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section 24 Neurological disorders 5886 of narcolepsy). This is taken at night and acts as an anaesthetic, resulting in very deep sleep. Side effects include bed wetting and nausea, and, due to the large salt load, hypertension. Prognosis Narcolepsy is a lifelong condition. However, it may evolve over the first few years, and there can be a delay from the onset of sleepi- ness to the occurrence of cataplexy. The cataplectic symptoms may become less prominent over the years as people are better able to control them. The sleepiness (independent of treatment) tends to remain unchanged but can deteriorate in late adulthood because of the occurrence of other sleep disorders (in particular, obstructive sleep apnoea). Morbidities and mortality Narcolepsy has a considerable impact on quality of life, despite therapy, and this is age dependent. At all ages excessive daytime somnolence can affect concentration and memory (e.g. working memory). Children with narcolepsy can have educational dif- ficulties, decreased general well-being, and poorer self-image. Adolescents with narcolepsy report fewer relationships with friend and fewer leisure activities than others their age. Adults with narco- lepsy can have problems with employment and driving. Both chil- dren and adults commonly suffer from depression. People with narcolepsy have a standardized mortality rate that is about 1.5 that of the general population. In addition, people with narcolepsy (perhaps due to higher body mass index) have in- creased rates of diabetes, obesity, back pain, and obstructive sleep apnoea. Future developments The increased understanding of the pathogenesis of narcolepsy and the regulation of sleep are likely to lead to future therapies. Drugs, gene therapies or cell therapies that target the hypocretin system would seem to be approaches that are most promising in order to develop a cure. A less ambitious aim, to improve present therapies, may be achieved through drugs that act on specific neurotrans- mitter systems (eg histaminergic system) or through understanding the mechanisms by which sodium oxybate works (GABA(B) and γ-hydroxybutyrate receptor systems). Lastly, immunotherapy has received mixed reports. Failure of immunomodulatory therapies may be due to late diagnosis, emphasizing the need for tests that may enable early diagnosis and perhaps more effective disease modifying treatment. FURTHER READING Billiard M, et al.; EFNS Task Force (2006). EFNS guidelines on man- agement of narcolepsy. Eur J Neurol, 13, 1035–48. Dauvilliers Y, Arnulf I, Mignot E (2007). Narcolepsy with cataplexy. Lancet, 369, 499–511. Liblau RS, Vassalli A, Seifinejad A, Tafti

M (2015). Hypocretin (orexin) biology and the pathophysiology of narcolepsy with cataplexy. Lancet Neurol, 14, 318–28. Mahlios J, De la Herrán-Arita AK, Mignot E (2013). The autoimmune basis of narcolepsy. Curr Opin Neurobiol, 23, 767–73. Morgenthaler TI, et al.; Standards of Practice Committee of the American Academy of Sleep Medicine (2007). Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep, 30, 1705–11. Sturzenegger C, Bassetti CL (2004). The clinical spectrum of narco- lepsy with cataplexy: a reappraisal. J Sleep Res, 13, 395–406. Thannickal TC, et al. (2000). Reduced number of hypocretin neurons in human narcolepsy. Neuron, 27, 469–74. 24.5.3 Sleep disorders Paul J. Reading ESSENTIALS Dysfunctional sleep is an important cause of morbidity and is as- sociated with numerous long-term health problems. Sleep-related symptoms can loosely be divided into insomnias, disorders causing excessive daytime sleepiness, and parasomnias, with some condi- tions having elements of all three categories. Insomnia Chronic insomnia usually has a behavioural or psychological basis and responds best to cognitive or relaxation therapies, although secondary causes of insomnia such as restless legs syndrome may have specific therapies. Circadian rhythm disorders may also present as insomnia, and several neurological syndromes such as Parkinson's disease are also associated with poor quality and fragmented sleep. Excessive daytime sleepiness This usually has a specific identifiable cause, with sleep fragmenta- tion or disruption due to sleep-disordered breathing being the most common reason for severe cases (see Chapter 18.5.2). However, at least 2% of excessively sleepy subjects will have a primary sleep dis- order such as narcolepsy. Narcolepsy can be considered a primary disorder of sleep–wake regulation. An inability to stay awake for more than a few hours is usually the most obvious symptom, often in association with cata- plexy, sleep paralysis, and hallucinations. Disturbed nocturnal sleep and a variety of parasomnias are also common (see Chapter 24.5.2). Parasomnias Nonrapid eye movement sleep parasomnias—these are very common in children and rarely require investigation or treatment. Sleepwalking, confusional arousals, and night terrors occurring within 90 min of sleep form a spectrum of conditions reflecting ab- normal arousals from the deepest stages of sleep. Not infrequently, the phenomenon persists into adulthood and may sometimes

 require short courses of hypnotic agents or sedative antidepressant therapy to suppress the nocturnal disturbances. Parasomnias arising from rapid eye movement sleep—these are most common in middle-aged men and may be a harbinger of a neurodegenerative syndrome such as Parkinson's disease. Rapid eye movement sleep behaviour disorder occurs when the mechanism to paralyse voluntary muscles during dreams in rapid eye move- ment sleep fails, with the subsequent dream enactment some- times causing significant physical injury. Most patients respond to clonazepam although melatonin is increasingly used. Circadian rhythm disorders Circadian rhythm disorders—these are increasingly recognized. Most arise from jet lag or shift work; a few reflect abnormalities
of the intrinsic clock mechanisms, of which delayed sleep phase syn- drome is commonest, especially in adolescents, usually presenting with severe difficulties arising from bed for morning activities. Treatments are partially effective and include low-dose melatonin taken mid-evening and phototherapy given in the early morning. Introduction The need to sleep is imperative, reflecting the fact that sleepiness, similar to hunger and thirst, is a true drive state. Although its func- tion remains largely elusive, disordered sleep can be associated with profound adverse effects on cognition, mental health, and physical well-being. Moreover, sleep-related symptoms are very common, with 25% of people reporting problems that significantly and regu- larly impact on daily activities. Advances in our understanding of the neurobiology of sleep have challenged the

