal pH, together with video and audio monitoring. Polysomnography should be distinguished from polygraphy in which a range of physiological measurements are obtained, but without formal sleep staging. For example, in multichannel respiratory sleep studies, details of airflow, thoracic and abdominal movement, oxygen saturation and heart rate are obtained but without direct assessment of the sleep-wake state.

Practical aspects

It is difficult to undertake polysomnography at a subject's home so sleep needs to occur in an unfamiliar environment. The associated anxiety that this generates may distort the findings (so-called "first night effect") [3]. Many centers routinely record over two nights to offset this effect, especially in complex patients. Polysomnography is also dependent on skilled technical expertise and is more expensive than simpler automated studies. It does however enable changes in sleep to be correlated with simultaneous changes in other physiological indices.

The key parameters are recorded by the electroencephalogram (EEG), electro-oculogram (EOG), and electromyogram (EMG) through electrodes

Sleep Disorders in Neurology. Edited by S. Overeem and P. Reading.

fitted to the skin. The signals are filtered and amplified before being stored and displayed by computer [4].

Electroencephalogram recording

The scalp EEG reflects the synaptic activity particularly of parietal cells in the underlying cerebral cortex. These are radially orientated and the electrical field that they generate creates a potential difference between two points on the scalp from which recordings can be made. Although the EEG continuously and noninvasively monitors cortical activity, it is dependent on electrode location and will only produce data from limited locations. The 10–20 montage [5] is rarely employed for polysomnography although it can be essential if information about a localized lesion, such as the source of focal epilepsy, is important. Typically, a limited number of derivations is used. Recent guidelines advocate to record over frontal (e.g. F4-A1), central (e.g. C4-M1), and occipital (e.g. O2-M1) areas.

In non-rapid eye movement (non-REM) sleep the widespread projections of thalamocortical fibers cause synchronized waves of depolarization and hyperpolarization, which are readily detectable at the scalp surface. There may however be local variations in cortical activity. The site of maximum activity of delta waves, for instance, drifts forwards from the occipital towards the frontal cortex during the night.

Electro-oculogram recording

The potential difference between the cornea and the retina acts as an electrical dipole. Movement of the eye generates an electrical current, which can be detected by electrodes placed one centimeter above the outer canthus of the right eye (ROC) and one centimeter below the outer canthus of the left eye (LOC). Slow rolling eye movements occur at the onset of sleep and rapid eye movements, by definition, are characteristic of REM sleep.

Electromyogram recording

This is usually recorded by an electrode under the chin (submental) or on the chin. Other sites, particularly over the anterior tibial muscle, are used to detect activity in specific sleep disorders such as the periodic limb movement disorder. Changes in sustained muscle activity (tone) and the presence of intermittent (phasic) muscle activity are used to assess the presence and stage of sleep.

Sleep staging

The conventional criteria for staging of sleep were published as long ago as 1968 by Rechtschaffen and Kales [6]. They characterize the stage

which predominates during a 30-second epoch. As a result, they only poorly reflect the dynamic nature of sleep and can fail to evaluate rapid fluctuations between sleep stages and states of wakefulness or transitional forms of each of these. These criteria have been validated in healthy young adults but not in most other situations. In practice, there can be difficulty applying the criteria precisely in the presence of many sleep disorders. Computerized analysis of continuous trends in frequency and amptitude of the wave forms are likely to be refined over the next few years.

Wakefulness, non-REM sleep and REM sleep can be distinguished by the combinations of their EEG, EOG, and EMG features (figure 2.1). The EEG rhythms are classified primarily by their frequency, but also by their amplitude (table 2.1). The frequency of the EEG slows as sleep is entered with a loss of alpha, and increase in theta and delta waves. Stage 1 non-REM sleep is a transitional state between sleep and wakefulness. Stage 2 is characterized by sleep spindles and K-complexes which are probably sleep-maintaining mechanisms and which appear in response to either internal or external stimuli. In stages 3 and 4 non-REM sleep there is more extensive thalamocortical synchronization with an increase in delta wave activity.

The traditional parameters for sleep staging have recently been updated although the recommendations are yet to be universally accepted or widely used. The new guidelines include more formal definitions of the Rechtschaffen and Kales stages, including the transitions between stages [7]. A more extensive scalp montage is suggested. Stages 3 and 4 are combined into a single stage, N3. Finally, associated events such as apneas, hypopneas and (periodic) limb movements are defined in detail.

The EEG of REM sleep is similar to that of relaxed wakefulness with a wide range of frequencies and low and irregular amplitude waves. The EEG appears to be "desynchronized" but there may be sawtooth waves which precede the rapid eye movements. Skeletal muscles are actively inhibited at the level of the anterior horn cell and this is detected by the absence of any submental EMG signal. There may, however, be occasional phasic muscle twitches. The EOG electrode readily detects the rapid eye movements in this state of sleep.

