Sleep Disturbances in General Medical Disorders

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Introduction

General medical disorders through metabolic, toxic, or anoxic disturbances may cause a disruption of neuroanatomic substrates for sleep/wakefulness by indirectly affecting the sleep-/wake-promoting neurons. It is therefore incumbent upon the sleep specialist, general internist, and primary care physician to have a high index of suspicion for the presence of sleep disorders so that appropriate steps for assessment and management of these patients can be instituted. This chapter deals with medical disorders—excluding neurologic diseases—associated with sleep dysfunction, which may cause added distress to the existing complaints related to the medical disorders and which may need special attention. For example, if a patient suffering from bronchial asthma or coronary artery disease, complaining of difficulty initiating or maintaining sleep, unrefreshing sleep, and excessive daytime sleepiness, seeks the attention of a physician, these complaints are obviously causing additional distress and need special attention. The latest edition of the International Classification of Sleep Disorders (ICSD-3) [1] does not list a separate category of sleep disturbances associated with medical disorders, in contrast to the first edition. These medical disorders are mentioned within the seven major categories of sleep disorders as well as in Appendix A of the ICSD-3 [1].

Gislason and Almqvist [2] did an epidemiologic study in a random sample of 3201 Swedish men ages 30–69 years. Difficulty initiating or maintaining sleep and too little sleep were the major complaints, followed by excessive daytime somnolence or too much sleep. Sleep maintenance problems became more frequent with increasing age. The following conditions were associated with the sleep complaints: systemic hypertension, bronchitis and bronchial asthma, musculoskeletal disorders, obesity, and diabetes mellitus. The authors suggested that the reported increased mortality among patients with sleep complaints might be related to the intercurrent somatic diseases.

In a questionnaire of 100 adult male medical and surgical patients in a teaching hospital in Melbourne, Australia, Johns and coworkers [3] found that increasing age and ischemic heart disease were mostly associated with long-term sleep disturbances. In a three-year longitudinal study comprising 6800 men and women aged 65 and older, risk factors associated with insomnia included several medical conditions such as heart disease, cancer, diabetes, and stroke as well as hip fractures and use of sedatives [4]. Several other epidemiologic studies [5–8] attest to the frequent association of sleep disturbances with medical disorders. Stroe et al. [7] studied 2612 individuals drawn from an unselected adult population-based sample (18–65 years) to characterize excess daytime sleepiness (EDS) associated with a variety of chronic medical disorders (MD) using Epworth Sleepiness Scale (ESS) as a standardized measure. Sixty-seven percent of the sample reported a MD and the prevalence of 31.4 % in individuals with MD. Among general medical disorders the highest degree of sleepiness associated with significant sleep difficulties (e.g., sleep onset and maintenance problems with frequent awakenings) was found in patients with peptic ulcer diseases. They also noted significant sleep disturbance in those with colitis and that clinically significant EDS increased directly with the number of MD. Using self-reported measures of sleep habits and polysomnographic study (obtained in a subset) in a community-based sample of 3282 men and women aged 18–65 years, Budhiraja et al. [8] documented a prevalence of insomnia of 21.4 % with 2.2 times higher odds ratio for those with any medical disorders than in those without medical disorders. They also noted that prevalence of insomnia increased with increasing number of medical conditions. However, PSG evidence of disturbed sleep was noted in only a small subset of comorbid insomnia population.

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When a patient presents to a sleep specialist with sleep disturbance, with the complaint of either insomnia or hypersomnia, the first important step is to obtain a detailed medical history and other histories, followed by physical examination to uncover a cause for the sleep disturbance. Often, the patient presents to an internist or a family practice physician, who may then refer for a consultation to a sleep specialist if there are sleep complaints. Therefore, a comprehensive knowledge of major medical disorders that may present with sleep disturbance is essential. In this chapter, a review of the salient clinical diagnostic points of some important medical disorders presenting with sleep disturbance is offered, along with information on key laboratory investigations.

Medical Disorders that Cause Sleep Disturbances

Several medical disorders are associated with sleep disturbances, as listed here. The mechanisms and general features of sleep disturbances in medical disorders are also briefly described. For further details, readers should consult general textbooks of internal medicine.

- Cardiovascular diseases: cardiac arrhythmia, congestive cardiac failure, ischemic heart disease, and nocturnal angina
- Intrinsic respiratory disorders: chronic obstructive pulmonary disease, asthma (including nocturnal asthma), and restrictive lung disease
- Gastrointestinal diseases: peptic ulcer disease, reflux esophagitis, celiac disease, Whipple's disease, and functional bowel disorder
- Endocrine diseases: hyperthyroidism, hypothyroidism, diabetes mellitus, and growth hormone deficiency and excess
- Renal disorders: chronic renal failure and sleep disturbances associated with renal dialysis
- Hematologic disorders
- Rheumatic disorders, including fibromyalgia syndrome and systemic lupus erythromatosis
- Dermatologic disorders
- Acquired immunodeficiency syndrome
- Lyme disease
- Chronic fatigue syndrome
- Medical and surgical disorders of patients in medical and surgical intensive care units
- African sleeping sickness (trypanosomiasis)
- Cancer
- Medication-related sleep–wake disturbances.

Mechanism of Sleep Disturbances in Medical Disorders

Sleep disturbance may have an adverse effect on the course of a medical illness. Thus, a vicious cycle may result from the effect of sleep disturbance on the medical disease and the effect of the medical illness on sleep architecture.

Sleep may be disturbed in medical disorders by a variety of mechanisms, including

- Indirect effects on the hypnogenic neurons in the diencephalon and brain stem, and respiratory neurons in the brain stem, by metabolic disturbances (e.g., renal, hepatic, or respiratory failure; electrolyte disturbances; hypoglycemia or hyperglycemia; ketosis; and toxic states)
- Adverse effects on sleep organization and sleep structure by drugs used to treat medical illness
- Disturbances of circadian rhythm (i.e., sleep–wake schedule)
- Effects on the peripheral respiratory mechanism (including respiratory muscles) causing respiratory sleep-disordered breathing
- Esophageal reflux, which may be due to prolongation of acid clearance of the lower esophagus, aspiration, and reflex mechanism (see Chap. 11)
- Adverse effect on sleep structure after prolonged immobilization resulting from medical disorders
- Dysfunction of the autonomic nervous system caused by medical disorder (e.g., diabetes mellitus, and amyloidosis).

General Features of Sleep Disturbances in Medical Illness

Sleep architecture, sleep continuity, and sleep organization may be affected in a variety of medical illnesses. Patients may present with either insomnia or hypersomnolence, but the most medical disorders present with insomnia. Some patients may have a mixture of insomnia and hypersomnolence (e.g., those with chronic obstructive pulmonary disease or nocturnal asthma). Other sleep complaints include abnormal motor activity and behavior intruding into sleep (parasomnias), sleep-related breathing problems with sleep fragmentation and snoring during sleep, and disturbances of normal sleep–wake rhythm (circadian rhythm disorders). Table 47.1 lists the medical causes of insomnia. For medical causes of hypersomnolence, see Table 3.1 in Chap. 3.

Patients with insomnia may complain of lack of initiation of sleep, inability to maintain sleep, repeated arousals at

Table 47.1 Medical causes of insomnia

Congestive heart failure
• Ischemic heart disease
• Nocturnal angina
• Chronic obstructive pulmonary disease
• Bronchial asthma, including nocturnal asthma
• Peptic ulcer disease
• Reflux esophagitis
• Rheumatic disorders, including fibromyalgia syndrome
• Lyme disease
• Acquired immunodeficiency syndrome
• Chronic fatigue syndrome

night, and early morning awakening. Daytime symptoms of fatigue, inability to concentrate, irritability, anxiety, and sometimes depression may be related to the sleep deprivation. Polysomnographic (PSG) findings include prolonged sleep latency, reduction of rapid eye movement (REM) sleep and slow-wave sleep (SWS), more than 10 awakenings per night, frequent stage shifts, early morning awakening, increased waking after sleep onset (WASO), and increased percentage of wakefulness and stage 1 non-REM (NREM) sleep.

Patients with hypersomnolence may present with repeated daytime somnolence, fatigue, depression, headache, and intellectual deterioration related to repeated sleep-disordered breathing (SDB) and hypoxemia [9]. PSG findings consist of SDB, repeated arousals with oxygen desaturation at night, sleep fragmentation, sleep stage shifts, reduced SWS, shortened sleep-onset latency on the multiple sleep latency test, and sometimes REM sleep abnormalities [9].