traditional view that sleep is a passive or necessarily restful process. By contrast, rather than simply reflecting the absence of wakefulness, sleep is actively orchestrated, with a highly reproducible and complex internal architecture. A typical pattern seen in a healthy adult is shown in Fig. 24.5.3.1. Episodes of rapid eye move- ment (REM) and non-REM sleep recur through the night in four or five discrete cycles. It should be recognized that occasional arousals from nocturnal sleep are normal and that seemingly random body movements or shifts in position occur regularly throughout the night. In REM sleep episodes, however, despite high levels of cere- bral metabolic activity that loosely correspond to dream mentation, general motor activity is profoundly suppressed and any observable movements are confined to occasional minor jerks. Defining disordered sleep can be difficult: most classifications are now symptom based. The recently revised International Classification of Sleep Disorders (ICSD-3—see 'Further reading') recognizes seven categories: 1 Insomnias 2 Sleep-related breathing disorders 3 Central disorders of hypersomnolence 4 Circadian rhythm sleep–wake disorders 5 Parasomnias 6 Sleep-related movement disorders 7 Isolated symptoms, normal variants, and unresolved issues Insomnia Chronic insomnia is loosely defined as the perception of inadequate sleep for more than three nights a week for a period of more than 3 months despite an adequate opportunity and desire to sleep. To fulfil the diagnostic criteria, there also needs to be a significant ad- verse effect on daily functioning as a result of poor sleep. The inability to fall asleep or maintain continuous sleep is a common symptom and has several extrinsic or secondary causes (Table 24.5.3.1). It is rare for organic cerebral pathology to underlie primary insomnia, and persistently maladaptive attitudes or behaviours are usually responsible. An index event or illness can often be identified. The common forms of primary insomnia are probably best treated by behavioural modification, including a combination of cognitive– behavioural therapy and relaxation techniques. The intermittent use of short-acting hypnotics may be helpful, although long-term drug treatment is rarely beneficial. If symptoms of inadequate sleep date back to childhood, the term 'idiopathic insomnia' is sometimes used. Although its neurobiology remains obscure, at some level this disorder probably reflects a con- stitutionally impaired sleep drive such that the normal homoeostatic pressure to sleep is inadequate. The interplay between psychological distress and chronic in- somnia is complex, with each element potentially fuelling the other. Psychiatric input to treat any significant mood disorder can there- fore be helpful in attempting to resolve sleep-related symptoms. Hypersomnia Significant excessive daytime sleepiness is reported by 5% of the population and is most often due to poor quality or diminished overnight sleep (Table 24.5.3.2). It is important to distinguish true sleepiness or drowsiness from fatigue and lethargy, which often have 1 2 3 4 5 6 7 Time (hours through night) WAKING REM sleep NREM sleep stage I II III IV Typical hypnogram of young adult REM REM REM REM Fig. 24.5.3.1 A typical hypnogram of a young adult showing four cycles of nonrapid eye movement (non-REM) and REM sleep. Two
brief awakenings are shown that can be considered normal. The proportion of deep non-REM sleep (stages III and IV) is highest in the first few hours of sleep whereas REM sleep predominates towards the end of the sleep period.

 different causes. Within the abnormally sleepy population, approxi- mately 2% have a primary sleep disorder in which the most striking complaint is an inability to stay awake appropriately despite the desire to do so. Narcolepsy Introduction and clinical features Narcolepsy is not a rare disorder, with an estimated prevalence of 1 per 2000 in white populations. However, differences in case as- certainment and the availability of sleep services have led to con- siderable variance in reported rates worldwide. Moreover, there is

undoubtedly a spectrum of severity and many mildly affected indi- viduals are either undiagnosed or diagnosed only after many years of symptoms. It most often starts in adolescence, with a second minor peak in early middle age. Symptoms are generally life-long, although most people with the condition develop coping strategies to min- imize the impact of the syndrome. Narcolepsy is important, not least because it is usually disabling, influencing every aspect of daily living. Many people with narco- lepsy feel a sense of underachievement, partly because treatment is frequently either delayed or only partially effective. A perceived lack of medical interest in the disease, together with the adverse effects on schooling, careers, and relationships, understandably produces frustration. Secondary mood disorders are seen in many patients. Rather than reflecting true hypersomnolence over a 24-hour period, narcolepsy is best viewed as a primary disorder of sleep–wake Table 24.5.3.1 Some causes of primary and secondary insomnia Causes Comments Primary insomnia Intrinsic sleep disorders Psychophysiological insomnia Paradoxical insomnia Sometimes called ‘conditioned insomnia’, formerly called ‘sleep–wake misperception’ Idiopathic insomnia History dates back to childhood Extrinsic sleep disorders Poor sleep hygiene Environmental sleep disorder Examples include sleep-disordered bed partners or pets interfering with sleep; usually results in daytime sleepiness Altitude insomnia Mild hypoxaemia produces poor sleep because of unstable respiratory control overnight Drug-dependent insomnia Hypnotics, stimulants, or alcohol may be responsible Secondary insomnia Neurological conditions Restless legs syndrome An important and treatable cause of insomnia Parkinson’s disease Sleep fragmentation can be an integral part of the condition Morvan’s syndrome A rare paraneoplastic or autoimmune syndrome with neuromuscular hyperexcitability and severe insomnia as cardinal features Fatal familial insomnia A very rare familial prion disease with significant thalamic pathology as the presumed substrate for severe insomnia Medical disorders Asthma Gastro-oesophageal reflux An important and often overlooked diagnosis Chronic pain syndromes including fibromyalgia A high percentage of light non-REM sleep is often seen Psychiatric causes Secondary to medication Mood disorders including anxiety, depression, and mania REM, rapid eye movement. Table 24.5.3.2 Some extrinsic and intrinsic causes of excessive daytime sleepiness Intrinsic causes Extrinsic causes Primary causes Sleep deprivation or insufficient sleep Narcolepsy Drug-related hypersomnia Idiopathic hypersomnia Environmental sleep disorder Kleine–Levin syndrome (intermittent sleepiness) Shift-work sleep disorder Causes secondary to a chronic disorder Jet lag Sleep-disordered breathing Restless legs syndrome and periodic limb movement disorder Multiple sclerosis Head injuries Encephalitis

