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10 Sleep–wake disorders

 Introduction Disorders of sleep and wakefulness are a somewhat marginalized concern to most psychiatrists, which belies the advances that have taken place in sleep research in recent decades and their relevance to psychiatric training and practice. This is partly due to the fact that sleep research had focused on the physical causes of insomnia, such as obstructive sleep apnoea (OSA) (E Sleep-related breathing disorders, p. 444)—which is more the remit of respiratory physicians—or the neurological presentations, such as narcolepsy—which have yielded interesting genetic and neurobiological findings (E Hypersomnia 2: narcolepsy, p. 450). Having ventured down the cul-de-sac of dream/psychosis research in the 1960s and 1970s, few psychi atric units in the UK or Ireland still have facilities to conduct inpatient sleep monitoring. As a result, we have to rely on good relations with our phys ician colleagues in order to appropriately investigate possible sleep–wake disorders (E A brief history of sleep research, p. 434). Relevance to psychiatric practice Aside from the common-sense notion that ‘getting a good night’s sleep’ is good for both physical and mental health (see Box 10.1), it is vital that mental health professionals understand the effects that mental disorder and treatment may have on the normal sleep–wake cycle (E Sleep–wake dis orders related to psychiatric disorders 1, p. 478; E Sleep–wake disorders related to psychiatric disorders 2, p. 480; E Psychiatric medication and sleep, p. 482). Perhaps even more important is the need to recognize that disorders of sleep and wakefulness may themselves manifest bizarre and difficult-to-explain psychiatric symptoms, such as hypnic hallucinations and REM sleep behaviour, which ought not to be labelled as ‘psychotic’ in na ture (E Parasomnias: overview, p. 458 for cautionary notes). Psychiatrists also should be aware of the principles of good sleep hygiene (E Insomnia 2: general management strategies, p. 442) and not always be reaching for the prescription pad to sort out sleeping difficulties! The International Classification of Sleep Disorders In 2014, the American Academy of

Sleep Medicine (AASM) published a third revision of its International Classification of Sleep Disorders (ICSD-3), replacing ICSD-2 (2005). While ICSD-3 is intended for use by sleep ex perts, in this chapter, we have adhered to the structure laid out in ICSD-3 for the clinical syndromes (E ICSD-3 groupings (and DSM-5 equivalents), see below), rather than the much broader categories of ICD-10 or the older versions of DSM (E F50–F59 Behavioural syndromes associated with physiological disturbance and physical factors, p. 1102), as this provides a more valid way of conceiving the disorders. A similar approach has been taken in DSM-5, and ICD-11 will follow suit (moving 'Sleep–wake disorders' out of 'Mental and behavioural disorders' and into a section of their own). ICSD-3 groupings (and DSM-5 equivalents)

1. Insomnias (Insomnia disorder).
2. Sleep-related breathing disorders (Breathing-related sleep disorders).
3. Central disorders of hypersomnolence (Hypersomnolence disorder/ narcolepsy).

Introduction 4. Circadian rhythm sleep–wake disorders (Circadian rhythm sleep–wake disorders). 5. Parasomnias (Parasomnias). 6. Sleep-related movement disorders (DSM-5: no specific category—Parasomnias/other specified sleep–wake disorder). 7. Other sleep disorders (Other specified sleep–wake disorder). There are also two appendices for 'Sleep-related medical and neurological disorders' and 'ICD-10-CM coding for substance-induced sleep disorders'. ICD-11 proposals give 'Sleep–wake disorders' their own separate section, but the groupings are almost identical to DSM-5. Box 10.1 Sleep deprivation—the cost of not getting a good night's sleep The critical importance of sleep to good health and life is dramatically il lustrated in the classic animal studies of Rechtschaffen et al. (1989).1 Total sleep deprivation resulted in the death of all rats within 2–3wks. Selective deprivation of NREM and REM sleep also resulted in the death of the ani mals, but over a slightly longer period of time. With progressive sleep de privation, the rats became hypermetabolic, lost weight despite increasing food intake, and developed skin lesions and erosions of the GI tract, with hypothermia developing just prior to death. Subsequent investigation found that these rats died of sepsis, suggesting that sleep deprivation may impair the ability of the immune system to deal with infection.2 This is an important finding, as it is known that sleep-deprived critically ill patients in ICUs often succumb to sepsis. Although it is not ethical to study prolonged sleep deprivation in humans, there is now a large body of accu mulated knowledge documenting the adverse consequences of short term, total, or partial sleep deprivation on human learning, mood, risk of psych osis, behaviour, performance, the autonomic nervous system, and organ system functioning. Deviations from normal sleep have been shown to in crease mortality rates in patients with cancer and the incidence of cardio vascular diseases (e.g. coronary artery disease, hypertension, arrhythmias), diabetes, and obesity.3 PET studies have found that individuals deprived of sleep for 24hrs have d perfusion in the prefrontal and parietal asso ciation areas—areas important for judgement, impulse control, attention, and visual association. Operator fatigue due to sleep deprivation has been implicated in disasters, including the Exxon Valdez oil spill, the nuclear melt down at Three Mile Island, the Chernobyl nuclear accident, and the Space Shuttle Challenger explosion. It is also estimated that 1 in 6 fatal car crashes and >200,000 workplace-based accidents in the USA annually can be at tributed to sleep deprivation, with an economic cost of US$31.1 billion.4 1 Rechtschaffen A, Bergmann BM, Everson CA, et al. (1989) Sleep deprivation in the rat: X. Integration and discussion of the findings. Sleep 12:68–87. 2 Everson CA (1993) Sustained sleep deprivation impairs host defense. Am J Physiol 265:R1148–54. 3 Tobaldini E, Costantino G, Solbiati M, et al. (2016) Sleep, sleep deprivation, autonomic nervous system and

cardiovascular diseases. Neurosci Biobehav Rev 74(Pt B):321–9. 4 Shahly V, Berglund PA, Coulouvrat C, et al. (2012) The associations of insomnia with costly workplace accidents and errors results from the America Insomnia Survey. Arch Gen Psychiatry 69:1054–63.

434 Chapter 10 Sleep–wake disorders A brief history of sleep research ‘More has been learned about sleep in the last 60 years than in the past 6000.’ Allan Hobson (1989)1 Sleep has forever fascinated humankind. Dreams were important to many ancient cultures,2 and an interest in the nature of sleep is seen in the Greek writings of Alcmaeon (c.500 BC), Aristotle, and Hippocrates (c.300 BC). Many religious texts and poetic works speak of the importance of sleeping well and the prophetic nature of dreams. It was not until the early seventeenth century that scientific theories of sleep re-emerged. Descartes espoused a hydraulic model of sleep, in which the pineal gland played the gatekeeper role between sleep and alert ness. Thomas Willis, one of the fathers of neurology, wrote about sleep, sleepwalking, insomnia, and the effects of caffeine in The Practice of Physick (1692). In 1762, Albrecht von Haller, the father of modern physiology, theorized on the physiology of sleep in his Elementa Physiologiae Corporis Humani. In the nineteenth century, there were four primary theories of sleep: vas cular, chemical, neural, and behavioural. In The Philosophy of Sleep (1830), the Scottish physician Robert MacNish advocated the Greek idea that con gestive blood flow caused sleep; however, the observations of reduced CBF (in retinal arteries and direct viewing of the brain) during sleep by a number of physicians, including the German physiologist Johann Friedrich Blumenbach, appeared to contradict the older theories. Aristotelian ideas of sleep-inducing, food-related ‘fumes’ led to chemical theories of substances accumulating during wakefulness, inducing sleep. A number of primary ‘toxins’ were suggested, including lactic acid, carbon dioxide, ‘urotoxins’, d oxygen, and ‘leucomaines’ (proposed by the Belgian botanist Leo Errera). When Camillo Golgi demonstrated the nerve cell in 1873, a variety of different neural theories of sleep arose. In 1889, the neurologist Charles-Édouard Brown-Séquard wrote of sleep as an ‘inhibitory reflex’. The activity of sleep was seen as another type of behaviour, described by the Russian physician Marie de Manaceine in 1897 as the ‘resting state of consciousness’ and investigated by behaviourists, including Ivan Pavlov. Interest in specific disorders of sleep and wakefulness truly began when, in 1880, Jean-Baptiste-Édouard Gélineau described 14 cases of hypersomnia, distinguished primary from secondary hypersomnia, and coined the term ‘narcolepsy’ (Greek: ‘seized by somnolence’). In 1902, Loewenfeld noticed a common association between sleep attacks and par alysis during bouts of laughter, anger, or other strong emotions. This was 1 Hobson JA (1989) Sleep (Scientific American Library Series), 3rd printing edn. New York, NY: Holt, Henry, and Company. 2 See The Dream Book (c.1220 BC), part of the British Museum Collection. Google Arts & Culture: M https://www.google.com/culturalinstitute/beta/asset/the-dream-book/MwFiHsBS2T_Qug [ac cessed 21 June 2018].

A brief history of sleep research referred to as ‘cataplectic inhibition’ by Henneberg in 1916 and later as ‘cataplexy’ (Greek: ‘stupefaction’ or literally ‘strike down’) by Adie in 1926. The term ‘sleep paralysis’—a brief episodic loss of voluntary movement that occurs on falling asleep or awakening—was introduced by Wilson in 1928, although Mitchell had previously described the phenomenon as ‘night palsy’ as early as 1876. In 1903, the work of Cajal and Tello on the morphological changes in reptilian brains during hibernation led to a renewed interest in neuronal the ories of sleep. These culminated in von Economo’s work on patients dying from encephalitis lethargicans, following the 1917 epidemic. The idea that there were centres in the brain that controlled sleep caught the imagination of neuroscientists, focused attention on the hypothalamus,

and laid the foundations for further neurophysiological and neuropathological research. In 1924, Berger succeeded in recording the first human EEG. Filled with doubt, it took him 5yrs to publish his first paper in 1929, but he was the first to show that cerebral electrical activity was different during sleep than arousal. It took some time for the EEG to be accepted, but, in 1937, Loomis documented the slow-wave EEG patterns of non-REM (NREM) sleep [slow-wave sleep (SWS)]. The major breakthrough came in 1949 when Moruzzi and Magoun first investigated the neural components regulating the brain's sleep–wake mechanisms, discovering the relationship between the reticular formation [reticular activating system (RAS)] and EEG activa tion during transitions between sleep and wakefulness. This was followed in 1953 by Kleitman and Aserinsky publishing a paper in Science that described the REM stage of sleep and proposed a correl ation with dreaming. With his student, Dement, Kleitman also described the 'typical' architecture of sleep in 1957. Dement went on to show that REM sleep was characterized by a characteristic desynchronized, 'active' pattern, a finding confirmed by Jouvet in 1959. Jouvet described the control ling centres in the brainstem, clarified the role of the pontine centres, and, in 1962, presented a clear neurophysiological framework for the generation of REM sleep with associated muscle atonia. The first specific treatment for a sleep disorder came in 1959 when Yoss and Daly used methylphenidate (Ritalin®) to treat narcolepsy, and in 1965, Oswald and Priest began using the sleep laboratory to evaluate sleeping pills. Also in 1965, Gastaut and colleagues in Marseilles and Jung and Lugaresi in Bologna independently described obstructive sleep apnoea (OSA) and a variety of surgical treatments were proposed. The publication of Rechtschaffen and Kale's Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects in 1968, the identification of the suprachiasmatic nuclei (SCN) as the site of the biological clock in 1971, the first formal classification of sleep disorders in 1979, and the introduction of continuous positive airway pressure (CPAP) to treat OSA by Sullivan and colleagues in 1981 were all significant advances in the diagnosis, treatment, and neurobiology of specific sleep disorders and set the stage for the next generation of sleep researchers.

436 Chapter 10 Sleep–wake disorders Normal sleep: stages and cycles Sleep normally follows a typical pattern of stages and cycles that can be objectively measured using electroencephalography (EEG) (see Fig. 10.1).3,4 Non-REM sleep stages N1 (light sleep)5 As wakefulness declines, posterior α activity (8–13Hz) disappears, with slow θ (4–7Hz) and δ (0.5–2Hz) activity emerging, plus occasional vertex waves. This stage lasts only a few minutes but may recur briefly during the night during sleep stage transitions or following body movements. Sudden twitches and hypnic jerks may be associated with the onset of sleep during N1. Hypnagogic hallucinations may also be experi enced during this stage. During N1, there is loss of some muscle tone and most conscious awareness of the external environment. N2 Characterized by sleep spindles (0.5s-phase fast activity, maximal at the vertex), ranging from 11 to 16Hz (most commonly 12–14Hz) and K-complexes K complex Sleep spindle Theta waves N1 N2 N3 R Fig. 10.1 Sleep stages: characteristic EEG traces. 3 Rechtschaffen A, Kales A (1968) A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington, DC: US Government Printing Office, Public Health Service. 4 Iber C, Ancoli-Israel S, Chesson A, et al. (eds) (2007) The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specification. Westchester, IL: American Academy of Sleep Medicine. 5 In 2007, the AASM modified the Rechtschaffen and Kales (1968) standard guidelines. One of the major changes was a change in terminology: NREM sleep stages, formerly called stages 1, 2, 3, and 4 (S1, S2, S3, S4), are referred to as N1, N2, and N3, with N3 reflecting

SWS (R&K stages S3 + S4); REM sleep became stage R. The new manual also clarifies the definition of the sleep–wake transition, sleep spindles, K-complexes, SWS, and REM sleep, as well as arousals and major body movements. There is now an online and app-based version of the manual that is regularly updated. M http:// www.aasmnet.org/scoringmanual/default.aspx [accessed 21 June 2018].