The instability of normal sleep and arousals due to sleep disorders are poorly recognized by the conventional fixed scoring criteria. As a result, the concept of micro-arousals has been developed, characterized by episodes of increasing EEG frequency lasting at least 3 seconds and following at least 10 seconds of stable sleep [8]. Arousals are a feature of normal sleep and become more frequent with age. Within an otherwise stable phase of sleep, instability can also be detected during which periods of

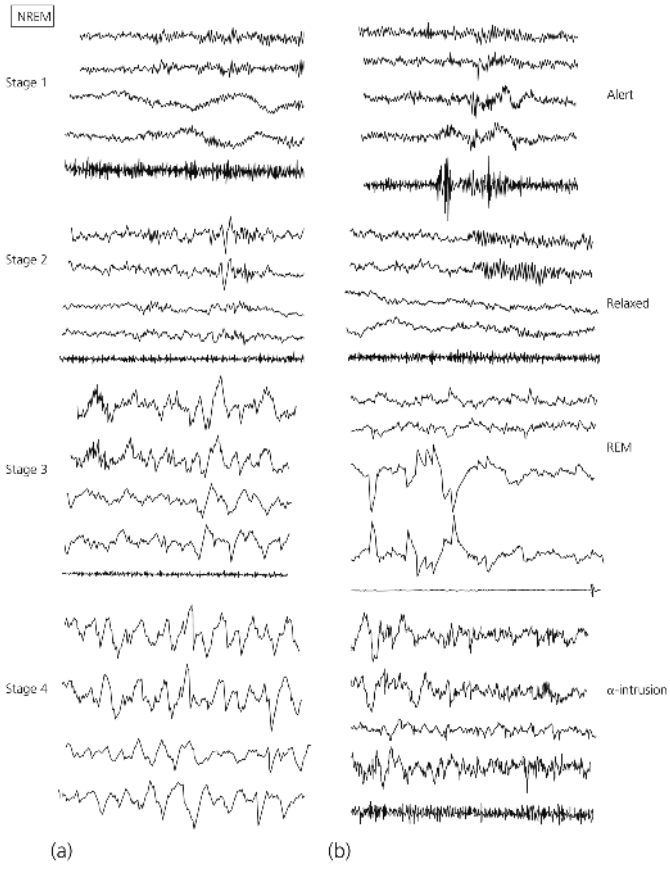

Figure 2.1 The EEG, EMG, and EOG appearances. (a) Stage 1 non-REM sleep: high-frequency EEG activity with slow rolling eye movements. Stage 2 non-REM: K-complex with spindles. Stage 3 non-REM: delta waves present in EEG for 20–50% of tracing and conducted to the EOG tracings, less chin EMG activity than in stages 1 and 2 non-REM. Stage 4 non-REM: the EEG shows slow high-amplitude delta waves throughout (or at least 50%) with no chin EMG activity. (b) Alert wakefulness: high-frequency EEG recording with eye movements and considerable chin EMG activity. Relaxed wakefulness: conspicuous alpha rhythm (8–13 Hz) on EEG tracing and chin EMG activity present. REM sleep: irregular mixed frequency EEG with frequent eye movements and absence of chin EMG activity. Alpha intrusion into stage 3 non-REM: alpha waves, superimposed on delta waves in EEG tracing and conducted to EOG recordings. EEG, electroencephalogram; EMG, electromyogram; EOG, electro-oculogram; NREM, non-rapid eye movement; REM, rapid eye movement.

partial arousal alternate with times of more stable sleep. This is known as the cyclic alternating pattern (CAP) [9] and can be identified from the EEG by complex computerized analysis. However, its role in clinical practice for detecting unstable sleep remains controversial. Subcortical (autonomic)

Table 2.1 Electroencephalogram features in sleep and wakefulness

Waveform	Frequency or duration	Amplitude, μV	Main sleep-wake state and stage
Beta	>13 Hz	10–20	Alert wakefulness, stage 1 NREM, REM
Alpha	8–13 Hz	20–50	Relaxed wakefulness
Theta	4–8 Hz	10–30	Wakefulness, stage 1 NREM
Delta	0.504 Hz	>75	Stages 2, 3, and 4 NREM
Vertex sharp waves	0.05–10.2 s	30–200	Stage 1 NREM
K-complexes	1 Hz, >0.5 s	>75	Stage 2 NREM
Sleep spindles	12–16 Hz, 0.5 s	20–40	Stage 2 NREM
Sawtooth waves	2–5 Hz, 0.25 s	20–100	REM

NREM, non-rapid eye movement; REM, rapid eye movement.

arousals can also be identified from changes in heart rhythm and blood pressure, which are often accompanied by alterations in respiratory frequency, movements of the limbs and facial muscles, or gross body movements. Autonomic arousals may occur without any overt surface EEG changes.

Of particular interest to physicians involved in the assessment of sleep-related breathing disorders, pressure gauges to assess thoracic and abdominal expansion are useful in discriminating obstructive from central apneas. Nasal airflow and snoring are also routinely recorded.

The data from polysomnograph recordings are often summarized in the form of a hypnogram (for examples, see figure 2.2). This shows the distribution of sleep stages and arousals through a night of recording and can be a useful aid, especially when explaining sleep study data to patients.

Indications

Excessive daytime sleepiness

The cause of excessive daytime sleepiness (EDS) is often multifactorial and polysomnography may be required in addition to a careful history and sleep diary to assess the relative contributions from several potential sources. These include discrete sleep disorders, sleep deprivation, and circadian rhythm-related problems such as shift work and time zone changes.

Polysomnography is however not generally required if EDS is associated with snoring and witnessed apneas, in the absence of features of any other primary sleep disorder. It is usually sufficient to carry out a respiratory sleep study confined to simple oximetry, measuring oxygen