 regulation (Fig. 24.5.3.2), with an inability to stay awake for more than a few hours as the most obvious symptom. Indeed, excessive daytime sleepiness not explained by another disorder remains an essential diagnostic criterion. Many patients describe sudden and irresistible urges to sleep, often in public or inappropriate situations, invariably worse if they are unoccupied or bored. In contrast to most other sleep disorders, short naps lasting minutes can often be re- storative. A few people with the condition are relatively unaffected by excessive daytime sleepiness and other features of the syndrome predominate. Cataplexy Cataplexy is a curious phenomenon, highly specific to narcolepsy and present to varying degrees in two-thirds of patients. It is par- ticularly important to identify typical cataplexy because its pres- ence in a person with excessive daytime sleepiness is practically diagnostic of narcolepsy. Full-blown episodes reflect an intrusion of profound muscle paralysis that descends over a few seconds from head to the lower limbs, often causing collapse to the floor. Identifiable triggers usually have an emotional content. Laughter or other positive emotions such as a pleasant surprise are the most

common precipitants, although frustration and anger can also reli- ably provoke episodes. In some individuals the mere thought or an- ticipation of an emotional event can cause collapse. Reassuringly, attacks are rare in dangerous situations and most patients report cataplexy only when relatively relaxed in familiar environments with friends. It is therefore very uncommon for doctors to wit- ness episodes, making a reliable history crucial for confident diag- nosis. Importantly, partial or focal attacks are common and can be subtle, perhaps confined to the jaw or neck. Occasionally, an inability to tell the punchline of a joke due to a stuttering dys- arthria may be the only manifestation. Facial twitching or head bobbing is very common as an episode starts and can lead to diag- nostic confusion. Crucially, awareness is preserved in cataplexy, although in rare instances, when attacks last more than a mi- nute or so, dream-like intrusions and altered consciousness may intercede. Severely affected individuals may have over 20 attacks a day, often reporting that the amusement or frustration induced by the cataplectic episodes themselves can prolong the period of weakness. It is widely thought that cataplexy occurs because REM sleep paralysis intrudes inappropriately into the wakeful state. Indeed, as in REM sleep, a person is rendered temporarily areflexic during an episode as a result of descending inhibitory neural impulses from lower brainstem centres directly on to motor neurons. Some evi- dence suggests that this phenomenon may occur to a minor degree during emotion in control individuals, adding credibility to the adage ‘going weak with laughter’. Sleep paralysis and hallucinations Sleep paralysis and hallucinations around sleep–wake transition are the other two components of the narcoleptic ‘tetrad’ first described in 1957. However, only 25% of patients have all four elements, and the presence of these other symptoms, particularly sleep paralysis, is not specific to narcolepsy. Sleep paralysis is usually frightening, primarily because of an inability to take deep breaths voluntarily. Most episodes occur at the point of waking, although people with narcolepsy may also report episodes at sleep onset. Accompanying sensations of being crushed, with or without vivid visual hallucin- ations, may add to the distress of the episodes. Similar to cataplexy, this phenomenon reflects the intrusion of REM sleep elements into the wakeful or drowsy state. Hallucinations occurring at sleep onset (hypnagogic) or as the person wakes (hypnopompic) are usually visual and can be MT Control Sleep stage Untreated narcoleptic Sleep stage W REM 1 2 3/4 MT 18.00 20.00 22.00 24.00 02.00 04.00 06.00 REM sleep REM Sleep Time of day Time of day 08.00 10.00 12.00 14.00 16.00 18.00 20.00 22.00 24.00 02.00 04.00 06.00 08.00 10.00 12.00 14.00 16.00 W REM 1 2 3/4 Fig. 24.5.3.2 Comparisons of typical hypnograms over 24 h in a control person and someone with untreated narcolepsy. In the narcoleptic trace, there is severe disruption of the usual pattern with numerous daytime naps containing REM sleep. Overnight, the usual sleep architecture is disorganized in the person with narcolepsy with several awakenings and associated movement. MT, significant movements; W, wake.

section 24 Neurological disorders 5890 both vivid and disturbing, especially in children. They repre- sent fragments of dream mentation intruding into the conscious state, reinforcing the notion that people with narcolepsy cannot adequately maintain a consistent and stable state of wakefulness or sleep. When questioned, most people with narcolepsy have frag- mented nocturnal sleep. Although this may be due to the intrusion of a parasomnia or obstructed breathing, both of which are more common in people with narcolepsy, the primary problem is one of sleep regulation and maintenance. The notion that people with narcolepsy have problems sleeping at night is counterintuitive to some but is an important addition to the original descriptions of the syndrome. Other symptoms In addition to obvious naps, most people with narcolepsy will experience numerous ‘micro-sleeps’ through the day, in which awareness during activities is compromised for