Systemic medical disorders may cause neurologic disturbances, which in turn may cause sleep disturbances either directly by affecting sleep–wake systems in the central nervous system (CNS) or indirectly by affecting breathing. Sleep-related breathing dysfunction and other sleep disturbances which may be seen in neurologic illness are described in Chap. 41.

Specific Medical Disorders and Related Sleep Disturbances

Cardiovascular Disease

It is generally well known that sleep disturbances may occur in cardiovascular diseases, particularly in patients with ischemic heart disease, myocardial infarction, or congestive cardiac failure (CCF). Cardiac arrhythmias and sudden cardiac death at night are also known to occur, although adequate objective tests, including PSG study to document such disturbances, are lacking.

Ischemic Heart Disease

A careful inquiry into history is most important in making the diagnosis. The patient complains of a sense of tightness in the middle of the chest and a band-like feeling around the chest. The pain is often induced by exertion and relieved by rest. Generally, it lasts only a few minutes. When the patient complains of pain on lying supine, it is known as *angina decubitus,* whereas pain that awakens the patient at night is known as *nocturnal angina.* Infrequently, the pain results in coronary artery spasm accompanied by transient ST-segment elevation in the electrocardiogram (ECG), and the entity is then known as *Prinzmetal's* or *variant angina.* The condition is most common in middle-aged men but may affect postmenopausal women. Complications include cardiac arrhythmias; left ventricular failure; acute myocardial infarction; and sudden cardiac, often nocturnal, death.

Sleep disturbances are very common in patients with ischemic heart disease. Pain may awaken the patient, causing frequent awakenings and reduced sleep efficiency. Obstructive sleep apnea syndrome (OSAS) is associated with arterial hypoxemia causing cardiac ischemia. Simultaneous recording of an ECG may show ST-segment depression at least 1 mm below the horizontal, whereas ST-segment elevation occurs in Prinzmetal's or variant angina. Often, the patient complains of discomfort in the arms during the retrosternal pain. Pain may sometimes radiate to the epigastrium or to the neck and the jaw. It may be accompanied by shortness of breath. An ECG is essential for the diagnosis of ischemic heart disease or myocardial infarction. Coronary angiography provides information about the site of coronary artery occlusion.

Treatment consists of avoiding exertion for patients susceptible to angina attacks and administration of drugs such as nitrates, β-blockers, and calcium channel antagonists.

Patients with severe symptoms that persist despite medical treatment may need surgical treatment in the form of coronary artery bypass grafting or stenting.

Factors contributing to myocardial ischemia, infarction, or arrhythmia include increased sympathetic surge during REM sleep, increased platelet aggregability, hypotension associated with SWS and altered balance between fibrinolytic and thrombotic factors, oxygen desaturation, and increased ventricular diastolic pressure and volume associated with supine posture. There is also increased risk of CCF among patients with the onset of myocardial infarction at night [10]. Patients with diabetes, advancing age, and impaired ventricular function are at an increased risk for developing nocturnal myocardial infarction [11, 12].

"Nondippers" (those hypertensive patients whose blood pressure during sleep does not decline or declines less than 10 % from daytime to nighttime readings) have significant risk for developing cardiac arrhythmias, stroke, and death from cardiovascular disease [13]. Newman et al. [14] have shown that daytime sleepiness associated with sleep disturbances in elderly patients, especially women, is a predictor of cardiovascular morbidity and mortality and CCF.

Nocturnal Angina, Myocardial Infarction, and Sleep Disturbance

Nocturnal angina or myocardial infarction may cause frequent arousal, sleep maintenance insomnia, and impaired sleep efficiency. Nocturnal angina is known to occur during both REM and NREM sleep stages. Karacan et al. [15] found increased sleep-onset latency, reduced SWS, decreased sleep efficiency, and very little change in REM sleep on PSG study in 10 patients with a history of nocturnal angina. In several reports, circadian susceptibility to myocardial infarction (attacks are most likely between midnight and 6:00 AM) has been described [16, 17]. Broughton and Baron [18] in an early report found decreased sleep efficiency, increased sleep stage shifts, increased awakenings, and decreased REM sleep in 12 patients with acute myocardial infarction studied in the ICU. Sleep patterns became normal by the ninth day of the illness.

Coronary artery disease (CAD) is one of the most frequent causes of morbidity and mortality [19]. Sleep-disordered breathing (SDB) and CAD have a bidirectional relationship [20]. Impairment of cardiac function by CAD determines the severity of SDB [21]. Fifty percent of patients with CAD have SDB and if the cardiac function is impaired most apneas are of obstructive nature. In contrast, in patients with acute myocardial infarction (MI) causing impaired cardiac function, half of the SDB patients will have obstructive and the other half will have predominantly central apneas [22]. Cross-sectional and case-control studies have documented increased prevalence of calcified and noncalcified coronary artery plaques (subclinical coronary atherosclerosis) in SDB [21, 23, 24].

In several epidemiologic studies, there is a clear relationship between increased cardiovascular morbidity and mortality and sleep disturbances associated with SDB. Patients with CAD and obstructive sleep apnea (OSA) may have an increased cardiac risk due to nocturnal myocardial ischemia triggered by apnea-associated oxygen desaturation. In many case-control studies in the past, an association between sleep apnea and increased risk of myocardial infarction was noted [25–27]. Epidemiologic data from the Sleep Heart Health Study demonstrated a linear relationship between the apnea–hypopnea index (AHI) and risk of CAD, including myocardial infarction [28]. In a population-based prospective study including a postal questionnaire regarding sleep complaints in a random sample of 1870 subjects, Mallon et al. [29] provided evidence at the 12-year follow-up that there was an association between difficulty falling asleep and CAD mortality in men. In a more recent population-based prospective Sleep Heart Health Study, Gottlieb et al. [30] noted that OSA was a significant predictor of incident CAD in men 70 years or less but not in older men or women of any age.

A high prevalence of OSA in patients with CAD has been noted in several other studies [31–43]. An important early observational study was done by Marin et al. [35] recruiting men with OSA or simple snorers from a sleep clinic and a population-based sample of healthy men matched for age and body mass index with untreated severe OSA patients (total $N = 1651$). All had PSGs and were followed up at least once per year for a mean of 10.1 years; compliance with treatment of OSA with continuous positive airway pressure (CPAP) was checked with a built-in meter. Multivariate analysis adjusted for confounders showed that untreated severe OSA increased the risk of fatal and nonfatal myocardial infarction and stroke compared with healthy participants; CPAP treatments reduced this risk. The authors also noted that mild-to-moderate untreated OSA patients had an intermediate risk for these events, indicating a dose–effect relationship. The survival benefit to CPAP therapy in these patients as shown by Marin et al. [35] is also supported by other studies [32, 44, 45]. Prior to the study by Marin et al. [35], long-term beneficial effects of CPAP treatment in patients with OSA and CAD were shown by Milleron et al. [46]. These authors treated 25 of 54 patients with OSA and CAD (29 declined treatment). At a mean follow-up of 87 months, the treatment significantly reduced the risk of occurrence of cardiovascular death, acute coronary syndrome, hospitalization for heart failure, or need for coronary revascularization. Similar results were observed by Doherty et al. [47], who reported that deaths from cardiovascular disease were more common in an untreated group (61 patients who were intolerant to CPAP) than in a CPAP group (107 patients) after follow-up of 7.5 years [47].

There are some more recent studies showing adverse short-term and long-term outcomes in patients with acute MI and SDB. There is evidence that patients with acute MI and SDB have more severe CAD predisposing them to the development of heart failure [21, 37–41]. Recent long-term outcome studies in patients with acute MI and SDB are all observational in nature, precluding from making any definite conclusions [21]. The study by Lee et al. [48] enrolling 120 patients with an acute MI showed that those with comorbid severe OSA had higher incidence of adverse events than those with less severe or no OSA after a follow-up period of 18 months. In another case-control study [40], including MI patients with and without OSA, those who received CPAP treatment for OSA had a lower risk of recurrent MI than untreated OSA patients and similar to those without OSA after a follow-up period of six years. However, long-term effects of CPAP treatment in patients with acute coronary syndrome and OSA in terms of preventing development of heart failure and recurrent MI and mortality cannot be determined definitely without further randomized control studies using larger number of patients and a longer follow-up [21].