Normal sleep: stages and cycles (symmetrical high-voltage vertex waves) that arise both spontaneously and in response to sudden stimuli. During this stage, muscular activity, as measured by electromyography (EMG), decreases and conscious awareness of the ex ternal environment disappears. This stage occupies 45–55% of total sleep in adults. This lasts 15–30min, followed by the gradual appearance of high- voltage waves (>75μV) in the delta range in a semi-symmetrical distribution over both hemispheres, occupying <20% of the EEG recording. N3 (deep or SWS) Defined by the presence of a minimum of 20% δ waves (0.5–2Hz; peak-to-peak amplitude >75μV). This is the stage in which parasomnias, such as night terrors, nocturnal enuresis, sleepwalking, and somniloquy, occur. Other texts may still describe stage 3 sleep (S3) with 20– 50% δ waves, and stage 4 sleep (S4) with >50% δ waves; these have officially been combined as stage N33. N3 lasts 30–45min, before reversion to N2. REM sleep (stage R) The end of the first sleep cycle is marked by a brief period of arousal before the onset of REM sleep. This has characteristic low-voltage, desynchron ized EEG activity, with associated muscle atonia (paralysis may be neces sary to protect organisms from self-damage through physically acting out scenes from the often vivid dreams that occur during this stage) and epi sodic REMs. Occasional bursts of EMG activity (myoclonia) may be seen in association with the phasic eye movements. There are no sleep spindles or K-complexes. and α activity is rarely seen. Sleep cycles A typical night’s sleep has four or five cycles of these sequential stages, each lasting 90–110min (see Fig. 10.2). As the night progresses, the amount of time spent in δ sleep decreases, with consequent increase in REM sleep. Hence, the first REM period may last 5–10min, while the last, just before waking, may last up to 40min. Although the total amount of sleep needed varies between individuals and with age, total sleep time in adults is usually between 5 and 9hrs. Remarkably, REM sleep occupies 20–25% of the total sleep time in all ages. Time Awake Drowsy R N1 N2 N3 0100 0500 Fig. 10.2 Typical hypnogram.

438 Chapter 10 Sleep–wake disorders Assessing sleep–wake disorders Sleep history Always try to obtain a third-party account from the patient’s bed partner or from an informant such as a parent or carer. The main areas covered should include the following. The presenting complaint(s): onset, duration, course, frequency, severity, effects on everyday life. Pattern of symptoms, timing, fluctuations, exacer bating/relieving factors, environmental factors, relevant current stressors. The usual daily routine: waking (time, method, e.g. alarm, natural), usual morning routine. Daily activities (start/finish times), any daily naps (when, duration). Bedtime (preparations for bed, time of going to bed, time of falling asleep, activities in bed, e.g. TV, reading, sex). Description of sleep: behaviour while asleep. Dreams/nightmares. Episodes of wakening (and how they are dealt with). Quality and satisfac tion with sleep. Daytime somnolence: general level of alertness during the day. When/ if sleep occurs (e.g. when active, mealtimes, walking, driving, operating ma chinery). Effects on work/social activities. Any periods of confusion. Any episodes of collapse. Family history Past and current history of medical or psychiatric problems Drug and alcohol history • General review of regular medications (alerting/sedating effects), including timing of administration. • Specific questions regarding: caffeine-containing drinks (tea, coffee, soft drinks), smoking, alcohol, and

other recreational drugs. Previous treatments • Types of treatment tried. • Benefits/problems/side effects. Third-party/other information • Breathing problems (snoring, gasping, choking, stopping breathing). • Motor activity (muscle twitches, limb movements, unusual or complex behaviours, e.g. sleep-talking/sleepwalking/dream enactment). • Frequency of occurrence and any clear pattern. • Any recent mood changes. • Any recent change in use of drugs or alcohol. Methods of further assessment Sleep diary To create a record of the sleep–wake pattern over a 2-wk period in order to clarify any pattern or particular factors that may be present. Important information includes: daily activities, pattern of sleeping, mealtimes, con sumption of alcohol/caffeine/other drugs, exercise, and daytime sleepi ness/napping.

Assessing sleep–wake disorders Video recording A useful component of assessment, particularly for parasomnias. Routinely used in sleep laboratory studies; however, home videos of sleep-related behaviour may be just as informative. Actigraphy A method of both quantifying circadian sleep–wake patterns and identi fying movement disorders occurring during sleep. Actigraphs incorporate a piezoelectric motion sensor, often in a wristwatch-like unit, that collects data on movement over several days, for later computer analysis. Indications Circadian rhythm sleep disorders, jet lag, paediatric sleep disorders, moni toring leg movements (e.g. in ‘restless legs syndrome’ or periodic move ments of sleep) or other movement disorders (e.g. Parkinsonian tremor). Polysomnography (PSG) Detailed recording of a variety of physiological measures, including EEG, electro-oculogram (EOG), and EMG. Other parameters may be added as required: ECG, respiratory monitoring (nasal/oral airflow, diaphragm EMG), pulse oximetry, actigraphy, penile tumescence, and oesophageal pH (for oesophageal reflux). Audio and video recording help to assess noc turnal behaviours, vocalizations, and snoring. Time coding of all these meas ures allows temporal correlations to be made of the various parameters. In general, one night of testing, followed by a daytime multiple sleep latency test (MSLT), is sufficient to diagnose most conditions. Indications Hypersomnia (where common extrinsic causes, e.g. medication, shift work, have been excluded; to diagnose suspected periodic limb movements of sleep, sleep apnoea, or narcolepsy), insomnia (where periodic limb move ments of sleep or sleep apnoea are suspected and initial treatment has been ineffective), parasomnias (where the clinical history is unclear, initial treat ment has been unsuccessful, and PSG is likely to aid the diagnosis, e.g. REM sleep behaviour disorder or multiple parasomnias), to validate the accuracy of a sleep complaint (where a more objective measure is needed), to assess the benefits of treatment (e.g. CPAP), suspected nocturnal epilepsy, serious cases of sleep-related violence (SRV). Multiple sleep latency test Devised to assess daytime somnolence but also helps in identifying daytime REM sleep, e.g. in narcolepsy. The patient is put to bed at 2-hr intervals starting at 8 a.m., with the objective of measuring time to sleep onset (sleep latency). In adults, a mean sleep latency of 5min or less indicates a patho logical level of daytime somnolence; 5–10min is ‘indeterminate’ but may reflect a primary psychiatric disorder; over 10min is regarded as normal. The ICSD-3 suggests specific MSLT criteria for a diagnosis of narcolepsy (E Hypersomnia 2: narcolepsy, p. 450).

440 Chapter 10 Sleep–wake disorders Insomnia 1: overview Essence Persistent difficulties (at least 3 days/wk for at least 1mth) with sleep initi ation, duration, consolidation, or quality that occurs despite adequate op portunity and circumstances for sleep, and results in some form of daytime impairment. Individuals are preoccupied and excessively concerned with their sleep problems and distressed by them, and social or occupational functioning is affected. Prevalence Common complaint (730% general population), ♀ > ♂, greater in the eld erly. ‘Clinically significant insomnia’

(causing marked personal distress or interference with social and occupational functioning) 9–12%. A note on ICSD-3/DSM-5/ICD-10 categories ICSD-3 abandoned the ICSD-2 distinction between primary (caused by both extrinsic and intrinsic factors) and secondary (due to medical or psychiatric illness, other sleep disorders, or substance misuse) chronic insomnias, since the direction of causation is often difficult to prove and in clinical practice, there is little evidence that many ICSD-2 subtypes (e.g. psychophysiological insomnia, idiopathic insomnia, inadequate sleep hy giene, and paradoxical insomnia) represent distinct phenotypes. It is good practice to specify comorbidities (and their role in aggravating sleep dis ruption), along with the diagnosis of insomnia. Insomnia due to a drug of abuse (E Sleep-wake disorders related to psychiatric disorders 2, p. 481) or medication (E Psychiatric medication and sleep, p. 482; see Box 10.2) are classified by DSM-5 in the 'Substance-related and addictive disorders' subsection. ICD-10 'Non-organic insomnia' specifically excludes organic, neurological, medical, psychoactive substance, or medication causes. DSM- 5 'Insomnia disorder' has the additional specifiers: with non-sleep disorder mental comorbidity, with other medical comorbidity, with other sleep disorder. Box 10.2 Common medication causes of insomnia • Antidepressants (e.g. MAOIs, SSRIs, venlafaxine, reboxetine). • Anti-Parkinsonian medication. • Bronchodilators (e.g. aminophylline, theophylline, pseudoephedrine). • Cardiovascular medication (e.g. β-blockers, clonidine, high-dose digoxin, verapamil). • Chemotherapy agents. • Corticosteroids/anabolic steroids. • NSAIDs (high dose). • Stimulants (e.g. dexamfetamine, methylphenidate, amphetamine cocaine, caffeine, nicotine). • Levothyroxine. • Withdrawal (e.g. hypnotics, opiates, alcohol, or cannabis).

Insomnia 1: overview Chronic insomnia disorder (F51.01/G47.0) The patient reports, or the patient's parent or caregiver observes, one or more of the following: difficulty initiating and/or maintaining sleep; waking up earlier than desired; resistance to going to bed on appropriate schedule; difficulty sleeping without parent or caregiver intervention. In addition, there is evidence of: fatigue/malaise; attention, concentration, or memory im pairment; impaired social, family, occupational, or academic performance; mood disturbance/irritability; daytime sleepiness; behavioural problems (e.g. hyperactivity, impulsivity, aggression); reduced motivation/energy/ini tiative; proneness for errors/accidents; concerns about, or dissatisfaction with, sleep. Complaints cannot be explained purely by inadequate oppor tunity or circumstances for sleep or another sleep disorder. The sleep dis turbance and associated daytime symptoms occur at least three times per week and have been present for at least 3mths. Short-term insomnia disorder (F51.02/G47.9) All of the criteria for chronic insomnia are met, with the exception of dur ation which is <3mths. There is commonly an identifiable trigger or precipi tant such as particular daytime stressors. Other insomnia disorder (F51.09/G47.09) Full criteria for chronic/short-term insomnia are not met, but patients com plain of typical insomnia symptoms such as persistent sleep difficulty despite adequate sleep opportunity and associated daytime dysfunction. Isolated symptoms and normal variants Excessive time in bed (F51.01/G47.9) Individuals report isolated insomnia features such as difficulties falling asleep or prolonged awakenings during the night, without a complaint of insomnia and no daytime consequences. Short sleeper (R29.81) Individuals who sleep, on average, fewer than 6hrs per night, yet have no sleep/wake complaints and no daytime dysfunction.

 Insomnia 2: general management strategies Education about sleep Many myths surround sleep, and the clinician should be able to educate the patient about the stages of sleep, sleep cycles, changes in sleep patterns with age, and the nature of the particular sleep problem or disorder with which the patient presents. Sleep hygiene Establishing good sleep

habits Control environmental factors (noise, light, temperature); ‘wind down’ time (71hr) before going to bed—distract from the day’s stresses (reading, watching television, listening to music, having a warm bath); avoidance of caffeine-containing drinks after about 4 p.m.; not smoking for at least 1hr before bed; regular exercise (not late at night); late ‘tryptophan’ snack (warm milk or other milky drink); avoid naps during the day (or confine naps to the early afternoon, not longer than 740min); set aside time during the day to reflect on problems and stresses. Stimulus control Go to bed only when sleepy; avoid other activities (with the exception of sex) while in bed; if sleep does not occur, do not remain in bed for >10–20min, get up and go to another room (without turning on all the lights), returning to bed only when sleepy; establish a regular time to get up, with no more than 1hr variation (even at weekends and during holidays). Relaxation training Regular practice of relaxation techniques during the day (particularly progressive relaxation) may help to provide patients with the means to reduce general arousal, which can be used, if necessary, while in bed. Sleep restriction When sleep is fragmented, a sleep restriction strategy may help to reduce total time spent in bed and improve the quality of sleep by ‘consolidation’. There are a number of steps to sleep restriction, and to complete the programme does require motivation and encouragement (see Box 10.3). Box 10.3 Sleep restriction • Keep a sleep diary for 5–14 days to allow the calculation of TST and SE. • TST = (total time spent in bed) – (time spent awake during the night). • SE = (TST × 100)/total time spent in bed. • For the first few nights of a sleep restriction programme, spend only the same number of hours in bed as the average TST for the past week. No naps allowed during the day (despite initial tiredness). • Continue to keep sleep diary. When the calculated mean SE for five nights reaches 85% or better, go to bed 15min earlier. • Repeat the procedure with increases of 15min if mean SE remains 85% or better, or decreases of 15min if the mean SE falls below 85%, until a satisfactory amount of night-time sleep is achieved.

Insomnia 2: general management strategies Medication6 Prescribing should be the last option, rather than the first. Before a hypnotic is prescribed, the cause of insomnia should be established, underlying fac tors addressed, and any primary medical or psychiatric disorder effectively treated. Only use to treat insomnia when it is severe, disabling, or extremely distressing. Ideally, hypnotics should be short-term adjuncts to other forms of therapy, and avoid prolonged administration. Interrupted courses (i.e. five nights with medication, two without) for no more than 4wks may help avoid tolerance and reduce ‘rebound insomnia’ often accompanying ces sation. Choices (see Table 10.1) include: BDZs, the ‘Z-drugs’ [zopiclone, zolpidem, zaleplon (no longer available in the UK)—usually first line], chloral hydrate, sedating antidepressants (e.g. trazodone, mirtazapine), sed ating antipsychotics, and possibly melatonin agonists. 6 BAP Consensus Guidelines (2010) M https://www.bap.org.uk/pdfs/BAP_Guidelines-Sleep.pdf [accessed 4 July 2018]. Table 10.1 Pharmacokinetic data for drugs used as hypnotics (in order of decreasing T1/2) Drug Availability (%) Plasma-bound (%) Time to Tmax (hr) T1/2 (hr) Mirtazapine 85 0.25–2 16.3–40 Nitrazepam 85–87 0.5–5 15–40 Olanzapine 93 5–6 24–30 Temazepam 96–98 0.75–3 2–25 Promethazine 12.3–25 – 4.39 18.6 Trazodone 60–80 89–95 1–2 6–15 Lormetazepam 70–80 2 7.9–12 Chloral hydrate – 0.76–8.2 9.3–10.9 Quetiapine – 1–2 5.3–7 Zopiclone 70–80 45–80 0.25–1.5 3.5–6.5 Zolpidem 90–92 0.5–2.6 1.5–4.5 Agomelatine <5 1–2 1–2 Zaleplon 60 0.25–1.5 0.9–1.1 Melatonin – 0.83 0.75