a few seconds. The resulting lapses lead to automatic and inappropriate behaviours, with worrying consequences for complex and potentially dan- gerous tasks such as driving. Although difficult to characterize, many people with narcolepsy also report significant problems with memory and concentration as a result of their sleep–wake diffi- culties. Furthermore, increasing evidence suggests abnormalities of appetite, particularly at night, with cravings for sweet foods. Moderate obesity is more common in narcolepsy and may have a metabolic explanation because there is no link with excessive food intake. Indeed, some evidence suggests that overweight people with narcolepsy eat less than average. Pathogenesis and diagnosis Since the discovery in 1984 that Japanese people with narcolepsy were extremely likely to carry the human leucocyte antigen (HLA) haplotype DR2, an autoimmune basis for the syndrome has been thought likely. The predisposing antigen has since been established to be DQ-B1*0602, which is present in over 90% of people with narcolepsy and cataplexy and around 50% of those without cata- plexy, compared with a frequency of 20% in control populations. Of interest, homozygosity for DQ-B1*0602 appears to confer an even greater risk for the syndrome. Direct evidence for auto- immunity, in the form of either serum markers or cerebrospinal fluid (CSF) abnormalities, remains elusive and narcolepsy is rarely associated with other manifestations of autoimmunity. A minority of patients studied close to disease onset appear to have increased titres of specific immunoglobulins such as antistreptolysin O, al- though the significance of this remains uncertain. Further possible support for an autoimmune aetiology comes from the observation in Finland and Sweden that a significant surge in childhood cases appeared to associate temporally with vaccination against pan- demic H1N1 influenza. This association has also been observed in Ireland and the United Kingdom but not in other European coun- tries and case-control studies will be needed to clarify the potential link. However, of interest, a threefold increase in narcolepsy was reported in China in 2009 following the H1N1 pandemic in the absence of a significant vaccination programme. This may imply that any nonspecific activation of the immune system may confer an increased risk of narcolepsy, potentially in those with a predis- position for the disease. A major breakthrough in understanding the neurobiology of narcolepsy occurred in 1999 when two groups independently demonstrated abnormalities of a recently described neuropep- tide, hypocretin (also called orexin), in separate animal models. The well-established autosomal recessive Doberman model was shown to have dysfunctional hypocretin receptors, whereas a mouse hypocretin knockout model developed convincing clinical features of narcolepsy with cataplexy. Subsequently, it has been demon- strated that CSF hypocretin is virtually absent both in sporadic ca- nine models and in people with narcolepsy and cataplexy. Indeed, a CSF hypocretin level of less than 110 pg/ml is now considered diagnostic. Postmortem evidence has confirmed that pathology in narcoleptic brains is confined specifically to hypocretin neurons, potentially supporting the theory that they are destroyed by an auto- immune process. Confusingly, however, in rare familial narcolepsy and in sporadic cases without typical cataplexy, hypocretin levels can be preserved, implying that there is more than one pathogenic mechanism for certain forms of the syndrome. Following the unexpected involvement of the hypocretin system in human narcolepsy, it has been intensely studied in intact animals. Around 30 000 neurons containing the peptide are confined to the lateral hypothalamus but innervate all the arousal systems in the brain. Levels of hypocretin rise towards the end of the waking day, especially in the presence of peptide hunger signals or if the person is expecting food. Activity of hypocretin neurons therefore appears to stabilize a state of wakefulness when the organism needs to be alert. In narcolepsy their absence leads to inappropriate switches be- tween sleep and wakefulness. Moreover, transitions between behav- ioural states may be incomplete, explaining the intrusion of REM sleep phenomena such as paralysis into wakefulness. The mech-

anism by which emotional stimuli (in particular) trigger cataplexy remains elusive. However, recent evidence from functional brain imaging techniques suggests that narcoleptic patients may have abnormal processing of emotional information. If typical cataplexy is absent and CSF hypocretin levels cannot easily be measured, a positive diagnosis of narcolepsy can be made following a multiple sleep latency test. This test measures the pro- pensity for a person to fall asleep by recording the average length of time to reach light sleep in a conducive environment over four or five nap opportunities between 9.00 am and 3.00 pm. If the mean sleep latency is less than 8 min and REM sleep is achieved within 15 min on at least two occasions, the criteria for narcolepsy are fulfilled. Reliable results depend on ensuring a reasonable night's sleep pre- ceding the investigation, and the test also requires a strict protocol to avoid false-negative results. Secondary narcolepsy Narcoleptic symptoms including cataplexy have been reported in other neurological conditions. Given the recent advances in the understanding the neurobiology of the primary syndrome, it is not surprising that pathology in the region of the hypothalamus such as tumours around the third ventricle can lead to secondary narco- lepsy, presumably by depletion of hypocretin-containing neurons. However, the mechanism of severe sleepiness or sleep–wake dysregulation after head injury or as components of other condi- tions such as multiple sclerosis and Parkinson's disease can be diffi- cult to explain. The various subtypes of narcolepsy are shown in Table 24.5.3.3.