In an important study, Kripke et al. [49] noted increased mortality rates among patients with ischemic heart disease, stroke, and cancer who slept 4 h or less, or more than 10 h. Wingard and Berkman [50], in their study of approximately 7000 adults over a period of 9 years, also found excessive mortality from ischemic heart disease in short sleepers (less than 7 h) and long sleepers (more than 9 h). Poor sleep was thus associated with increased risk of future cardiovascular morbidity or mortality. These results, however, were contradicted by a later study by Mallon et al. [29] observing that short or long sleep duration did not influence the risk of CAD mortality or total mortality for either gender. In a later study, Meisinger et al. [51] reported a modest association between short sleep duration and difficulty maintaining sleep, and risk of occurrence of myocardial infarction in middle-aged women, but not men, from a general population sample in Germany. In a more recent study [52], a positive association was noted between short sleep duration and poor sleep quality, and CAD in a selected sample of Indian adults. Therefore, short sleep duration and poor sleep quality can be considered modifiable CAD risk factors, at least in this population.

Heart Failure

Heart failure is the preferred term instead of congestive heart failure as pulmonary congestion, although common, is not a universal feature [53]. There is a strong association between advancing age and HF, and 10 % of the population over the age of 80 has HF. Furthermore, in the USA, HF is the leading cause of hospitalization for those older than 65 years. Chronic HF is a growing public health problem affecting more than 2 % of the adult population, and HF is a leading cause of morbidity and mortality [53, 54]. SDB is the most common comorbidity in HF and newly diagnosed CSA and OSA are independently associated with increased mortality in HF [55–60]. There are two phenotypes: HF with reduced (<50 %) ejection fraction (EF) [HFrEF] or what is known as systolic HF; and HF with preserved (exceeding 50 %) EF (HFpEF) and this is now the preferred term instead of what was known as diastolic HF [60]. About 40–50 % of patients with HF belong to HFpEF. HFpEF is often associated with comorbidities (e.g., hypertension, type 2 diabetes mellitus, and atrial fibrillation) and is commonly seen in older individuals [53, 60, 61]. SDB occurs in 70 % or more of the HF patients (OSA and CSA–CSB, each in about half of these patients). Rostral fluid shift from the lower extremities in the recumbent position at night in HF patients worsens OSA [62, 63]. CSA–CSB relates in part to the instability of the central respiratory controllers in the brain stem [53, 59, 64–67].

Mechanism of Central Apnea and Cheyne–Stokes Breathing in Heart Failure

CSB (see Fig. 41.6b in Chap. 41) is characteristic of heart failure.

The following factors play a role in the complex mechanism of CSA–CSB during sleep in HF [52–66, 68–79].

1. Increased loop gain;
2. Increased arterial circulation time;
3. Decreased functional residual capacity (FRC);
4. Altered apnea threshold;
5. Decreased reactivity of cerebral blood flow; and
6. Physiologic instability of the respiratory control system during transition to sleep, sleep stage shifts, and arousals.

Loop Gain (see also Chap. 25)

This is an engineering term implying a ratio of the ventilatory response to internal or external stimuli (e.g., a disturbance in ventilations such as apnea–hypopnea). In HF, there is an augmented chemosensitivity (i.e., increased loop gain) caused by both a pulmonary congestion and an unstable respiratory controller [59, 60, 64, 78, 79] causing increased ventilation in response to increased partial pressure of arterial carbon dioxide ($PaCO_2$) and also to an extent decreased partial pressure of oxygen (PaO_2) resulting in further instability in the central controller. Recent work has shown that CO_2 plays a key role in the pathophysiology of CSR (see further on) [59, 66, 78]. The increased loop gain in HF results from three major components [59]:

1. Increased chemosensitivity (increased central controller gain);
2. Decreased FRC (i.e., increased plant gain causing a large change in $PaCO_2$ for a given change in ventilation); and
3. Increased circulation time (mixing gain).

Increased Arterial Circulation Time These results from a combination of cardiomegaly, decreased cardiac output, and increased pulmonary blood volume. This delayed circulation time prolongs the time it takes for pulmonary blood $Paco_2$ and Pao_2 to reach the central and peripheral chemoreceptor sites. The longer the delay is, the longer is the cycle of CSB. The circulation delay is very common in HFrEF but the circulation time may be normal in HFpEF.

Decreased Functional Residual Capacity (FRC) It is due to a combination of pleural effusion, enlarged heart, and pulmonary congestion causing decreased pulmonary compliance in patients with heart failure. FRC decreases further in the supine position, promoting CSB. Decreased FRC causes underdamping—that is, for a given change in ventilation (e.g., transient cessation of breathing), there is an increased response to changes in Pao_2 and $Paco_2$ [4, 59, 65].

Altered Apnea Threshold Respiration during NREM sleep depends entirely on the metabolic control system (mainly $Paco_2$ levels) and so a small change in $Paco_2$ level will have intense effect on ventilation [58–60, 80, 81]. The apnea threshold (defined as the level of $Paco_2$ below which breathing stops) is close to the actual level of $Paco_2$ during sleep. This proximity of the two $Paco_2$ levels is called $Paco_2$ reserve which is further narrowed in some HF patients promoting development of CSA in HF. Furthermore, HF patients chronically hyperventilate due to pulmonary congestion resulting from rostral fluid shift in the supine position stimulating pulmonary irritant receptors to stimulate ventilation [59, 64, 66] which lowers the CO_2 crossing the apnea threshold [81]. The resultant apnea promotes increase in CO_2 causing hyperventilation. Thus, a vicious cycle of crescendo–decrescendo (CSR) pattern of breathing is perpetuated.

Decreased Reactivity of Cerebral Blood Flow A change in $Paco_2$ causes alteration in cerebral blood flow (CBF) which is called cerebrovascular reactivity [59, 66]. The physiologic homeostatic regulation of CBF in response to changes in $Paco_2$ protects brain including central chemoreceptors. Patients with HF have decreased cerebrovascular response to $Paco_2$ causing breathing instability during sleep [59, 66, 82].

CSB occurs during sleep and wakefulness, although it is pronounced during sleep. It has been shown that HF patients with CSB during daytime wakefulness have almost a four-fold increased mortality [78]. In many patients with heart failure, there is low $Paco_2$ and a failure of rise of $Paco_2$ during sleep, unlike that which occurs in normal individuals as a result of increased venous return in the supine position, increased respiratory rate, and increased ventilation. Heart failure patients with $Paco_2$ less than 35 mm Hg have a high probability for developing central apnea because the low $Paco_2$ is close to the apnea threshold (i.e., the level of $Paco_2$ at which breathing ceases due to a lack of chemoreceptor stimulation).

Mechanism of Obstructive Apnea in Heart Failure CSB itself may predispose to obstructive apnea by decreasing the tone of the upper airway dilator muscles at the end of the ventilatory cycle (the lowest point or nadir). Other factors for obstructive apnea in heart failure include venous congestion in the oropharyngeal region in right heart failure, especially in the supine position, and comorbid obesity [59, 64]. The presence of periodic breathing (e.g., CSB) in heart failure may increase the morbidity and mortality and so it is important to be aware of this. Treatment with CPAP/bilevel positive airway pressure (BIPAP) with or without low-flow (1–2 L/min) supplemental oxygen inhalation and assisted servo-ventilation (ASV) in selective cases may improve the pattern of breathing (see further on).

Clinical-Pathologic Consequences of Heart Failure and Sleep Apnea

The common symptoms of heart failure in obstructive sleep apnea patients include paroxysmal nocturnal dyspnea, orthopnea, daytime sleepiness and fatigue, and sleep onset and maintenance insomnia. Recurrent episodes of apnea and hypopneas accompanied by repeated arousals, hypoxemia, hypercapnia, and sympathetic activation adversely affect cardiovascular function, particularly in patients with CAD and incipient cardiac dysfunction. Indications for overnight PSG in these patients include witnessed apneas, habitual snoring, nocturnal angina, and unrefreshing restless sleep; overnight PSG is also indicated in patients requiring cardioverters or defibrillators: those requiring cardiac transplantation and those with cardiac arrhythmias. It should be noted that many patients with HF may not present with the classic symptoms of sleep apnea such as snoring, daytime sleepiness, and obesity explaining an underdiagnosis of CSA in HF [58, 59, 78, 83]. Many of these patients may actually have unexplained insomnia and have reduced quality of life and increased mortality [59, 78, 83]. Therefore, a high index of suspicion for possible SRBD in HF patients is needed and many even recommend routine screening for SRBD in these

patients to improve outcome and prevent adverse consequences. The pathophysiological consequences resulting from repeated episodes of apnea, hypoxemia, reoxygenation, and arousals throughout the night consist of increased sympathetic nervous system activation, oxidative stress, systemic inflammation, and endothelial dysfunction. CSA–CSB is associated with malignant nocturnal cardiac arrhythmias (e.g., ventricular tachycardia and premature ventricular contractions) in part due to increased sympathetic activation [59, 66]. Atrial fibrillation is also common in HF patients with CSA. Patients with severe CSB may show reduced heart rate variability suggesting autonomic dysfunction [78, 84, 85] which may be associated with increased mortality in HF patients [86]. Treatment of CSA improves nocturnal cardiac arrhythmias and the associated increased mortality [66, 78, 79, 83].