444 Chapter 10 Sleep–wake disorders Sleep-related breathing disorders 1 Essence Sleep-related breathing disorders commonly lead to chronic insomnia and daytime tiredness. They are often missed in psychiatric patients despite ob vious risk factors. Caused by CNS dysfunction,

pathological processes af fecting normal lung function, and environmental factors with which they are associated: hypertension, coronary artery disease, stroke, congestive heart failure, AF, type 2 diabetes mellitus, mood disorder, and cognitive dysfunction. In DSM-5, ‘Breathing-related sleep disorders’ are subdivided into three distinct disorders on pathophysiology: obstructive sleep ap noea hypopnoea, central sleep apnoea (CSA) [idiopathic, Cheyne–Stokes breathing (CSB), comorbid with opioid use], and sleep-related hypoven tilation (idiopathic, congenital central alveolar hypoventilation, comorbid sleep-related hypoventilation). Obstructive sleep apnoea Also known as Pickwickian syndrome (G47.33)7,8,9 (see Box 10.4). Repeated episodes of upper airway obstruction (hypopnoeas) or cessa tion of breathing (apnoeas) during sleep, usually associated with reduced blood oxygen (O2) saturation, snoring, body jerks or movements, brief re spiratory effort-related arousals (RERAs), dry mouth, morning headaches, and daytime somnolence. Usually middle-aged (30–60yrs), overweight ♂, with large neck circumference and excessive body fat. Prevalence 1–2%. ICSD-3 criteria (adults): sleepiness, non-restorative sleep, fatigue, or insomnia symptoms; waking with breath-holding, gasping, or choking; ha bitual snoring, breathing interruptions, or both during sleep; presence of comorbidity; PSG or out-of-centre sleep testing (OCST) demonstrates: 5+ predominantly obstructive respiratory events (obstructive and mixed apnoeas, hypopnoeas, or RERAs) per hour. Alternatively, 15+ predomin antly obstructive respiratory events (apnoeas, hypopnoeas, or RERAs) per hour of sleep during PSG or OCST, without other features. ICSD-3 criteria (paediatric): snoring; laboured, paradoxical, or ob structed breathing during sleep; sleepiness, hyperactivity, behavioural prob lems, or learning problems; PSG 1+ obstructive apnoeas, mixed apnoeas, or hypopnoeas per hour of sleep and a pattern of obstructive hypoventi lation [hypercapnia (PaCO2 >50mmHg] 25%+ of total sleep time), associ ated with snoring, flattening of the inspiratory nasal pressure waveform, or paradoxical thoracoabdominal motion. 7 Scottish Intercollegiate Guidelines Network (SIGN) (2003) Management of obstructive sleep ap noea/hypopnoea syndrome in adults. Guideline 73. M http://www.lothianrespiratorymcn.scot.nhs.uk/wp-content/uploads/2010/11/SIGN-73-Management-of-Obstructive-Sleep-Apnoea_Hypopnoea-Syndrome-in-Adults.pdf [accessed 4 July 2018]. 8 National Institute for Health and Care Excellence (2015) Obstructive sleep apnoea syndrome– summary. Clinical Knowledge Summary. M http://cks.nice.org.uk/obstructive-sleep-apnoea- syndrome#!topicsummary [accessed 4 July 2018]. 9 Morgenthaler TI, Kapen S, Lee-Chiong T, et al. (2006) Standards of Practice Committee, American Academy of Sleep Medicine. Practice parameters for the medical therapy of obstructive sleep apnea. Sleep 29:1031–5.

Sleep-related breathing disorders 1 Management This will depend on symptom severity, with more options for mild apnoea. Moderate to severe apnoea should be treated with nasal CPAP.10 • General—conservative measures and prevention: weight loss, avoidance of sedative drugs (at least 4–6hrs before bedtime), reduction of alcohol consumption/smoking, alternative sleeping position (not lying on the back), avoidance of sleep deprivation. • Specific: mechanical measures—oral appliances [for milder cases, e.g. sleep and nocturnal obstructive apnoea redactor (SNOAR); nasal CPAP; bi-level positive airways pressure (BiPAP)]. • Surgical (for severe cases): nasal reconstruction, tonsillectomy, soft palate implants,11 uvulopalatopharyngoplasty (UPPP), bimalleolar advancement, and rarely tracheostomy. • Pharmacological: not usually part of primary treatment. CNS stimulants (e.g. modafinil, armodafinil) sometimes used for residual daytime sleepiness despite optimal use of CPAP (unlicensed in the UK). Box 10.4 Mr Dickens’s ‘Pickwickian’ syndrome ‘Mr. Lowton hurried to the door . . . The object that presented itself to the eyes of the astonished clerk was a boy—a wonderfully fat boy— . . . standing upright on the mat,

with his eyes closed as if in sleep. He had never seen such a fat boy, in or out of a traveling caravan; and this coupled with the utter calmness and repose of his appearance . . . smote him in wonder.’ Charles Dickens (1836) The Posthumous Papers of the Pickwick Club The introduction of the name Pickwick and its association with obesity and daytime somnolence can be traced back to Caton’s 1889 paper on narcolepsy in the BMJ. The eponym is usually attributed to Sir William Osler, but it is in Burwell et al.’s 1956 paper in the American Journal of Medicine that the connection is made explicitly. Over the years, the term ‘Pickwickian syndrome’1 has proved controversial, justified more by poetic licence and medical fashions than literary history or clinical accuracy. 1 Bray (1994) What’s in a name? Mr. Dickens’ ‘Pickwickian’ fat boy syndrome. Obesity Res 2:380–3. 10 National Institute for Health and Care Excellence (2008) Continuous positive airway pressure for the treatment of obstructive sleep apnoea/hypopnoea syndrome. Technology appraisal guidance. M http:// www.nice.org.uk/nicemedia/pdf/TA139Guidance.pdf [accessed: 4 July 2018]. 11 National Institute for Health and Care Excellence (2007) Soft-palate implants for obstructive sleep apnoea. Interventional procedure guidance [IPG241]. M https://www.nice.org.uk/guidance/ipg241 [accessed 4 July 2018].

446 Chapter 10 Sleep–wake disorders Sleep-related breathing disorders 2 Central sleep apnoea syndromes Central sleep apnoea with Cheyne–Stokes breathing [CSB-CSA] (R06.3) Recurrent apnoeas and/or hypopnoeas, alternating with prolonged hyperpnoea in a crescendo–decrescendo pattern. In NREM sleep; associated with heart or renal failure and cerebrovascular disorders. Central sleep apnoea due to a medical condition without Cheyne–Stokes breathing (G47.37) Vascular, neoplastic, degenerative, demyelinating, or trau matic condition involving the brainstem. Central sleep apnoea due to high-altitude periodic breathing (G47.32) At heights of >2600m; symptoms include sleepiness, difficulty initiating or maintaining sleep, frequent awakenings or non-restorative sleep, awakening with shortness of breath, morning headache, or witnessed apnoea. Central sleep apnoea due to a medication or substance (G47.39) Most commonly associated with long-term opioid use, due to suppression of respir ation through μ-receptors in the ventral medulla. Primary CSA (G47.31) Unknown aetiology, characterized by recurrent episodes of breathing cessation during sleep, without associated respiratory effort. Leads to excessive daytime sleepiness (EDS), insomnia, or breathing dif ficulties during sleep. PSG—no evidence of hypercapnia and 5+ apnoeas/hr. Primary sleep apnoea of infancy/prematurity (P28.3) Developmental or secondary to other medical problems. Treatment-emergent central sleep apnoea (G47.39) Apnoeas/hypopnoeas occur during sleep testing with positive airway pressure treatment. Management • General: as for OSA—treat the underlying disorder, e.g. descending to a low altitude for high-altitude periodic breathing; nocturnal dialysis/ optimizing medical treatment for CSB-CSA in renal and heart failure. • Specific: positive airway pressure, adaptive servo ventilation (ASV), O2, added dead space, CO2 inhalation, and overdrive atrial pacing. • Medication: acetazolamide and theophylline in CSA due to heart failure or high altitude; sedativehypnotic agents (temazepam, zolpidem) in non-hypercapnic CSA. Sleep-related hypoventilation disorders Obesity–hypoventilation syndrome [OHS] (E66.2) Obesity leads to raised PaCO2 during sleep, associated with daytime hypoventilation (PaCO2

> “ 45mmHg); 90% will have associated OSA. Idiopathic central alveolar hypoventilation (G47.34) Alveolar hypoven tilation, leading to sleep-related

> hypercapnia and hypoxaemia in individuals where no physical cause is found.

Sleep-related breathing disorders 2 Congenital central hypoventilation syndrome [CCHS] (G47.35) ‘Ondine’s curse’: the extremely rare (1:200,000) failure of automatic cen tral control of breathing in infants who do not breathe spontaneously, or only shallowly and erratically; linked to a mutation in the PHOX2B gene.12 Late-onset central hypoventilation with hypothalamic dysfunction [LO-CHS/HD] (G47.36) Similar to CCHS, but after infancy and with evidence of hypothalamic dysfunction: hyperphagia, hypersomnolence, thermal dysregulation, emotional lability, and endocrinopathies. Sleep-related hypoventilation due to medication or substance (G47.36) Due to inhibition of respiratory drive. Sleep-related hypoventilation due to a medical disorder (G47.36) Specific pulmonary disease: COPD, cystic fibrosis, and interstitial lung dis ease; other causes of abnormality in lung or vascular pathology, lower air ways obstruction, neuromuscular or chest wall disorders. Management • General: weight loss; avoidance of alcohol, nicotine, and other drugs. • Specific: treat the underlying disorder—approaches may include ventilation, home O2, surgery (e.g. bariatric procedures, diaphragmatic pacing, corrective surgery for kyphoscoliosis). • Medication: limited benefit—respiratory stimulants (acetazolamide, theophylline, medroxyprogesterone). Sleep-related hypoxaemia (G47.36) Characterized by periods of significantly reduced oxyhaemoglobin satur ation when sleep-related either hypoventilation is not present or the status is unknown. Causes relate to hypoventilation, V/Q mismatch, low partial pressure of O2, shunt, or a combination. • Management As for hypoventilation disorders—address the cause. Isolated symptoms and normal variants Snoring (R06.83) No apnoea, hypopnoea, RERAs, or hypoventilation. Symptoms—respiratory pauses, daytime sleepiness, fatigue, or insomnia. OSA needs to be ruled out (with PSG or OCST), especially if there is comorbid cardiovascular disease. Management—treatment of comorbidity, general measures, earplugs (for bed partners!), anti-snoring devices [nasal, oral, mandibular advancement devices [MADs)], rarely surgery (as for OSA). Catathrenia (G47.59) (‘sleep-related groaning’) Characterized by pro longed expiration, usually during REM and NREM sleep, with monotonous vocalization resembling groaning, prolonged bradypnoea, and/or cen tral apnoea, starting with the expiratory phase of the respiratory cycle and without oxyhaemoglobin desaturation. CPAP and sleep-consolidating pharmacotherapy may help. 12 In 2003, the paired-like homeobox 2B gene (PHOX2B) was found to be the disease-defining gene for CCHS (Amiel J, Laudier B, Attié-Bitach T, et al. (2003) Polyalanine expansion and frameshift mu tations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. Nat Genet 33:459–61). PHOX2B plays a key role in the development of the autonomic nervous system. For a detailed review see: Weese-Mayer DE, Berry-Kravis EM, Ceccherini I, et al. (2010) An official ATS clinical policy statement: Congenital central hypoventilation syndrome: genetic basis, diagnosis, and management. Am J Respir Crit Care Med 181:626–44.

448 Chapter 10 Sleep–wake disorders Hypersomnia 1: overview 0 Excessive sleepiness is a leading cause of RTAs. Essence ‘Hypersomnia’ covers a number of different forms of EDS. Patients may complain of ‘sleep attacks’ (recurrent daytime sleep episodes that may be refreshing or unrefreshing), ‘sleep drunkenness’ (prolonged transition to a fully aroused state on waking), lengthening of night-time sleep, almost constant EDS, and even recurrent periods of more or less permanent sleep lasting several days over several months. Diagnosis and treatment particularly

relevant when the individual works in an industry or profes sion where vigilance and concentration are essential (e.g. hospital workers, pilots, train drivers, the military). The most commonly used rating scale is the Epworth Sleepiness Scale (ESS) (see Table 10.2). DSM-5 differen tiates 'Hypersomnolence disorder' (with specifiers: with mental disorder; with medical condition; with another sleep disorder) and 'Narcolepsy' (with specifiers: with/without cataplexy, with/without hypocretin deficiency; autosomal dominant cerebellar ataxia, deafness, and narcolepsy; autosomal dominant narcolepsy, obesity, and type 2 diabetes; narcolepsy secondary to another medical condition). Prevalence Common: moderate (occasional) EDS reported in up to 15% in the general population (severe EDS 75%). Differential diagnosis • Sleep attacks in narcolepsy are usually irresistible and refreshing, whereas in other forms of hypersomnia, they tend to be more frequent, of longer duration, easier to resist, and unrefreshing. • The attacks also tend to occur in unusual, and often dangerous, situations in narcolepsy (e.g. talking, eating, standing, walking, or driving). • Disturbances and shortening of nocturnal sleep are more common in narcolepsy—in other causes of hypersomnia, nocturnal sleep is usually prolonged and there is difficulty in waking in the morning. • Always consider other conditions: Prader–Willi syndrome (PWS) (E Deletions and duplications syndromes, p. 808); syndrome of autosomal dominant cerebellar ataxia, deafness, and narcolepsy; delayed sleep-phase syndrome (E Circadian rhythm sleep-wake disorders, p. 454); autism; depression; diencephalic lesions; drug abuse; insufficient sleep syndrome (E Hypersomnia 3: other causes, p. 453); Kleine–Levin syndrome (E Hypersomnia 3: other causes, p. 452); medication effect (E Psychiatric medication and sleep, p. 482); Norrie disease (cataplexy

- monoamine oxidase deficiency); poor sleep hygiene; post-traumatic narcolepsy; i ICP (E Hypersomnia due to a medical condition, p. 452); and even conversion disorder, factitious disorder, and malingering (E Medically unexplained symptoms, p. 858).

Hypersomnia 1: overview Table 10.2 Epworth Sleepiness Scale (ESS)* Chance of dosing situation Scorea Sitting and reading 0 1 2 3 Watching television 0 1 2 3 Sitting inactive in a public place (e.g. in a theatre or a meeting) 0 1 2 3 As a passenger in a car for an hour without a break 0 1 2 3 Lying down to rest in the afternoon when circumstances permit 0 1 2 3 Sitting and talking to someone 0 1 2 3 Sitting quietly after a lunch without alcohol 0 1 2 3 In a car, while stopped for a few minutes in traffic 0 1 2 3 a Patient is instructed to use scale to choose the most appropriate number for each situation: 0 = no chance of dozing, 1 = slight chance, 2 = moderate chance, 3 = high chance. Maximum score on this scale is 24; however, scores of >10 often considered to be consistent with some degree of daytime sleepiness, while scores of >15 are considered to be consistent with EDS.

- Reprinted from Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 14: 540–5 with permission from Oxford University Press.