 Treatment Advice on lifestyle helps some people with narcolepsy. Planned naps, especially after meals, may improve wakefulness. Furthermore, the avoidance of large meals rich in refined carbohydrates is re- portedly beneficial to some. Most people with narcolepsy, how- ever, benefit from medication to improve daytime wakefulness (Table 24.5.3.4), although few are normalized. Modafinil is the most widely used wake-promoting agent and has partly replaced traditional psychostimulants. Its mechanism of action remains ob- scure, but a direct effect on arousal centres in the hypothalamus is postulated. It has no definite positive effect on cataplexy. Side effects are rare and include headache or gastrointestinal upset. Interactions with the oral contraceptive pill and uncertainty over safety in pregnancy may limit its use in young women. In severe sleepiness or if modafinil is unsuccessful, central stimulants with a predominantly dopaminergic action, such as dexamfetamine, are helpful, especially if used flexibly. Despite pre- scriber concerns, it is rare for psychological addiction to occur in narcolepsy, although tolerance may require increasing doses with time. Cardiovascular side effects such as hypertension are rela- tively rare but necessitate caution in older people. Given the dif- ferent mechanisms of action, a combination of modafinil and a psychostimulant is appropriate. Additional use of caffeine and setting aside time for planned naps may reduce the need for medication. A further drug with a novel mode of action is also being used in patients who fail to respond adequately or who are intolerant to es- tablished wake-promoting treatments. Pitolisant appears to act as an inverse histamine (H3) receptor agonist and effectively increases histamine release from the posterior hypothalamus to increase alertness. About a half of people with narcolepsy also require specific treatment for cataplexy. Although the evidence base is small, most antidepressants will suppress cataplexy by increasing cerebral monoaminergic activity and inhibiting the tendency to enter REM sleep, although the side-effect profile of most antidepressant drugs, Table 24.5.3.3 Subtypes of narcolepsy and associated features Narcolepsy with cataplexy (sporadic) (%) Narcolepsy without cataplexy (sporadic) (%) Familial narcolepsy (%) Secondary (symptomatic) narcolepsy (%) REM sleep reached within 15 min on two or more occasions in MSLT 85 100% (by definition) Uncertain 75 HLA DQ-B1*0602 positivity 85–93 35–56 65–79 Uncertain Presence of low or undetectable CSF

Hcrt-1 levels

> 90 14 38 Variable Reported instances of very low levels in individual cases Proposed or presumed pathogenesis Autoimmune destruction of Hcrt-synthesizing neurons Partial Hcrt deficiency Multiple genotypes Damage to Hcrt-containing neurons in the lateral hypothalamus Unknown mechanism in many Hcrt system very rarely involved directly CSF, cerebrospinal fluid; HLA, human leucocyte antigen; Hcrt-1, hypocretin-1; MSLT, multiple sleep latency test; REM, rapid eye movement. Table 24.5.3.4 Commonly used drug treatments for the narcoleptic syndrome Drug Total 24-h dose range (mg) Comments Excessive daytime sleepiness Modafinil 200–600 Different mechanism of action to traditional psychostimulants Dexamfetamine 5–60 Tolerance can develop but dependence rare Methylphenidate 10–80 Similar to amphetamine but possibly smoother action; long-acting preparation available Sodium oxybate 4.5–9 g Taken through the night; may act synergistically with daytime stimulants Pitolisant 20–40 A novel mode of action that produces increased histamine levels in the hypothalamus Cataplexy Venlafaxine 75–225 Possibly the antidepressant with most anticataplectic properties Clomipramine 10–150 Potent but side effects often limit use Fluoxetine 20–40 Appropriate for mild cataplexy; few side effects Sodium oxybate 4.5–9 g Taken at night; up to 90% of attacks may be abolished after 4 weeks of treatment Disturbed nocturnal sleep Clonazepam 0.5–2 Sleep continuity improved but sleep quality not usually refreshing; intermittent rather than continuous use advisable Sodium oxybate 4.5–9 g Deep non-REM sleep increased; overall sleep quality improved REM, rapid eye movement.

section 24 Neurological disorders 5892 particularly the tricyclics, may limit their usefulness. A new ap- proach for troublesome cataplexy is to use sodium oxybate, and trial evidence suggests that this drug helps daytime sleepiness as well. It is a liquid preparation taken before bed and—due to its short half- life—once during the night if the person is awake. The effects on cataplexy are striking after several weeks of therapy, with almost 90% of attacks abolished. Inadvertent daytime naps, and objective and subjective measures of daytime sleepiness also improve. The agent appears to work, in part, by inducing deep restorative sleep early in the night, such that the sleep drive is effectively dissipated by the fol- lowing morning. The drug should be used with extreme caution in any patient living alone or with young children in case confusional episodes from deep sleep are provoked. However, if disturbed noc- turnal sleep is a major symptom, it appears a logical treatment given that standard benzodiazepine hypnotic agents rarely induce re- freshing sleep in narcolepsy. Following the recent findings that most people with narcolepsy are deficient in the neuropeptide hypocretin, an obvious therapeutic goal will be to develop replacement therapy. There appear to be clin- ical effects if hypocretin levels are increased in animal models by intracerebral infusion, hence the development of an oral analogue that penetrates the blood–brain barrier is a current pharmacological goal for treatment in humans. In line with the theory that narcolepsy may have an autoimmune basis, several small open trials have examined various forms of immunomodulation in treatment, especially if it is diagnosed near disease onset. However,