There is an increased mortality associated with sleep apnea and heart failure [87–89]. He et al. [88] reported for the first time that, among 385 men with OSA, those with an apnea index of more than 20 per hour had an increased mortality when compared to those who had been treated with either CPAP or tracheotomy. This was a retrospective study, but later studies confirmed these earlier observations [32, 34]. In a more recent study, Gami et al. [90] reported occurrence of sudden death from cardiac causes in 46 % of patients with OSA as compared to 21 % without OSA from midnight to 6:00 AM. It should be noted that several factors have been associated with the development and progression of CCF and increased mortality in OSA. The following factors are thought to be responsible for vascular endothelial dysfunction causing CAD, hypertension, and stroke: increased sympathetic activity, repeated hypoxemias, re-oxygenation, hypercapnia, hypercoagulopathy, release of endothelin, abnormal endothelial-dependent vasodilation and vascular growth factor and apoptosis, increased levels of inflammatory mediators, increased concentration of adhesion molecules, and oxidative stress [65, 67, 91–94]. Randomized controlled trials with CPAP in patients with OSA have shown improved cardiac function, sympathetic nervous system activity, quality of life, reduction of blood pressure, and reversal of the various neural, hormonal, and biochemical abnormalities, suggesting a cause-and-effect relationship [95–97].

Most of the more recent studies confirmed an increased mortality with a hazard ratio of 2.1–5.7 for CSB [75, 78, 98–101] excepting two studies [102, 103]. Khayat et al. [55] reported the results of the largest prospective study evaluating the effect of SRBD on post-discharge mortality in 1117 hospitalized inpatients with acute heart failure (AHF) with a median follow-up of three years. They concluded that newly diagnosed CSA and OSA are both independently associated with post-discharge mortality in patients with AHF and reduced EF. An independent relationship between SRBD and mortality in untreated patients with stable chronic HF has been reported in several studies [56, 101, 104]. The effect of treatment, however, of CSA or OSA on survival in HF remains unknown.

Principles of Treatment of Heart Failure and Sleep Apnea
The principles of treatment of HF with sleep apnea (both OSA and CSA–CSB) are outlined in the following five steps:

1. The initial step is optimizing medical therapy for HF;
2. General measures;
3. Treatment of OSA;
4. Treatment of CSA–CSB; and
5. Miscellaneous other measures.

I. **Medical therapy for HF**. It is beyond the scope of this chapter to describe in detail medical therapy and the readers are referred to standard texts for this [54]. Briefly, diuretics (both thiazide and loop diuretics) are used to relieve pulmonary congestion, beta-blockers are used to reduce sympathetic activation, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) a combination of ARBs and neprilysin inhibitor and aldosterone antagonist are used to reduce ventricular afterload and improve cardiac output [59, 60, 64, 66, 78, 105, 106]. It is notable that digitalis glycosides which were a mainstay of treatment for decades had no beneficial effect on mortality in HF in a major clinical trial, and these cardiac glycosides are no longer first-line therapy for HF [105].

II. **General measures**. These include weight loss, avoidance of supine sleep, smoking, alcohol ingestion, and sedative-hypnotic use before bedtime (see Table 47.2).

III. **Treatment of obstructive sleep apnea**. The gold standard for treatment of OSA in heart failure is treatment with CPAP or BIPAP (see Chap. 34). Adequate treatment of OSA in heart failure utilizing the measures outlined in Table 47.2 eliminates excessive daytime somnolence (EDS) and improves sleep of these patients. Such treatment may also decrease blood pressure in hypertensive patients and may help reduce the dose of antihypertensive medications. The treatment of OSA with CPAP increases ventricular ejection fraction significantly even within one month after therapy [58, 59, 107–109]. In a meta-analysis of studies involving both OSA and HF, CPAP treatment improved left ventricular ejection fraction [110]. The most recent addition to OSA treatment is hypoglossal nerve stimulation by an implanted device trial in an observational study in 126

Table 47.2 Principles of treatment of obstructive sleep apnea and heart failure

Adequate treatment of heart failure
General Measures
• Weight reduction if needed
• Follow general sleep hygiene measures
• Avoid alcohol and sedative-hypnotics
• Cessation of smoking
• Avoid supine position in subset of patients with positional OSA
Treatment of OSA
• Treat any nasal abnormalities (e.g., septal deviation)
• Nocturnal CPAP/BIPAP
• Supplemental oxygen through CPAP if needed
• Dental appliances
• Upper airway surgery
• Hypoglossal nerve stimulation
• Tracheostomy

BIPAP Bilevel positive airway pressure; *CPAP* Continuous positive airway pressure; *OSA* Obstructive sleep apnea

individuals (OSA without HF) who could not tolerate or accept CPAP [111]. The data on HFpEF are limited. Arias et al. [112] reported that 15 of 27 consecutive patients with OSA had impaired left ventricular relaxation. The authors performed a double-blind sham-controlled crossover trial of CPAP for 12 weeks and noted an improvement in diastolic function.

IV. **Treatment of CSA–CSF**. Treatment of central sleep apnea in heart failure is more difficult than treating OSA. The general measures for treating central apnea/CSB are listed in Table 47.3. Adequate treatment of heart failure may improve or eliminate periodic breathing and decrease circulation time due to increased stroke volume, decreased pulmonary congestion, increased FRC, and decreased sympathetic activity. Javaheri et al. [75, 79, 113, 114] have clearly shown improvement after aggressive treatment of heart failure with diuretics, ACE inhibitors, ARBs, β-blockers, and positive airway pressure devices. CPAP treatment for central apnea has not produced as dramatic results as in OSA. Javaheri has shown that, in mild-to-moderate central apnea patients, overnight use of CPAP improved central apnea in 43 % of patients with systolic heart failure (HFrEF) [115, 116]. The number of premature ventricular contractions, bigemini, and episodes of ventricular tachycardia also decreased. However, severe central apnea patients with heart failure did not respond to short-term CPAP treatment. Treatment lasting from one-to-three months with nasal CPAP in patients with heart failure showed a reduction in the AHI with desaturation and decrease in plasma and urinary norepinephrine, in addition to an increase in ventricular ejection fraction. There are other reports of quality of life [117] improvement and reduction of mortality in such patients after CPAP treatment [35, 118–121], although a large Canadian CPAP trial for congestive heart failure (CANPAP) contradicted this [113]. However, a later study by Arzt et al. [122] showed suppression of central sleep apnea by CPAP and transplant-free survival in heart failure. Cardiac transplantation will virtually eliminate central apnea, but a large number of such patients develop OSA due to weight gain [123]. Cardiac pacing and cardiac resynchronization therapy have been shown to improve some patients with central apnea in heart failure [124–128]. Atrial pacing was thought to improve patients with obstructive apnea [124, 128], but other studies [129–132] did not support such an improvement. Nocturnal nasal supplemental oxygen therapy improves central apnea in heart failure patients [133–140]. Such treatment decreases muscle sympathetic nerve activity and improves left ventricular ejection fraction and quality of life. Additional studies, however, are needed to determine whether such treatment decreases the morbidity and mortality in patients with HFrEF [65, 140]. Bordier et al. [140] in a recent review analyzed 17 studies to determine the effects of nocturnal oxygen therapy (NOT) as an alternative treatment for sleep apnea in HF patients. They concluded that NOT was effective in approximately 50 % of cases with a 50 % reduction of AHI in CSA–CSB but had no effect on obstructive respiratory events. Furthermore, there were no reports of NOT-related death or other harmful effects on the myocardium.