450 Chapter 10 Sleep–wake disorders Hypersomnia 2: narcolepsy Narcolepsy 1 (G47.411) First described by Westphal in 187713 and given its name by Gélineau in 1880,14 narcolepsy is now divided into two separate entities: narcolepsy 1 (with cataplexy) and narcolepsy 2 (without cataplexy). Narcolepsy seriously impacts on education, work, relationships, the ability to drive, and recre ational activities, and can have negative effects on self-esteem and mood. Prevalence The most common neurological cause of hypersomnia; estimated prevalence 0.20–0.40 per 1000 in the general population. ♂:♀ = 1.64:1. Age range: 10–50+ yrs—bimodal, with peaks at 15yrs and 35yrs (70–80% before 25yrs). Aetiology Genetic predisposition, abnormal neurotransmitter functioning

and sensitivity, and abnormal immune modulation. Recent research suggests human leucocyte antigen (HLA) subtypes and abnormal hypocretin (orexin) neurotransmission lead to abnormalities in monoamine and ACh synaptic transmissions, particularly in the pontine RAS. Clinical features • The classical 'tetrad' of symptoms—excessive sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations—are suffered by only a minority of patients with narcolepsy. • EDS and associated cataplexy (sudden bilateral loss of muscle tone, with preserved consciousness, triggered by a strong emotional reaction such as laughter or anger) are by far the most common complaints. More often, a cataplectic attack will be partial, e.g. involving jaw muscles (difficulty with articulation), facial muscles (grimacing), or thigh muscles (brief unlocking of the knees). Attacks vary from seconds to minutes, with a frequency of a few a year to several a day, and very rarely repeated 'status cataplecticus'. • Other REM sleep phenomena also occur but are not necessary for the diagnosis to be made. These include sleep paralysis (sometimes up to 10min long) and vivid hallucinations on falling asleep (hypnagogic) or, less commonly, on waking up (hypnopompic). • Sleep may also be disturbed due to frequent awakenings, disturbing dreams, sleep-talking, and REM-related sleep behaviours (from phasic muscle twitching to more dramatic dream enactment). ICSD-3 criteria • Daily periods of irrepressible need to sleep or daytime lapses into sleep, occurring for at least 3mths. • The presence of one or both of the following: (1) cataplexy and a mean sleep latency of ≤8 min and 2+ sleep-onset REM periods (SOREMPs) on MSLT; (2) CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay. 13 Westphal C (1877) Eigentümliche mit Einschlafen verbundene Anfälle. Arch Psychiat Nervenkrankeheiten 7:631–5. 14 Gélineau J (1880) De la narcolepsie. Gaz Hôp (Paris) 53:626–8; 635–7.

Hypersomnia 2: narcolepsy Course Usually chronic, although some of the symptoms may improve or remit. Hallucinations and sleep paralysis present variably, and sometimes cataplexy may disappear over time. Poor sleep quality tends to persist. Treatments are directed at the most troublesome symptoms. Investigations • PSG (sleep EEG and MSLT): SOREMP is highly specific (25–50% of cases); i N1 sleep and repeated awakenings (see E ICSD-3 criteria, p. 450). • CSF hypocretin-1 levels: levels ≤110pg/mL are highly specific and sensitive for narcolepsy with cataplexy (in 10%, levels may be normal or even high). • HLA typing: there is a strong association between HLA-DR2 haplotypes coded on chromosome 6 and narcolepsy—HLA DQB1*0602 and DQA1* 0102 are found in up to 85–95% of individuals, compared with 12–38% in the general population. • Imaging: MRI useful to exclude some rare causes of secondary narcolepsy (abnormalities of the brainstem and diencephalon). Management • Daytime somnolence Regular naps, stimulants (modafinil, methylphenidate, dexamfetamine). Possibly sodium oxybate (GHB). • Cataplexy TCAs (clomipramine 10–75mg/day is licensed) or SSRIs (and possibly other antidepressants: venlafaxine, nefazodone, mirtazapine, atomoxetine). These drugs may also improve REM-related symptoms, hypnagogic/hypnopompic hallucinations, and sleep paralysis. Note: abrupt withdrawal of antidepressants may potentially cause cataplectic episodes or even 'status cataplecticus'. Sodium oxybate is newly licensed for cataplexy (under specialist supervision); it is not associated with a rebound cataplexy on withdrawal but can cause significant side effects (nausea, nocturnal enuresis, confusional arousals, headache), and there is a danger of abuse. • Other treatments for poor sleep and REM-related symptoms: BDZs (e.g. clonazepam) and possibly sodium oxybate. Narcolepsy 2 (G47.419) Nocturnal sleep is usually less disturbed than in narcolepsy 1, but other symptoms may still be present, e.g. automatic behaviour, hypnic hallucin ations, or sleep paralysis. Cataplexy may develop later in the course of the disorder. Investigations and management as for

narcolepsy 1. ICSD-3 criteria • As for narcolepsy 1, but without cataplexy and CSF hypocretin-1 levels have not been measured or are >110pg/mL. • Symptoms cannot be explained by any other condition (E Differential diagnosis, p. 448).

452 Chapter 10 Sleep–wake disorders Hypersomnia 3: other causes Idiopathic hypersomnia (G47.12) Clinical features Objective EDS without cataplexy, and with no more than one SOREMP on MSLT, that cannot be explained by another disorder. Course A chronic condition with marked impact on social and occupa tional functioning. Diagnosis Detailed history (to exclude other causes of hypersomnia); PSG normal; MSLT <8min (longer than narcolepsy), <2 SOREMPs. Differential diagnosis Narcolepsy, sleep apnoea syndromes, periodic limb movement disorder (PLMD), or upper airways resistance syndrome. Management As for narcolepsy (but naps do not help). Kleine–Levin syndrome (G47.13) A rare syndrome of 'periodic somnolence and morbid hunger', occurring almost exclusively in ♂ adolescents (although a menstrual-related subtype is described), usually following a course of decreasing frequency of attacks, which may persist for many years before complete cessation. Clinical features Periods lasting from days to weeks of attacks of hypersomnia, accompanied by excessive food intake (megaphagia). Other behavioural symptoms may occur, including sexual disinhibition (which may appear compulsive in nature), along with a variety of other psychi atric symptoms such as confusion, irritability, restlessness, euphoria, hallu cinations, delusions, and schizophreniform states. Attacks may occur every 1–6mths, and last from 1 day to a few weeks. Between attacks, the patients recover completely, and the syndrome may easily be confused for other neurological, metabolic, or psychiatric disease. Management • Hypersomnia: stimulants (only effective for short periods of time). • Preventative measures: for sufficiently frequent episodes causing major disruption of social or occupational functioning—lithium, carbamazepine, or valproate. Hypersomnia due to a medical condition (G47.14) Differential diagnosis Neurological (altered ICP, diencephalic tu mours, thalamic infarcts, Parkinson's disease, MSA, NPH, Arnold– Chiari malformation, myotonic dystrophy, head injury—'post-traumatic hypersomnia': lesions (when they can be demonstrated) generally in volve the brainstem (the tegmentum of the pons or thalamic projections) or the posterior hypothalamus, infectious (EBV, atypical viral pneu monia, hepatitis B, Guillain–Barré syndrome, viral encephalitis, sleeping sickness (trypanosomiasis—sleepiness, headache, trembling, dyskinesias, choreoathetosis, mood changes), metabolic, and endocrine disorders (hypothyroidism, acromegaly, cause OSA).

Hypersomnia 3: other causes Hypersomnia due to a medication or substance (F10–19.x82) (E Psychiatric medication and sleep, p. 482.) Differential diagnosis Dependency-related sleep disorders (alcohol, hypnotics, opiates), toxins (arsenic, bismuth, mercury, copper, other heavy metals, CO, vitamin A), medication-related (e.g. anticonvulsants, antidepressants, anti-emetics, antihistamines, anti-Parkinsonian drugs, antipsychotics, anxiolytics/hypnotics, clonidine, methyldopa, prazosin, re serpine, hyoscine, progestogens). Hypersomnia associated with a psychiatric disorder (F51.13) (E Sleep–wake disorders related to psychiatric disorders 1, p. 478.) EDS due to underlying (undiagnosed) psychiatric disorder, e.g. bipolar II disorder, dysthymic disorder, seasonal affective disorder (SAD), undiffer entiated somatoform disorder, adjustment disorder, personality disorder. Prevalence May be the cause of up to 7% of hypersomnia referred to sleep centres. More common in women. Clinical features Marked reported EDS, high ESS scores, sleep perceived as poor quality and non-restorative, excessive time spent in bed during both day and night ('clinophilia'). Diagnosis Careful history essential. PSG (not usually necessary): i sleep latency, i wake time after sleep onset, low sleep efficiency (SE). MSLT usu ally normal.

Management Directed at the underlying psychiatric disorder. Insufficient sleep syndrome (F51.12) Persistently failing to obtain sufficient nocturnal sleep required to support normally alert wakefulness. Prevalence Unknown, but may be the most common cause of hypersomnia in the general population, particularly among parents of young children, doctors, students, long-distance lorry drivers, and other occupa tions where unsociable long hours of work are commonplace. Clinical features Periods of excessive sleepiness concentrated in the afternoon and early evening. Rest days usually characterized by late rising from bed and frequent naps. Associated reduced productivity, difficulty in concentration and attention, low mood or irritability, and somatic symp toms (usually GI or musculoskeletal). Diagnosis Made on history alone. Management Directed towards scheduling i time asleep, either at night or with regular short naps during the day. Isolated symptoms and normal variants Long sleeper (R29.81) Sleep is normal in architecture and quality but lasts longer than normal (i.e. >10hrs). The person may complain of EDS if they do not get their usual amount of sleep.

454 Chapter 10 Sleep–wake disorders Circadian rhythm sleep–wake disorders (CRSD) 1: overview Essence When an individual's sleep/wake schedule is not in synchrony with the sleep–wake schedule of their cultural environment or society, it may lead to complaints of insomnia or EDS, causing marked distress or interference with social or occupational functioning. ICSD-3 categories are used here, but it is worth noting that in DSM-5, 'jet lag' has gone and 'Circadian rhythm and sleep–wake disorders' includes: delayed sleep phase type (familial or overlapping with non-24-hour type), advanced sleep phase type (familial), irregular sleep–wake type, non-24-hour sleep–wake type, shift work type, and unspecified type. Investigations • Comprehensive history. • Use of a 14-day sleep–wake chart. • Actigraphy—objective measurement of the rest–activity cycle. • Physiological measures of endogenous circadian timing (e.g. salivary or plasma dim light melatonin onset and urinary 6-sulphatoxymelatonin) can be useful. • PSG is rarely needed.
Differential diagnosis • Poor sleep hygiene. • Depressive disorder. • Misuse of drugs (particularly stimulants or sedatives) and alcohol. Note: lifestyle factors are also clearly important. • Physical conditions such as: dementia, head injury, other causes of brain damage or injury, and recovery from coma. Delayed sleep–wake phase disorder (DSWPD) (G47.21) The late appearance of sleep (typically around 2 a.m.), but normal TST and architecture, which may lead to complaints of sleep-onset insomnia and difficulty awakening at the desired time in the morning. Some cases are related to head injury, psychiatric disorder, or personality traits (e.g. schizoid, avoidant). Predisposing/precipitating factors: evening chronotype, adolescent age, polymorphism in the circadian clock gene hPer3, d exposure to light in the morning or i exposure to bright light late in the evening, changes in work and social schedules, travel across time zones, and shift work. Usually presents in adolescence, running a continuing course until old age. Individuals may adapt to the condition by taking evening or night jobs. Advanced sleep–wake phase disorder (ASWPD) (G47.22) The opposite of DSWPD, this syndrome leads to complaints of evening sleepiness, early sleep onset (e.g. 18.00–20.00), and early morning wakening. May be confused with depression (due to early morning wakening), particularly in elderly patients in whom the syndrome occurs

455 CIRCADIAN RHYTHM SLEEP–WAKE DISORDERS 1: OVERVIEW more frequently. Although heritability is evident in some families, definite genes have not been identified. ASWPD has also been observed in children with neurodevelopmental disorders (ASD and Smith–Magenis syndrome) with abnormal melatonin secretion profiles. Irregular sleep–wake rhythm disorder (G47.23) Sleep occurrence and waking behaviour are very variable, leading to con siderable disturbance of the

normal sleep–wake cycle and complaints of insomnia (inadequate nocturnal sleep and EDS/frequent napping). The idio pathic form is rare, and it is associated with old age, neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, Huntington's disease), head injury, neurodevelopmental disorders in children, and hypothalamic tumours. In institutionalized individuals (especially the elderly), this disorder can be related to poor sleep hygiene and insufficient exposure to synchron izing agents (light, activity, and social schedules). Non-24-hr sleep–wake rhythm disorder (G47.24) Rare occurrence of a >24-hr sleep–wake period (also called 'free-running' or 'non-entrained'), leading to a chronic pattern of 1–2hr daily delays in sleep onset and wake times, with an 'in-phase' period every few weeks (free of symptoms). Common in totally blind individuals. In non-blind patients, some environmental conditions can lead to its appearance (insufficient or time-inappropriate exposure to circadian-entraining agents such as light). DSWPD may predispose, and it may occur after chronotherapy in adults with TBI. Also associated with schizoid personality traits. Shift work disorder (F51.22) Symptoms of insomnia or excessive sleepiness occur as transient phe nomena in most people working shifts. Adaptation to a change in shift work schedule usually takes 1–2wks; however, rotating day/night shifts may pre sent particular difficulties. Often sufferers consult with somatic complaints (general malaise, GI upset), rather than the underlying disorder of sleep. Predisposing/precipitating factors: chronotype, presence of other sleep disorders (e.g. OSA), and social pressures. Jet lag disorder (F51.21) Sleep disorder secondary to moving between time zones. Symptoms in clude varying degrees of difficulty in initiating or maintaining sleep, daytime fatigue, decrements in subjective daytime alertness and performance, feel ings of apathy, malaise, or depression, and somatic symptoms (GI upset, muscle aches, or headaches). Circadian rhythm sleep–wake disorder NOS (G47.20) The specific criteria for one of the circadian rhythm sleep–wake disorders listed in the previous sections are not met. This category includes those with alterations in circadian sleep–wake patterns due to underlying medical, neurological, and psychiatric disorders.