results have generally been disappointing and it is thought placebo effects on cataplexy, for example, may have been substantial. Idiopathic hypersomnia Idiopathic hypersomnia is a diagnosis of exclusion most often made when excessively sleepy patients do not completely fulfil the diagnostic criteria for narcolepsy. Depending on precise definitions, it is probably 10 times less common than narcolepsy. Classic cases report difficulty waking in the morning followed by prolonged unrefreshing daytime naps despite long and deep nocturnal sleep. Low mood and frequent automatic behaviours are commonly re- ported. However, no specific narcoleptic features such as cataplexy are present, and CSF hypocretin levels are generally normal. Sleep investigations should confirm a shortened daytime sleep latency of less than 8 min, preceded by normal but prolonged nocturnal sleep. A new category of idiopathic hypersomnia without prolonged overnight sleep has been proposed, but this is controversial and distinction from atypical or monosymptomatic narcolepsy can be difficult. As in narcolepsy, although usually with less satisfactory results, the treatment of idiopathic hypersomnia consists of modafinil alone or in combination with traditional psychostimulants. Some prelim- inary evidence suggests that flumazenil, given orally, may benefit some patients. This finding is of great interest given the demonstra- tion of an endogenous benzodiazepine-like substance in the cere- brospinal fluid of some patients. Kleine–Levin syndrome Kleine–Levin syndrome is a rare and poorly characterized sleep disorder most commonly seen in adolescents. The primary feature is periodic hypersomnia lasting days to weeks, recurring at inter- vals of weeks to months. During symptomatic periods the person is generally drowsy and usually displays abnormal behaviours. These include simple irritability, hallucinations, hypersexuality, and ab- normal appetite, producing hyperphagia. Investigations are gener- ally unhelpful, although an excess of REM sleep is occasionally seen during episodes. Intermittent hypothalamic dysfunction is a specu- lative but plausible mechanism to explain the symptom complex. Secondary causes are very rare and reportedly include a wide variety of neurological conditions, such as multiple sclerosis and Prader– Willi syndrome. Treatments are empirical and usually ineffective, although the syndrome tends to resolve spontaneously after several years. An amphetamine may help during episodes and lithium may be used as a prophylactic agent. Parasomnias and sleep-related
movement disorders Parasomnias are loosely defined as intermittent undesirable events arising from sleep that are not epileptic in nature. The spectrum is large, ranging from visual imagery at sleep onset to complex motor behaviours, occasionally with violent components. Family mem- bers and bed partners are usually more concerned than the indi- viduals themselves, who often remain oblivious to any nocturnal disturbance. Parasomnias are generally classified according to the sleep stage from which they arise, although some are not ‘state dependent’. A simple yet valid scheme to explain most parasomnias is shown in Fig. 24.5.3.3. The brain can function in three distinct and mu- tually exclusive states, namely wakefulness, non-REM sleep, and REM sleep. The brain normally switches seamlessly and relatively quickly between these states through the sleep–wake cycle. Most parasomnias result from abnormal state transitions such that elem- ents of one state intrude into another: a person can be considered ‘caught’ for a variable period of time in a separate abnormal state somewhere between wake and sleep. With the exception of certain REM sleep disorders, the neuroana- tomical basis of parasomnias remains obscure. The high prevalence of familial aggregation suggests genetic factors and predominance in childhood implies a maturational component, particularly in non- REM parasomnias. Parasomnias at the sleep–wake transition It is an almost universal experience to have occasional unpleasant sensations of falling through space at the point of sleep onset, with resulting brief muscular contractions. In some individuals these hypnic jerks can regularly interfere with sleep onset and recur through the night.

In others there are accompanying explosive sen- sory phenomena, sometimes with severe head pain as a component. Treatments with short-acting benzodiazepines may be justified in severe cases. More complex and prolonged phenomena comprising a variety of rhythmical movements also tend to occur during extreme drowsi- ness just before sleep. Head banging is the most common manifest- ation in children. The problem tends to resolve with time, although can persist into adulthood and disturb bed partners. Various patterns

 of movement are seen, with the head, neck, and trunk most commonly involved. The view that the movements are semi-voluntary, as part of a sleep-inducing habit, does not concord with the observa- tion that the phenomenon arises only from deep or even REM sleep in a few individuals. Parasomnias arising from deep non-REM sleep Non-REM parasomnias are characterized by sudden but partial arousals from deep sleep, usually stage 4, resulting in behaviours for which the person usually has no subsequent clear recollection. Based on clinical features, sleepwalking, confusional arousals, and night terrors are recognized as three separate phenomena, all due to abnormal arousal from deep sleep. Within this notional spectrum, however, there may be considerable overlap and the type of episodes may change with age. In sleepwalking the person will typically leave the bedroom and may well engage in complex behaviours such as cooking and eating. Communication is possible at a basic level, but it is usually clear to observers that the person is not fully alert or responsive. Concerns often arise when there are attempts to leave the house or if there are any violent elements to the episodes. Confusional arousals refer to brief episodes of disorientation in which the person may sit up in bed and survey the environment be- fore returning to sleep. Night terrors are dramatic episodes, often lasting for several min- utes, in which the person suddenly arouses from sleep, typically with a loud scream and extreme agitation. Motor and autonomic indications of extreme fear are usually alarming to parents and observers. All these arousal disorders tend to occur within an hour of sleep, when non-REM sleep is at its deepest. It is rare for events to recur through the night. If there is any recall, it is usually vague and re- lated to a nonspecific fear or urge to leave the bedroom in the case of night terrors. Particularly deep sleep after a period of deprivation or induced by drugs (including alcohol) may increase the likelihood of events. General stress, changes in schedule, and sleeping in a new environment are further recognized precipitants. Non-REM parasomnias are common in the first decade of life, affecting at least 6% of children on a regular basis. Persistence into adulthood occurs in around 15% of these. A confident distinction between nocturnal epilepsy and parasomnias can usually be made from clinical features alone, although investigations and video ana- lysis may be required in some cases. Particularly in adults, overnight investigations may reveal an additional sleep disorder such as sleep apnoea or periodic leg movements that may partially arouse the person and help to trigger a parasomnia. It is rarely appropriate to treat non-REM parasomnias with medication, especially in children. However, if disturbances are frequent or likely to cause danger, short courses of benzodiazep- ines such as low-dose clonazepam before bed are usually helpful. In the absence of any substantial evidence, antidepressants such as paroxetine are also used to good effect, presumably by effects on sleep architecture. REM sleep parasomnias REM parasomnias include nightmares, REM sleep paralysis, and REM sleep behaviour disorder. Given the propensity for REM sleep to occur late in the night, these parasomnias are typically reported between 3.00 am and 6.00 am, in contrast to the earlier occurrences of arousal disorders from non-REM sleep. Nightmares represent arousals from unpleasant dreams and are universal experiences. However, up to 4% of adults have frequent or intrusive nightmares, often in the context of psychological stress or substance abuse. Nightmares with recurring themes are a