Since its introduction in 2001, adaptive servo-ventilation (ASV) has been shown to reduce CSA events and improve

Table 47.3 Principles of treatment of central apnea and Cheyne–Stokes breathing in heart failure

Aggressive treatment of heart failure
• CPAP/BIPAP
• Adaptive pressure support servo-ventilation
• Atrial overdrive pacing or biventricular pacing
• Supplemental oxygen
• Cardiac transplantation
Pharmacologic treatment (e.g., acetazolamide, theophylline, and diazepam) in selective cases

BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure

cardiac function in patients with CSB and HF [104, 141–148]. In contrast to these findings, the results of the recently published servo-ventilation heart failure (SERVE-HF) trial put the sleep community in turmoil [149]. Cowie et al. [149] included 1325 patients with symptomatic chronic HF (NYHA grades II–IV) with reduced ejection fraction (≤ 45 %) and predominant central apnea (AHI ≥ 15) who were randomized to treatment with a specific ASV device (ResMed Autoset CS) or conventional medical therapy (control group). ASV had no significant benefit on the primary outcomes and no beneficial effect on a broad spectrum of functional measures. In contrast, there was a significant increase in both all-cause and cardiovascular mortality with the ASV group. The increased mortality in this study is unexplained. In an editorial in Sleep Medicine Journal by Randerath [142] and in another editorial in New England Journal of Medicine by Magalang and Pack [140], several questions were raised and possible mechanism (some of which were also suggested by Cowie et al. [149]) were discussed. Until the issue is further clarified, the current recommendation [150] is not to use ASV in HF patients with predominantly CSA.

Miscellaneous Other Measures

1. Nocturnal supplemental carbon dioxide (or added dead space) has been used to increase $PaCO_2$ above the apnea threshold but is currently not recommended to treat CSA–CSB in HF [64, 66, 78].
2. Pharmacotherapy with theophylline (a respiratory and cardiac stimulant) and acetazolamide (a carbonic anhydrase inhibitor causing metabolic acidosis) has been used in small trials to treat CSA–CSB in HF with limited success. These agents are not commonly used in HF patients [55, 66, 78, 151].
3. Device-based therapy and cardiac transplantation. These measures have been described above briefly. The latest addition to device-based therapeutic armamentarium is phrenic nerve stimulation [152]. This is an implantable device-based therapy inserted intravenously into a thoracic vein. The phrenic nerve can be stimulated at a set frequency to prevent central apnea [59]. A multicenter randomized control trial (RCT) is ongoing [153].

Hypertension

A high prevalence (22–48 %) of sleep apnea and related symptoms (e.g., EDS) has been noted in patients with systemic hypertension [154–157]. In contrast, studies by Escourrour et al. [158] found no significant difference between 21 hypertensive and 29 normotensive patients in sleep stage distribution and disorganization, AHI and duration, and arterial oxygen saturation (Sao_2). The prevalence of hypertension in sleep apnea patients is approximately 50–90 % [5, 159–167]. In the Wisconsin Sleep Cohort study, a dose–response relationship between hypertension and the AHI as well as snoring has been described [168, 169]. Furthermore, studies have confirmed that treatment of sleep apnea by nasal CPAP reduces blood pressure [6, 170].

Previously Stradling and Davies and others [7, 171–175] made a persuasive argument based on a critical analysis of the literature, and taking into consideration the confounding variables (e.g., age, sex, smoking, obesity, and alcohol consumption), that there is no convincing evidence yet supporting the contention that OSA is a significant independent risk factor for sustained hypertension in humans. Silverberg and Oksenberg [176, 177], however, contended that, even when the confounding factors are taken into consideration, OSA is an independent risk factor for hypertension and that treatment of OSA reduces daytime as well as nighttime blood pressure.

There is now convincing evidence of an association between hypertension and sleep apnea [178–183]. Epidemiologic studies suggest that approximately 50 % of patients with OSA have hypertension and about 30 % of patients with hypertension develop OSA. Compelling evidence on the association between OSA and hypertension in

humans has been provided by epidemiologic studies [164, 179, 181, 184]. In drug-resistant hypertension, the prevalence of OSA is even higher; one study quoted a figure of 83 % [185]. The Sleep Heart Health Study, in a prospective cross-sectional analysis of more than 6000 subjects, showed an independent association between hypertension and OSA [179]. A subgroup analysis by Bixler et al. [180] failed to show this association in subjects older than 65 years. The Wisconsin Sleep Cohort Study [181] was able to show that OSA is an independent risk factor for high blood pressure during a 4-year follow-up study that also showed a dose–response relationship between OSA and blood pressure independent of confounding factors. A population-based case-control study failed to show an association between OSA and high blood pressure in postmenopausal woman [186]. OSA has been considered to be an important risk factor for hypertension [187]. Several reports including randomized, placebo-controlled studies revealed very significant reduction in mean blood pressure during sleep in the CPAP-treated group [188–193] (see Chap. 34 for a detailed discussion). Several recent studies [194, 195] supported these results. Oral appliances also have shown to improve hypertension. A number of well-designed studies [196–199], however, have failed to show significant improvement in blood pressure after CPAP treatment. In a prospective long-term follow-up study [200] of 83 patients with uncontrolled hypertension, coronary heart disease (CHD), and OSA randomized to control or CPAP groups, 73 patients completed the study. CPAP was used for 4.5 ± 1.1 h/night and the median follow-up period was 36 months (interquartile range = 24–54 months). Systolic blood pressure (SBP) decreased by 8 mm Hg ($P = 0.01$) but diastolic blood pressure (DBP) did not reach statistical significance (81 ± 10 mm Hg vs. 79 ± 8 mm Hg; $P = 0.49$). ESS was significantly reduced ($P < 0.001$) and hypertension control improved in the CPAP group. The same group of authors in another study sought to determine predictors of blood pressure fall with CPAP treatment in hypertensive patients with CHD and OSA [201]. Sixty-six patients with moderate-to-severe OSA had used CPAP for a mean of 4.3 h/night with a mean follow-up of 36 months (range 24–60). There was a reduction in both SBP and DBP as well as improvement of daytime somnolence as measured by ESS. These authors noted that baseline BMI, mean blood pressure, and CPAP compliance are independent predictors of a decrease of BP in these patients.

Thus, OSA is a risk factor for hypertension [202–204] but some studies found a lack of such relationship [205–207]. However, as stated above, several randomized control trials (RCTs) have shown a decrement of BP in OSA patients following CPPA treatment [204, 208–210]. In a meta-analysis covering six studies (observational and randomized control trials), the pooled estimate showed a favorable reduction of BP after CPAP treatment in patients with resistant hypertension and OSA [211]. A recent large meta-analysis including 1000 CPAP-treated patients with OSA from 16 RCTS showed significant but small reduction in BP [212]. Several recent RCTs also showed that the average fall of BP is small [207, 213, 214]. Daytime hypersomnolence [assessed by Epworth Sleepiness Scale (ESS)] has been cited as an important predictive factor for BP reduction after CPAP [201]. It should, however, be noted that CPAP does not cause significant reduction of BP on nonsleepy hypertensive patients with OSA [215, 216]. Huang et al. [201] cited the following factors contributing to hypertension in OSA patients: 1. increased sympathetic activation; 2. systemic inflammation; 3. oxidative stress; 4. endogenous vasoactive factors; 5. endothelial dysfunction; and 6. metabolic regulation.

It has been estimated that a fall of BP of 3.3 mm Hg is associated with a reduction of 20 % risk of stroke and a 15 % risk of coronary arterial disease [201].

Although the results have so far been promising, further studies are needed to confirm the beneficial effect of CPAP therapy on high blood pressure in OSA patients [211, 217, 218].

"Nondippers," those hypertensive patients whose blood pressure during sleep does not decline or declines less than 10 % from daytime to nighttime readings have significant risk for developing cardiac arrhythmias, stroke, and death from cardiovascular disease [13, 219, 220]. In addition, extreme dippers (whose BP during high time sleep falls excessively by 20 % or more) and reverse dippers (those in whom the BP instead of declining increases during sleep above the waking values) are similarly also at increased risk.

In addition to systemic hypertension, OSA may also cause severe pulmonary arterial hypertension, particularly in patients with preexisting cardiopulmonary diseases [65, 187]. Factors for developing pulmonary hypertension include several mechanisms such as repeated hypoxemia causing pulmonary vasoconstriction, left ventricular diastolic dysfunction resulting in increased left ventricular end-diastolic pressure, and possible pulmonary vascular remodeling [65]. It is important to remember that several long-term studies have shown improvement of pulmonary arterial hypertension following treatment of OSA with CPAP.