456 Chapter 10 Sleep–wake disorders Circadian rhythm sleep–wake disorders 2: management15 General measures These include education about the nature of sleep and establishing good sleep habits. This is particularly important for shift work sleep disorder in which alcohol, nicotine, and caffeine may be used to self-medicate symp toms. Other advice for shift workers should emphasize maintenance of regular sleep and mealtimes, whenever possible, use of naps to limit sleep loss, and minimization of environmental factors (noise, light, other interrup tions) when sleeping during the day. Chronotherapy DSWPD • Establishing a regular waking time, with only 1hr variability at weekends and holidays, may help initially. • If unsuccessful, 'phase-delay'16 methods may be employed to achieve a phase shift of the sleep–wake cycle. This involves: • Establishing a 27-hr day to allow progressive delay of the usual onset of sleep by about 3hrs in each sleep cycle. • Sleep should only be permitted for 7–8hrs, with no napping. • Disruption to the person's normal routine caused by undergoing this regime (which may take 5–7 days to complete) requires appropriate measures to be taken to ensure other family and work commitments are attended to. • An alternative strategy is to advise the individual to remain awake at the weekend for one full night, and to go to bed the next evening 90mins earlier than usual. • Sleep periods should again be limited to 7–8hrs, with no napping. • The procedure can then be repeated each weekend until normal bedtime is achieved. ASWPD • Delaying sleep onset by increments of 15mins may be effective. • Alternatively, 'phase-advance'17 methods may be used: • The patient goes to bed 3hrs earlier each night until the sleep cycle is advanced back to normal bedtime. • May be difficult to implement, particularly with elderly patients. 15 Auger RR, Burgess HJ, Emens JS, Deriy LV, Thomas

SM, Sharkey KM (2015) Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders: Advanced Sleep- Wake Phase Disorder (ASWPD), Delayed Sleep-Wake Phase Disorder (DSWPD), Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD), and Irregular Sleep-Wake Rhythm Disorder (ISWRD). An Update for 2015: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 11:1199–236. 16 Czeisler CA, Richardson GS, Coleman RM, et al. (1981) Chronotherapy: resetting the circadianclocks of patients with delayed sleep phase insomnia. Sleep 4:1–21. 17 Moldofsky H, Musisi S, Phillipson EA (1986) Treatment of a case of advanced sleep phase syn drome by phase advance chronotherapy. Sleep 9:61–5.

457 CIRCADIAN RHYTHM SLEEP–WAKE DISORDERS 2: MANAGEMENT Light therapy This includes both the use of bright light (2500–10,000lx), with ultraviolet (UV) rays filtered out, and light restriction. Bright light is assumed to sup press melatonin (which is sleep-promoting). DSWPD Exposure to bright light is scheduled on waking to prevent morning leth argy, usually for 2hrs daily for 1wk, often with adjunctive light restriction after 4 p.m. ASWPD Exposure to bright light is recommended 2hrs before the scheduled bed time, to delay this to a more sociable time.
Other disorders Evidence for the effectiveness of light therapy in other intrinsic circadian rhythm disorders of sleep (e.g. shift work sleep disorders, jet lag) is lacking, with the exception perhaps of the elderly with dementia and irregular sleep–wake rhythm disorder (alone or in combination with melatonin). Medication • Short-acting BDZ/hypnotics: • Should not be used in the elderly with dementia. • May help entrain circadian rhythms if appropriately timed in the treatment of jet lag (e.g. lormetazepam, zolpidem).18 • Melatonin (0.5–5mg): • Strategically timed administration may improve non-24-hr sleep–wake rhythm disorder in blind adults and irregular sleep–wake rhythm disorder in children/adolescents with neurological disorders. • May help in advancing the sleep phase and resetting the circadian rhythm in travellers with jet lag syndrome flying across five or more time zones, particularly in an easterly direction and especially if they have experienced jet lag on previous journeys.19 • Weak evidence of efficacy in DSWPD in: adults with or without depression and children/adolescents with or without psychiatric comorbidity. 18 Herxheimer A (2014) Jet lag. BMJ Clin Evid 2014:2303. 19 Herxheimer A, Petrie KJ (2002) Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev 2:CD001520.

458 Chapter 10 Sleep–wake disorders Parasomnias: overview Essence Parasomnias may be defined as undesirable physical and/or experiential phe nomena accompanying sleep. They include unusual behaviours and motor acts, autonomic changes, and/or emotional–perceptual events. Sometimes these events occur when arousal is incomplete or they are associated with REM sleep. Other episodes may arise during the transition from sleep to wakefulness or from wakefulness to sleep, or in transitions between sleep stages. They can usu ally be objectively diagnosed using PSG and successfully treated. Parasomnias are of academic interest, as they may provide insights into the biological under pinnings of species-specific behaviours such as locomotion, exploratory behav iour, appetitive states (hunger, sexual arousal), fear, and aggression, that may be released from control during sleep, itself a biological imperative. Points to note • The often ‘bizarre’ nature of the parasomnias frequently leads them to being misdiagnosed as psychiatric disorders, particularly if they appear temporally related to stressful situations. • This may, in turn, lead to inappropriate treatment, with associated problems, including exacerbation of the parasomnia. • Often there will be associated psychological distress or psychiatric problems secondary to the parasomnia. • Rarely there may also be forensic implications, e.g. due to SRV (E Sleep-related violence, p. 472), sexual activity (E Box 10.6, p. 463), or even driving (see Box 10.5 p. 461). Classification of parasomnias

ICSD-3 categories • NREM-related parasomnias: disorders of arousal, confusional arousals, sleepwalking, sleep terrors, sleep-related eating disorder (SRED). • REM-related parasomnias: REM sleep behaviour disorder (RBD), recurrent isolated sleep paralysis, nightmare disorder. • Other parasomnias: exploding head syndrome, sleep-related (hypnic) hallucinations, sleep enuresis, due to a medical disorder, due to medicine or substance, and unspecified. • Isolated symptoms and normal variants: sleep-talking. DSM-5 categories • Non-REM sleep arousal disorders (sleepwalking type, with/without sleep- related eating/sexual behaviour; sleep terror type). • Nightmare disorder (during sleep onset; with associated non-sleep disorder/medical condition/other sleep disorder). • REM sleep behaviour. • Restless legs syndrome (RLS) (E Restless legs syndrome (Willis–Ekbom disease) (RLS/WED) (G25.81), p. 474). ICD-10 There is no specific section for parasomnias in Section F, but sleepwalking, sleep terrors, and nightmares are listed. In Section G, parasomnias are listed—unspecified, confusional arousal, RBD, recurrent isolated sleep par alysis, in conditions classified elsewhere, and other.

Parasomnias: overview Parasomnia overlap disorder • Clinical features: the occurrence of disorders of NREM sleep (e.g. sleepwalking, sleep terrors), along with RBD.20 • Prevalence: 70% of cases are young men (mean age 34yrs). Idiopathic cases, occurring at a younger age, are associated with other medical (brain injury, nocturnal paroxysmal AF), psychiatric (PTSD, depression, schizophrenia), or substance abuse (alcohol, amphetamine) disorders. • Associated disorders: no i risk of psychiatric disorder. Status dissociatus (E Status dissociatus/agrypnia excitata, see below). • Differential diagnosis: confusional arousals and sleepwalking co-occurring with RBD; dream enactment behaviour (in the general population or patients with NREM-related parasomnias). • PSG: NREM sleep instability with a lack of REM sleep atonia (at times with dream enactment behaviours). • Management: resolve any comorbid condition that may be fragmenting sleep (e.g. sleep-disordered breathing, drugs, or alcohol). Customized bed alarm may help prevent sleep-related injury. Clonazepam (0.5–2mg nocte) may be effective, particularly when there is violent dream- enacting behaviour. Status dissociatus/agrypnia excitata Agrypnia (Greek: to chase sleep) excitata (AE)21 or ‘status dissociatus’ is a syndrome regarded as an extreme form of parasomnia overlap where fea tures of NREM sleep, REM sleep, and wakefulness coexist. • Clinical features: (1) disruption of the sleep–wake rhythm (disappearance of spindle-delta activities, persistence of N1 sleep, short bursts of REM sleep); (2) diurnal and nocturnal motor, autonomic, and hormonal over- activity (excitata), with markedly elevated NA secretion (associated with sweating, tachypnoea, and hypertension) and lack of the nocturnal melatonin peak; (3) oneiric stupor (‘wakeful dreaming’)—recurrence of stereotyped gestures mimicking simple daily life activities. • Associated disorders: AE is seen in such diverse conditions as FFI—an autosomal dominant prion disease; Morvan syndrome (MnS)—an autoimmune encephalitis; and delirium tremens (DT)—alcohol withdrawal syndrome. • Aetiology: AE is due to an intralimbic disconnection releasing the hypothalamus and brainstem reticular formation from cortico-limbic inhibitory control. In FFI, the pathogenic mechanism is thalamic degeneration; in MnS, it may depend on auto-antibodies blocking VGKCs within the limbic system; and in DT, sudden changes in GABA synapses down-regulated by chronic alcohol abuse. 20 Schenck CH, Boyd JL, Mahowald MW (1997) A parasomnia overlap disorder involving sleep walking, sleep terrors, and REM sleep behavior disorder in 33 polysomnographically confirmed cases. Sleep 20:972–81. 21 Provini F (2013) Agrypnia excitata. Curr Neurol Neurosci Rep 13:341.

460 Chapter 10 Sleep–wake disorders NREM-related parasomnias 1 Disorders of arousal (from NREM) (G47.59) • Clinical features: recurrent episodes of incomplete awakening from sleep, with inappropriate or absent responsiveness when others intervene or try to redirect, limited or no associated cognition or dream imagery, and partial or complete amnesia for the episode. Very common and usually can be managed solely with sleep hygiene measures. Confusional arousals ('sleep drunkenness') (G47.51) • Clinical features: confusion during and following arousals from sleep, most typically from deep sleep in the first part of the night. Individuals appear disorientated, incoherent, hesitant, and slow but may walk about, get dressed, and even perform complex motor behaviours. Violence, assault, and even homicide may occur (rare: planning or premeditation is not possible). • PSG: arousal from NREM sleep, usually in first third of the night. • Prevalence: almost universal in young children (under 5yrs), becomes less common in older childhood. Fairly rare in adulthood, usually occurring in the context of sleep deprivation, exacerbated by alcohol or other depressant drugs. • Associated disorders: sleep-related breathing disorders, narcolepsy, idiopathic hypersomnia, encephalopathy. • Differential diagnosis: acute confusional states, sleep terrors (evident autonomic arousal), sleepwalking (usually docile, not aggressive when challenged), and RBD (evident dream enactment; E REM-related parasomnias, p. 464). • Management: • Prevent the patient from falling into deep, prolonged NREM sleep— avoid sleep deprivation. • Restrict use of alcohol and other sedative drugs (illicit and prescribed). • Sleep hygiene measures (E Insomnia 2: general management strategies, p. 442). Sleepwalking (somnambulism) (F51.3) • Clinical features: complex, automatic behaviours (automatisms) [e.g. aimless wandering, attempting to dress or undress, carrying objects, eating (E Sleep-related eating disorder (G47.59), p. 462), urinating in unusual places, and rarely driving a car (see Box 10.5) or sexual behaviour (see Box 10.6)]. Episodes often follow a period of sleep deprivation or i stress. There is often a personal and/or family history of sleepwalking or other related disorders. Behaviours of variable duration usually occur 15–120min following sleep onset but may occur at other times. Eyes usually wide open and glassy, and talk is incoherent, with communication usually impossible. Injury may occur (e.g. falling down the stairs, exiting through a window). Activity never appears intentional or planned, and only rarely aggressive behaviour occurs. The person is usually easily returned to bed, falls back into normal sleep, and has no recollection of the episode the following morning. If awakened during the episode—confused and disorientated. Dream content (if present) is fragmented, without specific themes.

NREM-related parasomnias 1 • PSG: light, NREM sleep, with episodes sometimes preceded by hypersynchrony of generalized (non-epileptic) high-voltage delta waves. • Prevalence: up to 17% in childhood (peak age 4–8yrs); 4–10% in adults. Familial forms do occur. Precipitants similar to confusional arousals. • Associated disorders: sleep-related breathing disorders, PLMD, nocturnal seizures, medical/neurological disorders, febrile illness, alcohol use/ abuse, pregnancy, menstruation, psychiatric medication (lithium, anticholinergics), stress (no specific psychiatric illness). • Differential diagnosis: confusional arousals, episodic wandering (N2 sleep, second half of the night), epileptic fugue states, and RBD in the elderly. • Management: • Reassurance. • Protect the patient from coming to harm (e.g. closing windows, locking doors, sleeping downstairs). • Relaxation techniques and minimization of stressors. • Sleep hygiene measures (E Insomnia 2: general management strategies, p. 442). • Avoidance of sleep deprivation. • Medication—for patients with frequent episodes/high-risk behaviours: small night-time doses of a BDZ (e.g. diazepam 2–10mg, clonazepam 1–4mg) or a low-dose sedating antidepressant at night. Note: treatment of any concurrent psychiatric disorder does not control the parasomnia. Box 10.5 Sleep

driving and the Z-drugs Sleep driving is regarded as a highly unusual variant of sleepwalking but may be confused with impaired driving due to misuse or abuse of seda tive/hypnotic drugs when the driver may appear ‘asleep’. The majority of case reports relate to the Z-drugs1—especially zolpidem and zopiclone— and drivers have excessively high blood levels of Z-drugs, fail to take the medication at the correct time, or remain in bed for sufficient time and/ or combined Z-drugs with other CNS depressants/alcohol. True sleep driving can be distinguished by the fact that sleepwalkers are completely unable to understand or interact with the police but can stand and walk unaided. In contrast, drivers under the influence of sedative drugs are still able to respond to the police but are unable to stand up or maintain balance. If in doubt, sleep studies may be indicated, especially if there are significant legal proceedings. Treatment of sleep driving is as for sleep walking (E NREM-related parasomnias 1, p. 460). 1 Pressman MR (2011) Sleep driving: sleepwalking variant or misuse of z-drugs? Sleep Med Rev 15:285–92.