hallmark of post-traumatic stress disorder. Some drugs (e.g. β blockers), can trigger nightmares, as may the sudden withdrawal of antidepressant agents that normally suppress REM sleep. Symptoms of sleep paralysis, seen in around 40% of people with narcolepsy, can also occur as an isolated phenomenon, occasionally with a familial pattern. As in narcolepsy, the profound paralysis is usually disturbing. Typically, prolonged episodes can be aborted by a tactile stimulus from a bed partner. If treatment is thought neces- sary, tricyclic antidepressants are usually helpful. An increasingly recognized REM parasomnia occurs when ab- normal motor activity intrudes into REM sleep, reflecting a fault in the normal mechanisms that render dreaming individuals com- pletely atonic. So-called REM sleep behaviour disorder (RBD) is predominantly an affliction of middle-aged or older men and has an intimate relationship to several neurodegenerative dis- eases, particularly parkinsonism. Over 70% of people free of any movement disorder during wakefulness at the onset of symp- toms will develop Parkinson's disease within 10 years of follow- up. Increasing evidence suggests that RBD confers an increased Fig. 24.5.3.3 A graphical demonstration depicting the normal transitions of the mutually exclusive states of wakefulness, nonrapid eye movement (non-REM), and REM sleep. The switch from REM sleep to wakefulness can occur directly and would normally lead to a dream experience. Most parasomnias occur because of abnormal or inefficient state transitions. Sleepwalking and related phenomena occur when a person arouses incompletely from deep non-REM sleep. Hypnic jerks may occur when the brain fails to fall asleep in its entirety. The narcoleptic symptoms of sleep paralysis, cataplexy, and hallucinations at sleep–wake transition occur when elements of REM sleep intrude into wakefulness. Parkinsonian hallucinations probably represent REM sleep imagery occurring in the drowsy wakeful state. Some individuals report the ability to control their dreams (lucid dreaming) which can be considered as wakeful consciousness intruding into the REM sleep state. In some people with narcolepsy or severe dementia, it can be very difficult to stage sleep accurately and 'overlap' syndromes producing ambiguous sleep can occur. DLB, dementia with Lewy bodies; PD, Parkinson's disease.

section 24 Neurological disorders 5894 risk for relatively complex forms of Parkinson's disease, potentially with early cognitive impairment or neuropsychiatric manifest- ations. Indeed, if parkinsonism is present at the time RBD is recog- nized, prospective studies suggest that a significant proportion will develop early dementia. The nocturnal episodes of RBD are brief and generally explosive, usually involving the arms. There is often an apparently aggressive intent, but injuries to bed partners are incidental and violence is rarely directed. In mild cases, episodes are confined to vocalization or swearing with little observable movement. If awoken during an event, dream recall is the norm, although most remain oblivious to their behaviours if their sleep remains continuous. Intriguingly, pleasant dreams or those with a sexual content are very rare, whereas reports of being chased by aggressors or attacked by animals are typ- ical themes. It is often appropriate to treat this parasomnia on a long-term basis to prevent injury either to the person with the condition or to the bed partner. Clonazepam in a dose range of 0.25–2 mg is usually ef- fective, with melatonin used as a second-line agent at doses between 2 and 6 mg. If there are suspicions of an additional breathing-related sleep disorder, overnight investigations are warranted because, for example, clonazepam may worsen obstructive sleep apnoea. Periodic leg movements of sleep Periodic leg movements of sleep are characterized by stereotyped leg movements occurring in clusters every 30 s throughout sleep, especially in the light non-REM stages. The movements them- selves tend to be fairly slow, evolving over 1 to 5 s and typically involving both legs, although one or the other may predominate. An episode tends to start with great toe extension and spreads to include ankle dorsiflexion, followed by knee and hip flexion in se- vere

cases. It is relatively rare for individuals to be aware of the leg movements, but bed partners may complain. The phenomenon increases dramatically with age and is strongly associated with restless legs syndrome. If periodic leg movements of sleep are demonstrated after overnight investigation, it can be difficult to gauge their clinical significance, especially if there are no associated electroencephalography (EEG) arousals. Further complications may arise if there are other reasons for fragmented sleep such as obstructive sleep apnoea, in which case leg movements may be triggered as a secondary epiphenomenon. Treatments for restless legs syndrome also ameliorate periodic leg movements of sleep. Dopamine agonists are usually effective, al- though it is difficult to predict in advance whether any response will be clinically meaningful. Circadian rhythm disorders If both quality and quantity of sleep are normal over 24 h but a person is unable to sleep or stay awake at the desired or expected time, a circadian rhythm disorder may be diagnosed. Most com- monly this problem has a clear extrinsic cause such as shift work or long-haul jet travel, but in some situations there is almost certainly dysfunction of the internal clock mechanism. Behavioural or motiv- ational factors may contribute to the generation of highly irregular sleep–wake especially in younger individuals. In mammals the primary biological clock is sited in an area of the hypothalamus called the suprachiasmatic nucleus. The mechanism of the clock at a subcellular level has been extensively researched and appears very similar across all animal species, including hu- mans. In strict isolation with no external cues, the periodicity of the human clock is around 24.3 h. In real life this rhythm is entrained precisely to 24 h primarily by light cues acting on retinal cells that contain a newly discovered retinal pigment, melanopsin.
A retinal tract to the hypothalamus allows this information to influence the clock mechanism. People who are blind from birth frequently re- port difficulty in adapting to a conventional sleep–wake cycle be- cause their internal clocks run a little ‘slower’ than average without light entrainment. Very rarely, sighted individuals also have a similar non-24-h sleep–wake disorder, the precise mechanism of which re- mains obscure. Delayed sleep phase syndrome People diagnosed with delayed sleep phase syndrome can be con- sidered as extreme ‘night owls’ such that they are simply unable to sleep before 2.00 am or later. The main concern is usually the sub- sequent inability to wake effectively for school or work. It is im- portant to exclude significant mood disorder as a driver for the abnormal cycle. Similarly, delayed sleep phase syndrome would not be diagnosed in those who simply prefer the solitude of night and avoid daytime interactions. Sleep diaries and wrist actigraphy can help confirm the diagnosis, which mostly affects adolescents with a prevalence estimated at 1%. Those with the condition and their families are very commonly frustrated by this sleep disorder and the relative lack of its recognition. Treatment is difficult and starts with a strict schedule and general sleep hygiene measures. Melatonin taken around 2 h before desired sleep-onset time may help with sleep onset, but long-term use of hypnotics is usually unsuccessful. Phototherapy from a light box on waking may also help ‘reset’ the internal clock. Advanced sleep phase syndrome This is an extremely rare disorder but of interest because a familial form has been identified and the relevant gene analysed. The point mutation occurs in a period gene (hPer2) such that the circadian sleep–wake period is 23.3 h. This results in individuals sleeping and waking at least 4 h earlier than expected. Other indications of disturbed circadian rhythm include melatonin secretion and core temperature. Humans also generally show ‘phase advance’ with increasing age. Common experience suggests that many older people will fall asleep in the evening and wake early in the day, especially in in- stitutions where this may be encouraged as part of a convenient regimen. Shift-work sleep disorder An increasing number of people are employed in jobs requiring shift work in a variety of patterns. Rotating shifts, in particular, do not allow circadian rhythms to adapt and frequently lead to difficul- ties, either in