The recognition of the association of metabolic syndrome with OSA should direct attention to an early diagnosis and treatment with a view to preventing serious consequences such as stroke or myocardial infarction. The metabolic syndrome is a serious risk factor for cardiovascular disease and includes hypertension, hypertriglyceridemia (dyslipidemia), central obesity, glucose intolerance and insulin resistance (syndrome X) or hyperinsulinemia, and low levels of high-density lipoprotein cholesterol [51, 65, 221]. Kaplan

[221] spoke about a deadly quartet: upper body obesity, glucose intolerance, hypertriglyceridemia, and hypertension.

Cardiac Arrhythmias and Sleep

An understanding of the interaction between the autonomic nervous system (ANS), cardiac innervation, and sleep is important to appreciate the effects of sleep on cardiac rhythms. Readers are referred to Chaps. 11 and 41 for such review. It is known that there is an imbalance between sympathetic and parasympathetic tone during REM and NREM sleep. During REM sleep, there is an intermittent increase in sympathetic nerve activity, reaching even higher levels than in wakefulness. This surge causes intermittent increase in the heart rate and blood pressure, although at the same time, vagal tone (parasympathetic activity) is suppressed, causing irregular breathing, oxygen desaturation, and a few periods of apneas. These alterations in the sympathetic and parasympathetic balance can be clinically measured by recording heart rate variability (see also Chap. 11). The high-frequency (HF: 0.15–0.4 Hz) heart rate spectrum reflects parasympathetic tone, the low-frequency (LF: 0.01–0.05 Hz) spectrum reflects sympathetic tone, and the intermediate frequency (0.06–0.14 Hz) spectrum reflects a mixture of both activities. The LF/HF ratio is used in clinical practice to indicate overall sympathetic tone. Sudden cardiac death after myocardial infarction is associated with a decrease of heart rate variability. Based on heart rate variability studies, Bonnet and Arand [222] have clearly shown an increase in HF heart rate spectrum with a decrease of LF in NREM and an increase in LF and a decrease in HF in REM sleep and wakefulness.

A relationship between sleep and atrioventricular arrhythmias has been noted, but reports in the literature are somewhat contradictory. Atrial arrhythmias, such as atrial flutter, atrial fibrillation, paroxysmal atrial tachycardia [223], and first- and second-degree atrioventricular block [224], have been described in normal subjects during REM sleep, but no clear relationship between different sleep stages and atrial arrhythmias has emerged. A prominent sinus arrhythmia has been noted in several studies in normal subjects using Holter monitoring [225]. Brodsky and colleagues [226] monitored 24-h continuous ECGs in 50 male medical students with no apparent heart disease and observed sinus pauses of 1.8–2.0 s' duration in 30 % of them, as well as episodes of second-degree heart block (Mobitz type I) in another 6 %. Guilleminault and associates [227] noted 42 episodes of sinus arrest in four young, healthy adults that lasted 2–9 s during REM sleep. No associated apneas or significant oxygen desaturation was observed. Osuna and Patino [228] observed REM-related sinus arrest in a subject without any associated OSA or oxygen desaturation. The incidence of nocturnal bradyarrhythmias decreases with advancing age [229].

Contradictory results have been noted in human studies of the effects of sleep on ventricular arrhythmia, but the majority shows an antiarrhythmic effect of sleep on ventricular premature beats (VPBs) [230]. This seems to be due to enhanced parasympathetic tone during sleep, conferring protection against ventricular arrhythmia, and sudden cardiac death. Pitzalis et al. [231] evaluated 45 patients with frequent premature ventricular contractions to find out whether the phenomenon of sleep suppression may be a sensitive and specific parameter for predicting the antiarrhythmic effect of β-blockers and premature ventricular contractions. Based on Holter recordings, these authors concluded that sleep suppression of the premature ventricular contractions was a sensitive characteristic for identifying those patients with premature ventricular contractions who are likely to benefit from administration of β-blockers. Ventricular arrhythmias are also noted to occur during arousal from sleep [230]. A classic example was provided by Wellens and colleagues [232], who described a 14-year-old girl awakened from sleep by a loud auditory stimulus who had ventricular tachyarrhythmia. The authors postulated that increased sympathetic activity triggered these episodes, because they could be prevented by the β-blocker propranolol.

Lown's group [233] noted reduction of VPBs by at least 50 % in 22 subjects and 25–35 % in 13 others during sleep. De Silva [234] noted reduction in VPBs in all stages except REM sleep, with stages 3 and 4 NREM sleep showing the most effect. Pickering and colleagues [235] described 12 untreated patients with frequent ventricular extrasystoles who showed a significant decrease in both the heart rate and extrasystoles during sleep. Intravenous propranolol, and to a lesser extent intravenous phenylephrine, produced a similar decrease in the heart rate and ventricular arrhythmias during wakefulness. These changes appear to be mediated by the ANS, the sympathetic system dominating the parasympathetic system. They found that the frequency of ventricular arrhythmias was similar in both REM and NREM sleep. Their findings are similar to those of Lown and colleagues [233].

The observations of Pickering's group [235] also contrast with those of Smith et al. [236], who studied 18 patients in a coronary care unit to document frequency of cardiac arrhythmias in wakefulness and sleep. They found no significant difference in the occurrence of ventricular or atrial premature contractions during sleep and wakefulness. Similarly, Richards et al. [237], in a pilot overnight sleep study on nine patients with cardiovascular disease in the medical ICU, did not find any increase in incidence of dysrhythmias during any sleep stages or during sleep state in these critical

care unit patients. Disturbed sleep in coronary care patients [23] may explain the discrepancies in these data.

Cardiac Arrhythmias, Autonomic Deficits, and Obstructive Sleep Apnea Syndrome

Several investigators [94, 225, 238–242] reported a variety of cardiac arrhythmias in patients with OSAS (Fig. 47.1). These arrhythmias are determined by the changes in the ANS. The most common is bradytachyarrhythmia alternating during apnea and immediately after termination of apnea. The other dysrhythmias consist of the following: sinus bradycardia with less than 30 beats/min; sinus pauses lasting from 2 to 13 s; second-degree heart block; and ventricular ectopic beats, including complex and multifocal ectopic beats, and ventricular tachycardia. There is a clear relationship between the level of Sao_2 and premature ventricular contractions and sleep apnea syndrome. Patients with Sao_2 below 60 % are the most vulnerable. Hoffstein and Mateik [243], using nocturnal PSG, prospectively studied 458 patients with OSAS. They found a prevalence rate of 58 % of cardiac arrhythmias in these patients, and those with arrhythmias had more severe apnea and nocturnal hypoxemia than those without arrhythmias. Earlier studies showed a higher prevalence than more recent epidemiologic studies suggested. Roche et al. [244] performed a prospective study in 147 consecutive patients referred for assessment of OSAS. The authors found OSAS in over 45 % with AHI 10. They found significantly more nocturnal paroxysmal asystole in OSAS patients than in controls (10.6 % vs. 1.2 %). They further noted that the number of episodes of bradycardia and pauses increased with the severity of OSAS. CPAP treatment followed for one year showed amelioration of arrhythmic events in OSAS patients, indicating the usefulness of CPAP treatment. The Sleep Heart Health Study [242] investigated 228 patients with severe sleep apnea (AHI >30/h) and 338 individuals without sleep apnea, and found a significant relationship between nonsustained ventricular tachycardia, bigeminy, trigeminy, or quadrigeminy and severe OSA.

ANS dysfunction was implicated in cardiovascular morbidity and mortality in OSAS (e.g., hypertension, left ventricular failure, increased risk of coronary or cerebral events) [245]. CPAP treatment can prevent the cardiovascular risks associated with ANS dysfunction.