462 Chapter 10 Sleep–wake disorders NREM-related parasomnias 2 Sleep terrors (parvor nocturnes, incubus) (F51.4) • Clinical features: sudden awakening with loud, terrified screaming (the person may sit up rapidly), with marked autonomic arousal (tachycardia, tachypnoea, diaphoresis, mydriasis). Sometimes frenzied activity occurs—may lead to injury. Episodes usually last for 10–15min, with increase in muscle tone and resistance to physical contact. If wakened, individual appears confused and incoherent, but soon falls asleep, wakening next morning with no memory of the event. In children, usually occurs in the first third of the night. In adults, can occur at any time of the night. • PSG: abrupt wakening out of N3 sleep is seen on EEG, with generation of α activity, usually in the first third of the night. Partial arousals out of N3, occurring up to 10–15 times in one night, are also seen, even when a full episode is not recorded. • Prevalence: children—3%, adults—1% (may be more common in ♂), evidence for heritability. Deep and prolonged N3 is a predisposing factor, precipitated by fever, sleep deprivation, and depressant medication. • Associated disorders: as for sleepwalking. • Differential diagnosis: nightmares, nocturnal epilepsy, nocturnal panic attacks (NPs) (see Box 10.7 for drugs that cause vivid dreams or nightmares). • Management: reassure the individual (and partner/parents) of the benign character of the disorder. If episodes are frequent (more than once a week), use similar methods as for sleepwalking. Sleep-related eating disorder (G47.59) First reported in 1955; received very little attention until more recently. SRED22 is usually described in 20- to 30-yr-old women. Consists of re current episodes of involuntary eating and drinking during partial arousals from sleep. • Clinical features: sometimes there may be particularly unusual consumption of inedible (pica), or even toxic, substances such as raw meat, frozen pizza, or pet food. Sleep is disrupted, and patients report often significant (sometimes unexplained) weight gain. • PSG: reports show multiple confusional arousals with or without eating, arising predominantly from N3 sleep, but also occasionally from N1, N2, and REM sleep. • Differential diagnosis: can be either idiopathic or comorbid with other sleep disorders, e.g. sleepwalking, RLS-PLMD, OSA, narcolepsy, circadian rhythm disorders. Various medications associated with SRED, e.g. triazolam, zolpidem, olanzapine, and risperidone. • Management: treatment is best directed at any comorbid sleep disorder and cessation of provoking medication. If pharmacotherapy is indicated, case reports suggest use of: topiramate, dopaminergics, clonazepam, and fluoxetine. 22 Howell MJ, Schenck CH, Crow SJ (2009) A review of nighttime eating disorders. Sleep Med Rev 13:23–34.

NREM-related parasomnias 2 Box 10.6 The curious case of sexsomnia, ‘sleepsex’, or somnambulistic sexual behaviour Regarded as an NREM-related parasomnia variant, as most cases

have also been diagnosed with confusional arousals alone, but on occasion with sleepwalking, sleep-related driving (see Box 10.5), or SRED. The sorts of sexual behaviour seen during sleep can include:1 explicit vocalizations (with sexual content), violent masturbation, and complex sexual activities, including oral sex and vaginal or anal intercourse. Sexual behaviour during sleep may be associated with injury to the subject or his/her bed partner, when it is a special form of SRV (E Sleep-related violence, p. 472). Sexsomnia appears more common in men. There are sex differences in presentation, with women almost exclusively engaging in masturbation and sexual vocalizations, whereas men are more likely to engage in sexual fondling and intercourse. It can be quite challenging to distinguish between typical sleepwalking and sexsomnia, but uniquely there is often involve ment of a partner who is usually more than a witness. Most people with this disorder have a previous and/or family history of sleepwalking. PSG is necessary to confirm diagnosis, and diagnoses associated with sexual behaviour during sleep include not only NREM sleep somnambulism, but also RBD and frontal lobe seizures. Treatment involves general measures of good sleep hygiene and addressing precipitating factors such as sleep deprivation, drug misuse, alcohol, stress, RLS, and OSA. If medication is being considered, evidence supports the use of clonazepam (0.5–2mg nocte), sertraline, valproic acid, and lamotrigine. 1 Anderson ML, Poyares D, Alves RSC, et al. (2007) Sexsomnia: abnormal sexual behaviour during sleep. Brain Res Rev 56:271–82. Box 10.7 Drugs associated with vivid dreams or nightmares • Baclofen • β-blockers (atenolol, propranolol) • Clonidine • Digoxin toxicity • Famotidine • Indometacin • Methyldopa • Nalbumetone • Nicotine patches • Pergolide • Reserpine • Stanozolol • Verapamil • Withdrawal (alcohol, BDZs, opiates, and other hypnotics)

464 Chapter 10 Sleep–wake disorders REM-related parasomnias REM sleep behaviour disorder (G47.52) • Clinical features: vivid, intense, action-packed, violent dreams (reported as ‘nightmares’), dream-enacting behaviours (verbal and motor), sleep injury (ecchymoses, lacerations, fractures—of self and bed partner), general sleep disruption.23 • PSG: elevated submental EMG tone and/or excessive phasic submental/ limb EMG twitching during REM sleep, in the absence of EEG epileptiform activity. • Prevalence: a rare sleep disorder, more common in older ♂. • Associated disorders: over 80% associated with synucleinopathies (see Box 10.8); narcolepsy type 1 (characterized by lack of sex predominance, less complex and more elementary movements and less violent behaviour in REM sleep, earlier age of onset, and hypocretin deficiency); rarely associated with other psychiatric disorders but may be induced or aggravated by psychiatric drugs (e.g. TCAs, MAOIs, high-dose SSRIs, SNRIs), cessation/misuse of REM-suppressing agents (e.g. alcohol, amphetamine, cocaine), or severe stress related to traumatic experiences. • Differential diagnosis: sleepwalking, sleep terrors, nocturnal dissociative disorders, nocturnal epilepsy, OSA (where arousals from REM sleep associated with aggressive behaviour and vivid REM-related dreams), states of intoxication, malingering. • Management: • Ensure a safe sleeping environment (for the patient and sleeping partner). • Eliminate any factors that might be inducing or aggravating the condition (including treatment of any primary neurological, medical, or psychiatric disorder). • If symptoms persist and are problematic, clonazepam (0.5–1.0mg nocte) is the treatment of choice, effectively controlling both behaviours and dreams, with good evidence of long-term safety and sustained benefit. Alternatives include carbamazepine, melatonin, levodopa, and imipramine. Recurrent isolated sleep paralysis (G47.52) • Clinical features: the frightening experience of being unable to perform voluntary movements either at sleep onset (hypnagogic or pre-dormital form) or awakening (hypnopompic or post-dormital form), either during the night or in the morning. • PSG: atonia in peripheral muscles (as in REM sleep) despite desynchronized EEG

with eye movements and blinking (i.e. awake). H- reflex activity is also abolished during an episode (as in REM sleep). • Prevalence: as an isolated phenomenon, reported to occur at least once in the lifetime of 40–50% of normal individuals (usually due to sleep deprivation). As a chronic complaint, however, it is much less common. Familial sleep paralysis (without sleep attacks or cataplexy) is exceptionally rare. 23 Schenck CH, Mahowald MW (2002) REM sleep behavior disorder: clinical, developmental, and neuroscience perspectives 16 years after its formal identification in sleep. Sleep 25:120–38.

REM-related parasomnias • Differential diagnosis: narcolepsy (occurs in up to 40% of cases), periodic hypokalaemia (in adolescents, following a high carbohydrate meal, and with low-serum potassium levels during the attack). • Management: • Sleep hygiene (E Insomnia 2: general management strategies, p. 442), especially avoidance of sleep deprivation, may help to prevent episodes. • Persistent problems may respond to REM-suppressant medication (e.g. clomipramine 25mg or an SSRI). Nightmare disorder (F51.5) • Clinical features: frightening dreams that usually awaken the sleeper from REM sleep, without associated confusion. May be preceded by a frightening or intense real-life traumatic event. • PSG: i REM density, lasting about 10min, terminated by an awakening, usually in the second half of the night. • Prevalence: common (occasional occurrence in 750% of adults). Frequent nightmares (one or more a week) occur in about 1% of adults. • Differential diagnosis: sleep terrors, RBD, NPs (E Nocturnal panic attacks, p. 470), drug and medication side effects (see Box 10.7). • Management: treatment usually unnecessary. If episodes are frequent, distressing, or causing major disturbance to the individual's carers or bed partner—general measures: avoidance of stress, discontinuation of drugs that may potentially promote nightmares (see Box 10.7), principles of sleep hygiene (E Insomnia 2: general management strategies, p. 442); medication: REM-suppressing drugs (e.g. antidepressants). Note: sudden discontinuation may lead to exacerbation of the problem with REM rebound. Box 10.8 RBD and synucleinopathies Recent reports support the association between RBD and synucleinopathies, a set of neurodegenerative disorders that share a common pathological lesion composed of aggregates of insoluble asynuclein protein in selectively vulnerable populations of neurons and glial cells. The major synucleinopathies include Parkinson's disease, DLB, and MSA.1 Emergence of these disorders, often more than a decade after the onset of idiopathic RBD, is very common. Over 80% of patients with idiopathic RBD develop Parkinsonism/dementia, and conversely the rate of RBD in MSA is >90%, in DLB 50%, and in Parkinson's disease 46%. The fact that a sleep disorder might herald the full expression of a neurodegenerative disease means that an accurate diagnosis could allow early detection and possible early intervention (if such treatments could be developed) to stop or slow neurodegenerative deterioration before motor and cognitive symptomatology emerge. 1 Iranzo A, Santamaria J, Tolosa E (2016) Idiopathic rapid eye movement sleep behaviour disorder: diagnosis, management, and the need for neuroprotective interventions. Lancet Neurol 15:405–19.

466 Chapter 10 Sleep–wake disorders Other parasomnias Exploding head syndrome (G47.59) Despite its name,24 a benign condition characterized by the experience of a loud noise or the sense of an explosion in the head while falling asleep or awakening. May be associated with seeing a bright flash of light and occa sionally with pain. Management is usually just education and reassurance, but case reports suggest efficacy of pharmacotherapy (e.g. clomipramine, flunarizine, nifedipine, topiramate, carbamazepine, methylphenidate). Sleep-related hallucinations (R29.81) Not due to narcolepsy or other primary disorder (e.g. Parkinson's disease or dementia), these

hypnic hallucinations occur more frequently in adoles cents and young adults and may be associated with sleep-onset REM. Often are vivid enough to cause the person to react by jumping out of bed and may lead to injury. Sleep enuresis (N39.44) Also known as nocturnal enuresis or bedwetting; there are repeated epi sodes of involuntary micturition during sleep. Normal in infants and children under 5yrs; criteria require 2+ episodes per week. May be a secondary symptom in patients with PTSD, victims of abuse, and those with other medical conditions (e.g. diabetes). For management, see E Enuresis, p. 680. Parasomnia due to medical disorder (G47.54)/due to medication or substance (F10-19.x82)/unspecified (G47.50) These categories capture other parasomnias secondary to medical dis orders, medication, other substances, and unknown causes. 24 Coined in 1920 by the Welsh physician and psychiatrist Robert Armstrong-Jones. A more de tailed description was published in 1989 by the British neurologist John MS Pearce in the Journal of Neurology, Neurosurgery, and Psychiatry. For a recent review, see: Sharpless BA (2014) Exploding head syndrome. Sleep Med Rev 18:489–93.

Parasomnias: isolated symptoms and normal variants Parasomnias: isolated symptoms and normal variants Sleep-talking (somniloquy) (G47.8) The common uttering of words or sounds during sleep, without subjective awareness, and speech generally devoid of meaning. Rarely, emotionally charged long ‘tirades’ occur, with content related to the person’s occupa tion or preoccupation. • PSG: brief partial arousal during non-REM sleep is usually seen on EEG in about 60% of cases. Less commonly, somniloquy may occur during REM sleep, if related to dream content or in association with another disorder of REM sleep. • Associated disorders: confusional arousals, sleep terrors, RBD, SRED. • Management: unless the problem is leading to disruption of sleep in a bed partner or is a secondary symptom of other sleep pathology, treatment is rarely necessary. Sleep-related dissociative disorders (See Box 10.9.) Box 10.9 Sleep-related dissociative disorders First reported in 1976,1,2 there is usually a history of traumatic life events such as repeated physical and/or sexual abuse in childhood and/or adult hood. Dissociation also occurs during the day and may be associated with self-harm behaviours. Because they occur during wakefulness (as seen on EEG), they have not been included in parasomnia classifications. They are also known as dissociative pseudoparasomnias, nocturnal (psychogenic) dissociative disorders, and hysterical somnambulistic trance. They should not be confused with status dissociatus (E Status dissociatus/agrypnia excitata, p. 459). • PSG: complex and lengthy behaviours; appear to be re-enactments of previous trauma/abuse; occur during wakefulness after an episode of sleep. • Differential diagnosis: other disorders of arousal (these occur immediately on arousal, whereas dissociative disorders arise 15–60s after arousal, i.e. wakefulness). • Management: treatment involves long-term therapy for the dissociative disorder, which may require inpatient assessment. Night-time BDZs may exacerbate the problem and are best avoided. 1 Schenck CH, Milner DM, Hurwitz TD, et al. (1989) Dissociative disorders presenting as somnambulism: polysomnographic, video and clinical documentation (8 cases). Dissociation 2:194–204. 2 Rice E, Fisher C (1976) Fugue states in sleep and wakefulness: a psychophysiological study. J Nerv Ment Dis 163:79–87.

468 Chapter 10 Sleep–wake disorders Sleep-related epilepsy Both sleep and sleep deprivation may activate epileptiform discharges.25 Indeed there are some epilepsies that occur almost exclusively during sleep. It is generally accepted that NREM is a facilitator of seizure activity (due to progressive neuronal synchronizations that occur in deep sleep stages), whereas REM sleep is a suppressor. Sleep deprivation is thought to increase neuronal excitability and precipitates seizures,

especially in pa tients with awakening epilepsies. Epilepsies with a clear association with sleep occur in West syndrome, Lennox–Gastaut syndrome, benign epilepsy with centrotemporal spikes (BECTS), Panayiotopoulos syndrome, electrical status epilepticus during slow sleep (ESES), genetic generalized epilepsies [e.g. juvenile myoclonus epilepsy (JME), epilepsy with tonic–clonic seizures on awakening], nocturnal frontal lobe epilepsy (NFLE), and other focal noc turnal epilepsies. Nocturnal frontal lobe epilepsy NFLE is of particular interest because it may be confused with NREM parasomnias (sleepwalking and night terrors). It is a frontal lobe epilepsy, in which >90% of attacks occur during sleep (usually NREM). Idiopathic, spor adic, familial, or symptomatic forms exist. In fact, it was the first epilepsy in which a genetic basis was detected. The genetic form is heterogenous with autosomal dominant inheritance (ADNFLE). The most frequent (712%) mu tations involve genes coding for subunits of the heteromeric neuronal nico tinic AChRs (nAChRs), and the most frequent aetiology of symptomatic forms is type II focal cortical dysplasia. NFLE usually presents before 20yrs with different types of seizures: (1) brief stereotyped movements of the limbs, axial musculature, or head; (2) paroxysmal arousals that are sudden and brief (5–10s), sometimes accompanied by stereotyped movements, vo calizations, frightened expression, or fear; and (3) major attacks, (lasting 20–30s) with tonic or dystonic posturing, or complex movements such as pelvic thrusting, pedalling, or more violent movements of limbs. Nocturnal PSG with audiovisual recording is often normal, and when the diagnosis is unclear, sphenoidal electrode recording can be helpful. Management Treatment of sleep-related epilepsy involves anticonvulsant drugs, BDZs, high-dose steroids, and, for resistant cases, neurosurgery. Other sleep disorders that may worsen epilepsy (e.g. OSA or insomnia) should be ad equately treated to improve seizure frequency. It is worth noting that noc turnal seizures are an independent risk factor for sudden unexpected death in epilepsy (SUDEP), with 56% of events occurring during sleep. Compliance with medication, adequate control of seizures during sleep (especially gen eralized tonic–clonic seizures), night supervision, use of monitoring devices, avoiding prone position, and treating sleep disorder comorbidities all help to reduce the risk of this fatal complication of epilepsy. 25 Carreño M, Fernández S (2016) Sleep-related epilepsy. Curr Treat Options Neurol 18:23.