staying awake for employment or in sleeping effect- ively during daylight hours. Of potential concern are the secondary effects of sleep deprivation on cognitive performance in tasks demanding sustained attention or decision-making, especially

24.5.3 Sleep disorders 5895 in occupations involving heavy industry or transportation. Most shift workers find it increasingly difficult to adapt their sleep–wake cycle as they age. Moreover, additional sleep problems such as ob- structive sleep apnoea may worsen the situation. If shift work is causing significant symptoms and cannot be avoided, treatment is a challenging area if simple sleep hygiene advice fails to help. Planned naps may be beneficial, and shift pat- terns that rotate by delaying work time rather than advancing it are generally easier to cope with. Regular medication is controversial with concerns over dependency, especially with regard to hypnotic agents. Regular caffeine may be used, and wake-promoting drugs such as modafinil have been licensed in severe shift-work sleep disorder, although the concept of shift-work sleep disorder as a problem requiring drug treatment lies uncomfortably with many doctors. The assessment of sleep symptoms In assessing a patient with a sleep disorder, the importance of a de- tailed history from the person and, ideally, a bed partner or close family member cannot be overemphasized. Together with a sleep diary, when appropriate, most diagnoses can be made with mod- erate confidence on history alone. With important exceptions, such as sleep apnoea, where quantification of the problem is important, it is relatively rare for investigations to add useful diagnostic informa- tion, but they can be invaluable if a reliable history is not available (e.g. in the case of a person who sleeps alone). The availability of fa- cilities for studying sleep varies dramatically throughout the world, often dependent on how the tests are financed. The following section is based on a British perspective, where sleep medicine is relatively under-resourced. Insomnia Overnight tests are rarely useful when insomnia is an isolated symptom. In people who complain of extremely reduced overnight sleep, surrogate monitoring of sleep using wrist actigraphy may be useful in demonstrating paradoxical insomnia, in which there is a misperception of the amount of sleep obtained. An algorithm for assessing chronic insomnia is shown in Fig. 24.5.3.4. Chronic insomnia associated with daytime sleepiness and frequent naps is likely to have a secondary identifiable cause. Excessive daytime sleepiness If excessive daytime sleepiness is the primary complaint, it is nor- mally possible to identify an underlying cause, even if the answer is simply insufficient overnight sleep. Care should be taken in establishing that sleepiness itself is the symptom of concern and not lethargy or fatigue, which are more likely to have psychological or motivational substrates. An algorithm for assessing a sleepy person is shown in Fig. 24.5.3.5. Parasomnias Non-REM parasomnias are difficult to investigate and rely on a good history to allow confident diagnosis. Capturing an event on over- night recording is rare and investigations on asymptomatic nights are usually unremarkable. Particularly in adults, an additional sleep disorder may sometimes be precipitating a parasomnia. If so, it is appropriate to perform overnight investigations to detect arousals secondary, for example, to apnoea or leg movements. Differentiating non-REM parasomnias from nocturnal epilepsy can be difficult and video analysis—ideally of several episodes—can be crucial for diag- nosis. The provision of video recorders to patients’ families in order to capture events at home may be more productive and cost-effective than formal overnight recording in a hospital setting. Subject complains of inadequate sleep Is subject trying to sleep? Is a formal sleep disorder likely such as sleep-wake transition disorder, RLS or OSA? Is there shift work or a primary circadian disorder? Other causes of insomnia? NO NO NO NO YES YES YES ADVISE LIFESTYLE CHANGES ADVICE AND CONSIDERATION OF TREATMENT FURTHER HISTORY; DIARY AND/OR ACTIGRAPHY Confirms insomnia CONSIDER INVESTIGATIONS AND TREAT CONSIDER PARADOXICAL INSOMNIA If sleep hygiene and environment

largely responsible ADVICE AS APPROPRIATE If symptoms suggest conditioned insomnia CONSIDER PSYCHOPHYSIOLOGICAL INSOMNIA If insomnia is lifelong CONSIDER IDIOPATHIC INSOMNIA If anxiety and/or depression prominent factors CONSIDER PRIMARY PSYCHIATRIC ILLNESS YES YES Fig. 24.5.3.4 Algorithm for the assessment of a person with insomnia. OSA, obstructive sleep apnoea; RLS, restless legs syndrome.

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