Gami et al. [90], after reviewing the PSGs and death certificates of 112 Minnesota residents who have died suddenly from cardiac causes during the period from July 1987 to July 2003, concluded that OSAS patients had a peak sudden death from cardiac causes during sleeping hours, contrasting with the nadir of sudden death in those without OSAS and in the general population. Peltier et al. [246] recruited 32 patients complaining of EDS and snoring and performed PSG studies and 2-h oral glucose tolerance tests as well as autonomic testing consisting of heart rate response to deep breathing, Valsalva maneuver, head-up tilt, and quantitative sudomotor axon reflex testing (QSART). These authors found that 19 of 24 patients with OSAS had abnormal glucose tolerance, and cardiac autonomic dysfunction was more strongly associated with impaired glucose regulation than OSAS. They concluded that cardiovagal and adrenergic dysfunction are responsible for cardiovascular adverse effects in OSAS, but the question remains whether impaired glucose regulation in such patients may have been responsible for such ANS dysfunction. Further studies using

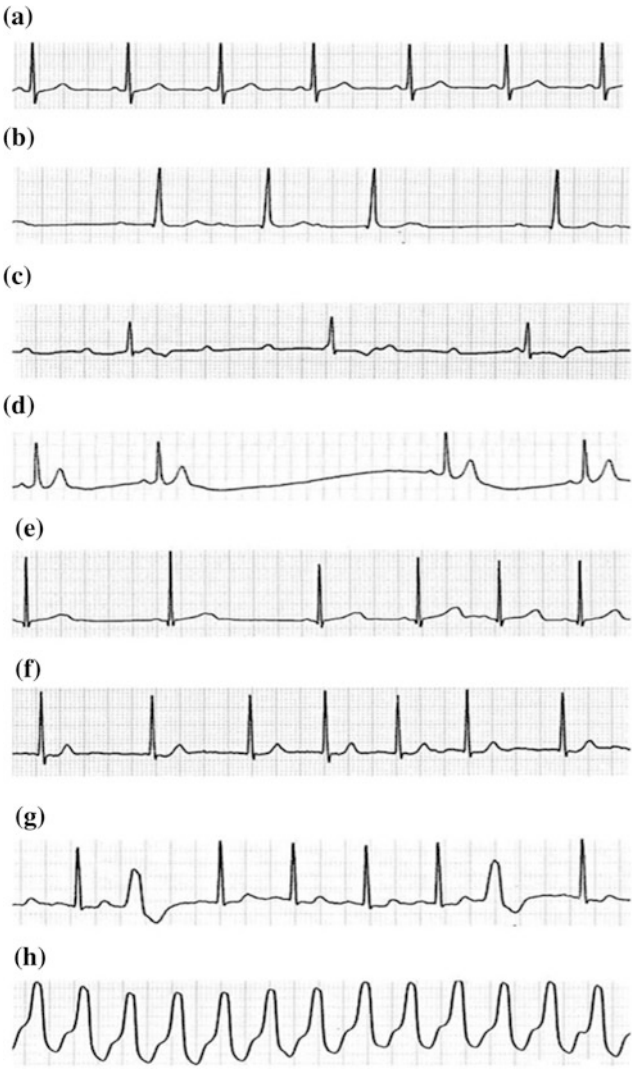

Fig. 47.1 Examples of various ECG rhythms that might be seen during sleep. **a** Normal sinus rhythm. **b**, **c** Atrioventricular conduction block: P wave is not followed by the QRS complex. **d** Sinus pause. **e** Atrial fibrillation: No P waves are visible. **f** Sinus arrhythmia. **g** Isolated extrasystoles. **h** Ventricular tachycardia. Note that the QRS complex is narrow in the supraventricular arrhythmias differentiating them from ventricular arrhythmias (in the absence of preexisting bundle branch block). (Reprinted from Ref. [94]) (Reproduced with permission [94])

larger numbers of patients are needed to resolve this complex relationship between OSAS, autonomic function, and glucose regulation.

Cardiac Arrhythmias and OSA

Recent studies have confirmed a high prevalence of cardiac arrhythmias in OSA patients [247–253] with improvement after effective CPAP therapy [247, 248, 250, 251]. Linz et al. [251] in a systematic literature search noted that the prevalence of OSA in atrial fibrillation (AF) patients is high (about 40–50 %). Effective CPAP therapy of OSA improves catheter ablation success rates in AF patients. Dediu et al. [248] found a favorable response after successful positive pressure therapy in patients with cardiac arrhythmias. Vizzardi et al. [250] conducted a meta-analysis including 1298 articles and observed that arrhythmias are frequent in OSA. Based on this analysis, the authors suggested that treatment with an implantable cardioverter/defibrillator and CPAP should be considered in some of these patients who may show improvement. Figueiras-Rama et al. [251] in a review article concluded that tachy-bradyarrhythmics including AF are highly prevalent in OSA (moderate–severe) which is an indifferent risk factor for such atrial arrhythmias. CPAP therapy has shown a significant effect in preventing or abolishing atrial arrhythmias. Some of the suggested mechanisms in the literature include hypoxia, hypercapnia, autonomic dysfunction, inflammation, negative intrathoracic pressure, and acute atrial stretch. Namveldt et al. [253] in a population-based study from Norway recruited 486 subjects (mean age of 49 with 55 % men) who underwent an overnight PSG study for suspected OSA. They found that 271 out of 486 (55.8 %) had OSA. The prevalence of ventricular premature complexes is increased in middle-aged patients with mild–moderate OSA suggesting an association between OSA and ventricular arrhythmias even in mild OSA patients.

Sudden Cardiac Death

An analysis of the time of sudden cardiac death in 2203 individuals by Muller et al. [254] revealed a low incidence during the night and a high incidence from 7:00 to 11:00 AM. Similarly, nonfatal myocardial infarction and myocardial ischemic episodes are more likely to occur in the morning. It is known that sympathetic activity increases in the morning, causing increased myocardial electrical instability; thus, sudden cardiac death (SCD) may result from a primary fatal arrhythmia.

LaRovere et al. [255] correlated increased cardiovascular mortality among patients with a first myocardial infarction with reduced baroreflex sensitivity. *Reduced baroreflex sensitivity* is defined as less slowing in heart rate for a given rise in arterial blood pressure, which indicates reduced vagal tone.

McWilliams [256] first suggested that ventricular fibrillation is the cause of sudden death and that sympathetic discharges play an important role in causing this fatal arrhythmia. During sleep, cardiovascular hemodynamic activity is decreased, as are heart rate and blood pressure, owing to withdrawal of sympathetic tone and increased vagal tone (see Chap. 11).

Reduced vagal tone, as measured by decreased heart rate variability in 24-h Holter monitoring, was found by Kleiger et al. [257] to be a powerful predictor of increased mortality and SCD after myocardial infarction. Autonomic imbalance (either sympathetic overactivity or parasympathetic underactivity) may trigger ventricular arrhythmias [258].

Besides myocardial infarction, another clinical entity known as *long QT syndrome* may cause syncope or sudden death [259–264]. Based on an evaluation of 54 patients with congenital long QT syndrome (LQTS) and 67 controls, Shamsuzzaman et al. [265] concluded that the presence and severity of OSA in patients with LQTS are associated with increased QT prolongation which is an important biomarker of sudden death. Treatment of OSA may reduce QT prolongation, thus reducing the risk of LQTS-triggered SCD. In long QT syndrome, the ECG shows a prolonged QT interval with abnormal U waves and torsades de pointes (polymorphic ventricular tachycardia). Gami et al. [266] included 10,701 consecutive adults who had PSG study between July 1987 and July 2003 to assess incident resuscitated or fatal SCD. During an average follow-up of 5.3 years, 142 patients had resuscitated or fatal SCD (annual rate of 0.27 %). The authors concluded that in 10,701 adults referred for PSG, OSA predicted incident SCD. The degree of nocturnal hypoxemia strongly predicted SCD. OSA is thus a novel risk factor for SCD. Another cause of sudden death in young adults in the Western literature is the Brugada syndrome, described in 1992 [267–270]. Patients with this syndrome present with life-threatening ventricular tachyarrhythmias without any structural cardiac lesions, and the ECG shows characteristic abnormalities of atypical right bundle branch block and ST-segment elevation over the right precordial leads. An involvement of the ANS is suggested, and abnormal I-MIBG single-photon emission computed tomography (SPECT) uptake in Brugada syndrome indicating presynaptic sympathetic dysfunction of the heart has been reported by Wichter et al. [271]. The Brugada syndrome has a genetic basis and links to mutation in *SCN5A,* the gene encoding the alpha subunit of the sodium channel. The ideal treatment suggested for this syndrome is implantation of a cardioverter/defibrillator. Sudden unexpected nocturnal death syndrome (SUNDS) is another disorder found in Southeast Asia with abnormal ECG findings similar to those noted in Brugada syndrome [272, 273]. It has been

suggested that both SUNDS and Brugada syndrome may have a common genetic and biophysical basis [274].

Intrinsic Respiratory Disorders

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), the third leading cause of death in the USA and worldwide, is caused largely by cigarette smoking and also combined with a genetic α_1-antitrypsin deficiency. Patil et al. [275] in a retrospective review reported a 2.5 % in-hospital mortality following acute exacerbation of COPD in 70,000 patients. The COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as an irreversible progressive airflow limitation causing an inflammatory response in the lung parenchyma giving rise to the clinical features of chronic bronchitis and emphysema [276].