Sleep-related epilepsy 469

470 Chapter 10 Sleep–wake disorders Nocturnal panic attacks Clinical features Although not included under NREM-related parasomnias, NPs26 may be difficult to distinguish from other sleep disorders and are characterized by waking from NREM sleep, with no obvious trigger, in a state of intense fear or discomfort, accompanied by cognitive and physical (autonomic) symp toms of arousal. Symptoms as for panic disorder (E Panic disorder 1: clin ical features, p. 368). Avoidance of sleep may lead to delayed sleep onset and chronic sleep deprivation. Polysomnography • Usually occurs in late N2 or early N3 sleep (particularly during the transition). Prevalence • Lifetime prevalence may be 3–5% in non-clinical populations. NPs are common among patients with panic disorder (44–71%). Risk factors • Periods of sleep deprivation, withdrawal from alcohol/drugs (especially BDZs, antidepressants); mitral valve prolapse; stimulant use (including caffeine). Aetiology • Physiological—respiratory drive dysregulation, possibly due to extreme hypercapnia or chronic hyperventilation; heart rate variability during NREM sleep. • Psychological—i discomfort related to relaxation, fatigue, and ‘letting go’ (possible fear of loss of vigilance); low-level somatic sensations of arousal or anxiety act like conditioned stimuli during sleep to elicit fear response and panic. Associated disorders • Panic disorder, PTSD, depressive disorder, other anxiety and related disorders, alcohol and substance misuse. Differential diagnosis • Panic attacks (after

awakening), nightmares (during REM sleep), withdrawal syndromes (especially BDZs), sleep terrors, sleep-related breathing disorders, sleep paralysis (E Recurrent isolated sleep paralysis (G47.52)`, p. 464), nocturnal seizures, PTSD nightmares, anxiety due to nocturnal hallucinations. Assessment • Full history, with an emphasis on possible comorbidity (i.e. other anxiety disorders), use of alcohol and drugs. Rating of severity using specific scales, e.g. Nocturnal Panic Screen,26 and self-monitoring using sleep 26 Craske MG, Tsao JC (2005) Assessment and treatment of nocturnal panic attacks. Sleep Med Rev 9:173–84.

Nocturnal panic attacks diary. Additional formal assessment may be necessary for difficult cases and to exclude other treatable sleep disorders (e.g. sleep apnoea, nocturnal seizures). Management • CBT—most evidence as for panic disorder (E Panic disorder 3: management guidelines, p. 372), including modification of maladaptive behaviours (e.g. sleeping with lights or TV on). • Pharmacological—little specific evidence (not systematically studied yet). Case reports support alprazolam or TCAs. Rational approach to prescribing as for daytime panic (E Panic disorder 3: management guidelines, p. 372) and/or short-term use of hypnotics to help with secondary sleep avoidance.

472 Chapter 10 Sleep–wake disorders Sleep-related violence Violence and sleep are commonly thought to be mutually exclusive but, in fact, can coexist (see Box 10.10 and Table 10.3). Particularly in more serious forensic cases, a sleep expert workup should include the following.27 History of any underlying sleep disorder • A complete description of the defendant’s lifetime history of any sleep- related problems—preferably with third-party corroboration– including details about age at onset, the usual timing of the event, the degree of amnesia, and both the duration and frequency of episodes. • Information about sleep/wake habits, drugs (prescribed or illicit), herbal products, and habitual caffeine and alcohol consumption/abuse. • Investigation of any family history of sleep disorders. Characteristics of the act • Information about the event including precipitating factors such as attempts to waken the defendant, possible ingestion of drugs/alcohol or medication (recent changes or covertly given), and other circumstantial factors—stressful events, sleep deprivation, excessive fatigue, and intake of alcohol and other substances. On return to consciousness • A description of the defendant’s reaction (corroborated, if possible), e.g. perplexity, horror, no attempt to escape, amnesia for the event. Box 10.10 Case reports in the medical literature A recent systematic review1 of medico-legal cases of SRV and sexual be haviour in sleep (SBS) from 1980 to 2012 identified 18 cases (9 SRV and 9 SBS). All SRV cases were related to a charge of murder or attempted murder, while in SBS cases, the charges ranged from sexual touching to rape. The most used defence was of sleepwalking in 11/18 cases. The outcome was in favour of the defendant in 14/18 cases. Defendants were young ♂ in all cases, and victims were usually adult relatives (in SRV cases) or unrelated young girls or adolescents (in SBS cases). The criminal events occurred 1–2hrs after sleep onset, and both proximity (usually in the same room) and other potential triggering factors (stress, sleep deprivation, excessive alcohol intake, and fatigue, along with caf feine overuse) were reported. 1 Ingravallo F, Poli F, Gilmore EV, et al. (2014) Sleep-related violence and sexual behavior in sleep: a systematic review of medical-legal case reports. J Clin Sleep Med 10:927–35. 27 Siclari F, Khatami R, Urbaniok F, et al. (2010) Violence in sleep. Brain 133:3494–509.

Sleep-related violence Investigations • Complete physical, neurologic, and psychiatric evaluations, along with administration of standardized questionnaires for sleep disorders. • PSG/video evidence

to identify or rule out other sleep disorders associated with abnormal motor behaviours (e.g. RBD, NFLE) or triggering events (e.g. OSA, PLMS)—best to combine sleep laboratory studies with home video/PSG recordings. Table 10.3 Disorders associated with sleep-related violence* Disorder State of occurrence Clinical features Circumstances of violence Confusional arousal Wake/NREM Incomplete awakening, reduced vigilance, impaired cognition, amnesia When being forced to wake from sleep Sleepwalking Wake/NREM Like confusional arousals with complex motor activity Incidental encounter or when approached Sleep terror Wake/NREM Incomplete fearful awakening from NREM sleep Linked to frightening dream RBD Wake/REM Acting out of dreams Linked to dream content RLS/PLMD All sleep stages Repetitive, stereotyped limb movements Accidental Nocturnal paroxysmal dystonia All sleep stages (especially N2) Bipedal automatisms, twisting of trunk/pelvis, vocalizations, posturing of head/limbs Accidental or related to hyperkinetic features Epileptic nocturnal wandering All sleep stages (especially N2) Like sleepwalking, but more directed violence possible Accidental or when approached/ restrained Confusional states Awake Variable Variable Dissociative disorder Awake Variable, frequently wandering, amnesia Self-harm, thrashing, assaults Malingering Awake Variable (evident primary or secondary gain) Variable

- Source: data from Mahowald MW, Bundlie SR, Hurwitz TD, et al. (1990) Sleep violence—forensic science implications: polygraphic and video documentation. J Forensic Sci 35: 413–32.

474 Chapter 10 Sleep–wake disorders Sleep-related movement disorders 1 Essence Usually relatively simple, stereotyped movements disturbing sleep, and causing insomnia and EDS. Can also be a cause of sleep-related violence (see Table 10.3) and lead to harm to self or others. In DSM-5, ‘Restless legs syndrome’ is the only specific sleep-related movement disorder (RMD) classified and is included within ‘Parasomnias’—all other disorders need to be diagnosed as ‘Other specified sleep–wake disorder’. In ICD-10, they may be diagnosed as ‘Other non-organic sleep disorder’ (F51.8) or coded in other sections—codes in brackets. Restless legs syndrome (Willis–Ekbom disease) (RLS/WED) (G25.81) Unpleasant, often painful sensations in the legs, particularly on sleep onset. Significantly interferes with the ability to get to sleep. Usually idiopathic or familial. Exacerbated by caffeine, fatigue, or stress. Associated with sleep disturbance, daytime fatigue, and involuntary, repetitive, periodic, jerking limb movements (when awake or asleep).28 • ICSD-3 criteria: an urge to move the legs, usually accompanied or thought to be caused by uncomfortable and unpleasant sensations in the legs that: (1) begin or worsen during periods of rest or inactivity (e.g. lying down or sitting); (2) are partially or totally relieved by movement (e.g. walking or stretching); and (3) occur exclusively or predominantly in the evening or night, rather than during the day. Features are not due to a medical or behavioural condition (e.g. leg cramps, positional discomfort, myalgia, venous stasis, leg oedema, arthritis, habitual foot- tapping). The symptoms cause concern, distress, sleep disturbance, or other functional impairment. • Prevalence: 710% of general population, ♂:♂ = 1:2 (related to parity), greater in over 50s, familial forms present before 45yrs. • Pathophysiology: genetic (autosomal dominant and recessive heritability linked to 12q, 14q, 9p, 20p, 4q, and 17p); abnormalities in the central subcortical DA pathways (SPECT—D2 receptor deficiency); reduced serotonin transporter availability in the brainstem (i 5HT levels); impaired iron homeostasis. • Associations/secondary causes: PLMD (85%), pregnancy, uraemia, rheumatoid arthritis, iron deficiency anaemia, folate deficiency, Mg2+ deficiency, hypothyroidism, poliomyelitis, peripheral neuropathy (e.g. diabetes, alcohol), chronic myelopathy, Parkinson’s disease, drug-related (e.g. antidepressants; phenothiazines; lithium; Ca2+

channel blockers; β-blockers; caffeine; withdrawal from barbiturates, other sedatives, and opiates). • Differential diagnosis: antipsychotic-induced akathisia, ADHD, nocturnal leg cramps, peripheral vascular disease. 28 Sharon D (2015) Management of restless legs syndrome/Willis Ekbom disease. Sleep Med Clin 10:xix–xx.

Sleep-related movement disorders 1 • Investigations: full history, examination, routine blood tests (FBC, B12, folate, urea, creatinine, fasting blood glucose, TSH, Mg2+, iron levels, ferritin, transferrin saturation, total iron-binding capacity), EMG and nerve conduction studies if neuropathy suspected, PSG rarely needed (unless sleep disturbance persists after treatment). • Management: • General Treat any secondary causes. Sleep hygiene measures. Avoid caffeine, alcohol, nicotine. Discontinue any medications that are not essential. • Non-pharmacological Exercise. Movement (walking, stamping) or stimulation of the legs (limb massage, hot/cold showers/baths, hot packs, ointments, vibratory or electrical stimulation). • Medication Possible agents include: anti-Parkinson agents [L- dopa with carbidopa, ropinirole, rotigotine (patch), pramipexole, bromocriptine], clonazepam, opiates (codeine, oxycodone, methadone, levorphanol tartrate), anticonvulsants (gabapentin, pregabalin), clonidine, iron salts, either alone or in combination. Periodic limb movement disorder (G47.61) Also called periodic leg movements in sleep (PLMS)29—periodic episodes of repetitive, stereotyped limb movements (involuntary, forceful dorsiflexion of the foot, lasting 0.5–5s occurring every 20–40s throughout sleep). Rare in children, common in over 60s (734%). May be a feature in up to 15% of patients with insomnia. Movements usually reported by bed partner. Associated with hypertension, headaches (migraine and tension-type), and learning and memory difficulties secondary to disrupted nocturnal sleep and daytime somnolence. PSG may aid diagnosis. • Differential diagnosis: sleep starts (E Sleep starts (hypnic jerks) (R25.8), p. 477), drug-related exacerbation (e.g. TCAs, lithium). • Management: reassurance, remove exacerbating factors, clonazepam, levodopa. Sleep-related leg cramps (G47.62) Sensations of painful muscular tightness or tension, in the calf (or the foot), occurring during sleep, which awaken the sufferer. • Prevalence: up to 16% of healthy individuals, more common in the elderly. • Associated problems: excessive muscular activity, dehydration, diabetes, arthritis, pregnancy, and Parkinson’s disease. • Differential diagnosis: PLMD (painless), muscle spasm due to spasticity following stroke, other neurological causes of muscle spasticity. • Management: only for severe, recurrent symptoms—heat, massage, muscle stretching; quinine sulfate (300mg nocte). 29 Fulda S (2015) The role of periodic limb movements during sleep in restless legs syndrome: a selective update. Sleep Med Clin 10:241–8.

476 Chapter 10 Sleep–wake disorders Sleep-related movement disorders 2 Sleep-related bruxism (G47.63) Clenching and grinding of the teeth during sleep that can result in arousals. The activity may be severe or frequent enough to result in symptoms of temporomandibular joint pain, wearing down of the teeth, or severe injury to the tongue and mouth. • Management: general sleep hygiene measures, removal of exacerbating factors, occlusal splints/night-time bite guard, use of clonazepam. Sleep-related rhythmic movement disorder (G47.69) Stereotyped, repetitive movements involving large muscles, usually head and neck (may lead to head injury), typically immediately prior to sleep, sustained into light sleep. Common forms: head banging (jactatio capitis nocturna), head rolling, body rocking, body rolling, leg banging, and leg rolling. Sometimes accompanied by loud sound emissions. • PSG: rhythmic movement artefacts during light non-REM sleep, without evidence of epileptiform activity. • Prevalence: common in young children (60% at 9mths), decline with age (25% at 18mths, 8% at 4yrs). More frequent in boys. • Associated

problems: developmental problems/psychopathology (older children). • Management: unnecessary in most cases. Parents can be reassured that, in the majority of infants, the disorder will resolve by around the age of 18mths. If injury or social disruption occurs, medication may be used (e.g. low-dose BDZ or antidepressant). Benign sleep myoclonus of infancy (R25.8) • A disorder of myoclonic jerks that occur during sleep in infants, typically from birth to 6mths, resolving spontaneously. Propriospinal myoclonus at sleep onset (R25.8) Recurrent, sudden muscular jerks in the transition from wakefulness to sleep, which may be associated with severe sleep-onset insomnia. Sleep-related movement disorder due to a medical disorder (G47.69)/due to a medication or substance (G25.79/F10- F19.x82) Those disorders that are secondary to either an underlying medical dis order or a particular medication of drug of abuse. Treatment is directed at treating the primary disorder or eliminating the causative agent. Sleep-related movement disorder unspecified (G47.60) and other sleep-related movement disorder, unspecified (G47.60) All other movement disorders that do not meet the specific criteria for the other categories.

Sleep-related movement disorders 2 Isolated symptoms and normal variants Excessive fragmentary myoclonus (R25.8) Small muscle twitches in the fin gers, toes, or corner of the mouth that do not cause actual movements across a joint. Often an incidental finding during PSG. Usually asymptomatic, but sometimes associated with EDS or fatigue. Hypnagogic foot tremor and alternating leg muscle activation (R25.8) Occurs at the transition between wake and sleep or during light NREM sleep. PSG shows recurrent EMG potentials in one or both feet that are longer than the myoclonic range (>250ms). Sleep starts (hypnic jerks) (R25.8) Occur at sleep onset and present as sudden, abrupt contractions of muscle groups, usually the legs, but some times also involving the arms, neck, or even the entire body. When wakened by jerks, an individual may have the feeling of falling in space (‘siderealism’). Sometimes this feeling is so intense and frightening that it can lead to fear of going to sleep, with subsequent sleep-onset difficulties. • PSG: occasional vertex waves, associated with muscular contraction. • Prevalence: 60–70% (essentially a universal component of the sleep onset process). • Differential diagnosis: nocturnal myoclonic jerks (with evident epileptiform activity on EEG), fragmentary myoclonus (during NREM sleep), nocturnal leg myoclonus/PLMD (often associated with RLS), and the rare ‘startle disease’ or ‘hyperekplexia’ syndrome (myoclonus occurs following minor stimuli both during wakefulness and sleep). • Management: treatment usually unnecessary. If there is significant interference with sleep—general measures (e.g. avoidance of stimulants such as caffeine and nicotine) or low-dose clonazepam at night.

478 Chapter 10 Sleep–wake disorders Sleep–wake disorders related to psychiatric disorders 1 Although unusual for psychiatric patients to present with a primary sleep dis order, it is not uncommon for psychiatrists to have to deal with secondary problems of insomnia (not getting enough sleep or feeling ‘unrefreshed’) or hypersomnia (feeling excessively sleepy during the day or sleeping too much), in the context of a primary psychiatric disorder or as a consequence of medication. Equally, sleep deprivation may have its own psychological con sequences or may precipitate the onset of a psychiatric illness, particularly a manic episode. Major affective disorders Alterations in sleep are central symptoms in mood disorders. Initial in somnia, frequent waking (for often prolonged periods), EMW, vivid or disturbing dreams, and daytime fatigue are frequently seen in major depres sive disorder. These features are associated with changes in sleep archi tecture: shortened REM sleep onset latency, i REM density, reduced TST, reduced SE, i awakenings, d N3 sleep (WS), and a shift of N3 from the first NREM cycle to the second. Occasionally,

hypersomnia may be a feature in atypical cases, bipolar affective disorder, and SAD. Episodes of mania may be characterized by marked insomnia and a d need for sleep associated with much reduced TST, reduction in N3 sleep, and no consistent change in REM sleep. Management • Treat the primary disorder. • Initial insomnia: use a more sedating antidepressant (e.g. TCA, trazodone, nefazodone, mirtazapine, agomelatine). • Hypersomnia: use a more 'activating' antidepressant (SSRI, reboxetine, bupropion, MAOI, RIMA). Note: most antidepressants are REM-suppressant and may exacerbate underlying primary sleep disorders (e.g. parasomnias and sleep-related movement disorders), either on commencement or on cessation. Anxiety disorders Anxiety disorders commonly disrupt the normal sleep pattern, leading to insomnia, which may be triggered by an acute stressful event. Symptoms include: initial insomnia, frequent waking, reduced TST, and EMW. Generalized anxiety Typically prolonged sleep onset latency, i stages N1 and N2, less N3, a smaller percentage of REM, and i or normal REM sleep latency. Panic disorder Sleep-related (nocturnal) attacks may occur with asso ciated intense fear, feelings of impending doom, autonomic arousal, som atic symptoms, and fear of going to sleep (leading to avoidance behaviour, which may present as 'insomnia') (E Nocturnal panic attacks, p. 470). As many as 70% of patients with panic disorder have difficulty with sleep-onset and maintenance insomnia, and often report sleep paralysis and hypna gogic hallucinations. Studies in non-depressed patients with panic disorder

Sleep–wake disorders related to psychiatric disorders 1 report normal sleep onset latency and modestly reduced TST and sleep. However, studies in patients with panic and comorbid major depression report features typical of major depression, with substantially prolonged sleep onset latency, reduced TST, sleep disruption, reduced N3, and early REM sleep onset. PTSD Sleep complaints almost universal in individuals diagnosed with PTSD; indeed, recurrent distressing dreams related to a traumatic event are a core feature of the disorder. Complaints include: nightmares, difficulties initiating and/or maintaining sleep (in 70–90%), sleep paralysis, and RBD. Sleep disturbance soon after the traumatic event is a risk factor for PTSD, and more severe sleep symptoms in PTSD are associated with depression severity, suicidal tendencies, anxiety, and substance use. Studies find i sleep onset latency, d SE, i wakefulness after sleep onset, d TST, reduction in N2 sleep, i N1 sleep, and variable effects on REM (normal parameters vs reduced REM latency and i REM density). Social phobia i sleep onset latency, awakening after sleep onset, and reduced TST. OCD Sleep can become restricted due to engagement in compulsive be haviours. Sleep studies show d TST, i awakenings, shortened REM latency, reduced N3 sleep, and reduced SE. Management • Treatment of the primary anxiety disorder will generally improve the patient's ability to initiate and sustain sleep. • Most anxiolytics tend to be sedating, and it is usual to prescribe a higher dose at night. • When less sedating drugs, such as SSRIs, are used, additional treatment may be necessary to target persistent sleep problems (e.g. cognitive behavioural techniques, short-term use of hypnotics, or a small dose of a more sedating antidepressant at bedtime). • Behavioural sleep interventions are effective in reducing night-time symptoms in PTSD, e.g. imagery rehearsal for chronic nightmares, stimulus control/sleep restriction for insomnia (see Box 10.3). • Prazosin, an α1-adrenergic receptor antagonist, has emerged as a promising treatment of PTSD-related sleep disturbance, including both nightmares and insomnia symptoms (off licence in the UK). Borderline personality disorder Sleep architecture changes very similar to those seen in depresssion: re duced TST, reduced SE, reduced N3, i N2, reduced REM latency, and i REM density.

480 Chapter 10 Sleep–wake disorders Sleep–wake disorders related to psychiatric disorders 2 Schizophrenia Patients with schizophrenia demonstrate i nocturnal wakefulness and day time

somnolence. PSG shows sleep continuity disturbance, reduced N3, d REM latency, and i REM sleep. It is often difficult to disentangle the ef fects of medication, active positive symptoms, persistent negative symp toms, and disorganized behaviour, and some studies show relatively little change in sleep. Research has suggested an inverse relationship between SWS (N3)/sleep maintenance and brain ventricle size/negative symptoms in schizophrenia. Management • EDS: monitor effects of antipsychotic medication; adjust timing and dosage. • Insomnia: general sleep hygiene measures, with emphasis on behavioural approach when 'disorganization' is a central feature; judicious use of hypnotics or higher dose of sedating antipsychotic before bedtime. Eating disorders Patients with bulimia may report EDS, but sleep studies show very little change in sleep parameters. Studies in anorexia nervosa have been more contradictory, perhaps due to the high rates of comorbidity with affective disorders and frequent family history of affective disorders in anorexia pa tients (hence, PSG similar to depression). In severe or untreated cases of anorexia nervosa, insomnia and frequent waking are very common. Sleep studies show reduced TST, d SE, i wakefulness after sleep onset, shortened REM latency, i N1, and d N3 sleep, which normalize after weight is gained. Management • Treatment of the primary eating disorder to establish better eating behaviours and re-establish normal BMI. • General principles for insomnia and EDS (E Insomnia 2: general management strategies, p. 442). • Possible use of SSRI or alternative antidepressant. Dementia Normal ageing is associated with i sleep latency, reduced TST, loss of NREM sleep, frequent arousals leading to fragmentation of nocturnal sleep, and an increase in daytime napping. • Some sleep–wake disorders (e.g. sleep apnoea syndromes, PLMD) occur more frequently in the elderly population. • Dementia generally causes further increases in sleep latency, further reductions in TST, and i fragmentation of nocturnal sleep, in proportion to the severity of the illness. • Disorders of normal circadian rhythm are also commonly seen, with a characteristic 'sundown syndrome' of confusion and agitation at bedtime (nocturnal agitated wandering).

Sleep–wake disorders related to psychiatric disorders 2 Management • General sleep hygiene measures (with an emphasis on establishing and reinforcing a normal 24-hr circadian cycle through the use of environmental cues, daily routine, avoidance of daytime napping, and regular activities). • 'Sundown syndrome' may respond to low-dose antipsychotics (e.g. haloperidol, risperidone) or antidepressants (e.g. trazodone). Alcohol use Alcohol most probably exerts its sedative effects through a combination of GABA facilitation and glutamate inhibition. The acute effects of alcohol lead to reduced sleep latency, i TST, i N3, mild suppression of REM sleep in the first half of the night, and subsequent i REM sleep in the second half, associated with sleep disruption, intense dreaming, and even nightmares. Chronic effects of alcohol abuse include loss of N3, sleep disruption, and significant insomnia. Withdrawal from alcohol is also associated with in somnia. Sleep architecture is disrupted, with i sleep latency, reduced TST, loss of N3, and i REM density and/or amount. 'Delirium tremens', with marked agitation, confusion, and hallucinations, is characterized by intense REM rebound. Use of other recreational drugs • Nicotine: this tends to cause initial insomnia and may be associated with sleep disruption and i REM sleep. Use of nicotine patches has been associated with vivid dreams and nightmares. • Cannabis: hypnotic effects modulated by cannabinoid-1 receptors. Appear to be similar to the effects of BDZs and alcohol, increasing NREM and suppressing REM sleep. Cessation may lead to problems of initial insomnia, sleep disruption, and REM rebound. • Opiates: although sleep is improved when opiates are used therapeutically for pain relief or in the treatment of RLS, misuse is associated with generalized sleep disruption. Changes in sleep architecture include decrease in SE, TST, N3, and REM sleep. Withdrawal symptoms include insomnia, with fragmentation of sleep and disruption of normal sleep

architecture, related to i arousal and REM rebound. • Stimulants: the effects of amphetamine and cocaine include reduced REM sleep and i sleep and REM latency. Xanthines (caffeine, theophylline) have similar effects, acting through adenosine receptors, directly interfering with the generation of sleep. Amphetamine derivatives, e.g. fenfluramine and MDMA (ecstasy), have a pharmacological action that is primarily serotonergic, which may lead to both daytime sedation and disturbed sleep (due to periods of drowsiness and wakefulness), as well as a reduced duration of REM sleep. SWS may be i during the withdrawal phase as a rebound phenomenon.

482 Chapter 10 Sleep–wake disorders Psychiatric medication and sleep Antipsychotic drugs Most antipsychotics cause drowsiness and impaired performance. There is a great degree of variability, even within groups of antipsychotics (see Table 10.4). Antidepressants Sedating • TCAs are usually sedative due to their anticholinergic effects. Amitriptyline, trimipramine, doxepin, imipramine, clomipramine are the most sedating, and nortriptyline is the least sedating. • Tetracyclic antidepressants (mianserin) and trazodone also have marked sedating properties, although less related to anticholinergic properties and may be due to 5-HT2 and histamine antagonism—properties shared by some newer antidepressants (e.g. mirtazapine). • Agomelatine may promote sleep by melatonin (MT1/MT2) agonism. Alerting MAOIs, SSRIs, NA reuptake inhibitors (NARIs) (reboxetine), DA re uptake inhibitors (DARIs) (bupropion), and SNRIs (venlafaxine, duloxetine) all tend to have alerting effects, which may be useful in the treatment of hypersomnolence associated with ‘atypical’ depression, and should be taken in the morning or early afternoon. Mood-stabilizing drugs • Lithium: mildly sedating (increasing N3 and reducing REM). • Carbamazepine: may cause drowsiness at start of treatment or when dose is being i, but this is usually a transient effect. • Sodium valproate: mild effects on sleep—less than carbamazepine. • Lamotrigine: iREM and dδ with little daytime somnolence—some patients (77%) may notice an alerting effect with associated insomnia. Benzodiazepines and associated hypnotics By definition, BDZs and barbiturates are sedating. Problems arise due to withdrawal insomnia on discontinuation, tolerance to the beneficial hyp notic effects after long-term use, and problems of dependence. Newer hyp notics, such as the z-drugs, share the sleep-enhancing properties of BDZs but may be less likely to cause rebound or dependence (see Table 10.5). Psychostimulant drugs Although very useful in the treatment of hypersomnia (particularly in nar colepsy) and ADHD and to suppress appetite, this group of drugs all tend to cause insomnia, with fragmented sleep due to frequent awakenings (e.g. dexamfetamine, methylphenidate, methamphetamine, mazindol, pemoline, and modafinil) and should not be taken in the evening. Cessation, with the notable exception of modafinil, leads to increases in TST and REM rebound.

Psychiatric medication and sleep Table 10.4 Sedative effects of antipsychotics Marked sedation Moderate sedation Mild sedation Minimal sedation Chlorpromazine Asenapine Flupentixol Amisulpride Clozapine Benperidol Haloperidol Aripiprazole Levomepromazine Droperidol Lurasidone Pericyazine Fluphenazine Paliperidone Loxapine Pimozide Olanzapine Pipotiazine Perphenazine Quetiapine Promazine Risperidone Thioridazine Sulpiride Zuclopenthixol Trifluoperazine Table 10.5 Polysomnographic effects of hypnotics Drug Acute effects Withdrawal Comments Barbiturates i TST, N2, spindles d WASO, REM n δ d TST Rapid development of tolerance, withdrawal insomnia, daytime sedation BDZs i TST, N2, spindles d SL, WASO, REM, δ d TST Wide variation in onset and duration of action (see Table 10.1) Long T1/2: EDS Short T1/2: tolerance, withdrawal insomnia Z-drugs/ melatonin i TST d SL n δ, REM n or i WASO No typical alteration of sleep architecture or withdrawal effects Key: BDZ = benzodiazepine; TST = total sleep time; WASO = waking after sleep onset; SL = sleep latency; δ = N3/slow-wave sleep; EDS = excessive daytime somnolence.