The salient clinical features include chronic cough, exertional dyspnea, tightness in the chest, and sometimes wheeze. Physical examination reveals inspiratory and expiratory sonorous wheeze (rhonchi) and crackles (crepitations or rales). Patients with resting hypoxemia and hypercapnia may exhibit cyanosis. Investigations should include radiographic examination of the chest and pulmonary function tests. Complications include polycythemia, pulmonary hypertension, cor pulmonale, and cardiac arrhythmias.

To understand sleep disturbances, it is important to have some knowledge of gas exchange during sleep [277]. In COPD patients, Sa_{O_2} and Pa_{O_2} fall and Pa_{CO_2} rises during sleep; these values worsen during REM sleep [278–280]. In some patients, SDB (e.g., apnea, hypopnea, or periodic breathing) is associated with reduced Sa_{O_2} saturation, which is generally short lived (less than 1 min) and mild to moderate in intensity [281–283]. Episodes of Sa_{O_2} desaturation during REM sleep last more than 5 min and are more severe than in NREM sleep [281, 284, 285]. Physiologic changes in respiration, respiratory muscles, and control of breathing (see Chap. 11) during sleep adversely affect breathing in these patients. In COPD patients, two basic mechanisms worsen hypoxemia during sleep: alveolar hypoventilation, which is worse during REM sleep, and ventilation–perfusion mismatch [286–289].

Other groups at risk for hypoxemia include the middle-aged and elderly (particularly men), postmenopausal women, and obese individuals [277]. Diminished ventilatory response to hypoxia and hypercapnia in some COPD patients contributes to increasing nocturnal oxygen desaturation [277]. Nocturnal hypoxemia causes repeated disruption and fragmentation of sleep architecture [277].

COPD patients are traditionally divided into two phenotypes, "pink puffers" and "blue bloaters" [290–292]. Pink puffers generally have normal blood gases, hyperinflated lungs, no hypoxemia or hypercapnia, no cardiomegaly, or cor pulmonale, and are cachectic and short of breath [277]. In contrast, blue bloaters are generally hypoxemic and hypercapnic, have cor pulmonale, polycythemia, an enlarged heart, reduced ventilatory response to hypoxemia and hypercapnia, have a stout body habit, and have less dyspnea [277]. In general, blue bloaters have more severe hypoxemia of longer duration than pink puffers [293, 294]. It should be noted that oxygen saturation for both groups is somewhat similar during wakefulness and in the upright position but is markedly different during sleep. The worse value is noted in blue bloaters. There are no absolute criteria for determining which groups of COPD patients have more severe nocturnal hypoxemia. Patients must be monitored at night, which is impractical considering the large number of patients who should be monitored. "Blue bloaters" phenotype is considered emphysema-predominant COPD, whereas "pink puffers" phenotype is considered airway (nonemphysematous)-predominant COPD (based on chest CT scans). "Pink puffers" type is associated with an increased risk of diabetes mellitus. There are contentious issues to be resolved regarding definition and staging and phenotyping of COPD as we know today which may be different from the classic phenotypes of "pink puffers" and "blue bloaters." In some patients, COPD may coexist with OSAS—a condition called *overlap syndrome,* a term introduced by Flenley [295]. In a study [296] of 265 consecutive unselected OSAS patients, COPD was found to be present in 30 (11 %) of these patients. Coexistence of COPD and OSAS results in a higher risk of pulmonary hypertension and CCF than in those with only OSAS [286, 287]. In addition, Bednarek et al. [297] noted that the course of SDB is more severe in subjects with overlap syndrome, but these authors found that COPD in subjects with OSAS was as frequent as in the general population. OSAS has a major impact on quality of life in patients with overlap syndrome [298]. COPD patients who are hypoxemic during wakefulness become more hypoxemic during sleep, which is most severe during REM sleep. Alveolar hypoventilation and ventilation–perfusion mismatching are the two most important factors (alveolar hypoventilation being the predominant factor) for worsening of nocturnal hypoxemia in these patients. Several factors contribute to worsening of hypoxemia during sleep in COPD patients [299]. 1. Diaphragm may be flattened and lengthened due to hyperventilation; 2. COPD patients have increased "dead space" (i.e., does not participate in gas exchange) due to rapid shallow breathing pattern during phasic REM sleep; 3. Many have increased airway resistance during sleep; and 4. Hypoxic and hypercapnic ventilator responses are

more blunted in COPD patients than in normal. Hypoxemia is worse in patients with overlap syndrome [300–302]. The consequences of sleep hypoxemia include pulmonary hypertension due to hypoxic pulmonary vasoconstriction and cardiac arrhythmias [303].

Changes in Sleep Architecture

Disturbances in sleep architecture in COPD patients have been reported by several authors [278, 304–313]. These disturbances may be summarized as follows: a reduction of sleep efficiency, delayed sleep onset, increased WASO, frequent stage shifts, and frequent arousals. Arand et al. [304] correlated these findings with EDS. These patients are more likely to have difficulty with falling and staying asleep as well as EDS [311]. Chronic coughing and nocturnal wheezing in addition to nocturnal oxygen desaturation are mostly responsible for arousals from sleep in these patients.

Nighttime symptoms of COPD patients impacting their sleep quality are often "a forgotten dimension" of COPD [314, 315] in 2011; an expert panel was convened in Barcelona, Spain, to address this gap [314]. It has been suggested that the prevalence of nocturnal symptoms and sleep disturbance may exceed 75 % in COPD patients. The panel concluded that nighttime symptoms are of multifunctional origin and warrant further investigation.

A number of factors cause sleep disturbances in COPD patients, resulting in disturbed electroencephalographic (EEG) sleep patterns, including the use of drugs that have a sleep-reducing effect, such as methylxanthines; increased nocturnal cough resulting from accumulated bronchial secretions; and associated hypoxemia and hypercapnia [286, 316], and comorbid disorders (e.g., OSA, RLS, depression, and cardiovascular diseases) [317, 318]. In a study by Calverley [309], administration of supplemental oxygen at 2 L/min by nasal cannula during sleep improved both oxygen saturation at night and sleep architecture, in terms of decreasing sleep latency and increasing all stages of sleep, including REM and SWS. Other reports did not note improved sleep quality, but the nocturnal hypoxemia did improve after oxygen administration [304, 305].

Aoki et al. [319] noted four patterns of SDB in the desaturation group of COPD patients: hypoventilation, paradoxical movement, periodic breathing, and unclassified pattern. Urbano and Mohsenin [310] listed the following eight mechanisms to explain nonapneic oxygen desaturation during sleep in COPD patients: decreased functional residual capacity, diminished hypoxic and hypercapnic ventilatory responses, impaired respiratory mechanical effectiveness, diminished arousal responses, respiratory muscle fatigue, diminished nonchemical respiratory drive, increased upper airway resistance, and the position of baseline saturation values while awake on the oxyhemoglobin dissociation curve.

Diagnostic Considerations

The most important test to document airflow obstruction and determine severity of COPD is spirometry. An FEV_1/FVC ratio (FEV_1 divided by forced vital capacity [FVC]) of less than 0.70 defines an obstructive defect [317, 320]. The COPD severity is determined by observing FEV_1 percent, predicted as follows: mild, less than 80 %; moderate, 50–80 %; severe, 30–50 %; and very severe, less than 30 % [321]. The spirometric measurements are performed before and after bronchodilator therapy, and other pulmonary function tests may also be important. In addition, pulse oximetry and arterial blood gas determinations, chest radiograph and high-resolution computed tomography chest scan, ECG, and determinations of α_1-antitrypsin levels may be useful. In patients suspected to have an associated OSA (overlap syndrome), an overnight PSG is essential.

Treatment Considerations

The cornerstone of treatment for COPD includes smoking cessation, bronchodilators or inhaled steroids, and pulmonary rehabilitation [320, 322]. The ultimate goal is improvement of sleep quality and quality of life as a result of improvement of lung mechanics and gas exchange. All patients must avoid risk factors by instituting smoking cessation, getting early pneumococcal and influenza vaccinations, and receiving patient education and exercise training. The mainstay of COPD treatment is bronchodilators, which include anticholinergics and β_2-agonists. Metered-dose inhalers and nebulizers both work well. In severe cases, in addition to short- and long-acting bronchodilators (long-acting agents such as salmeterol have largely replaced short-acting agents [albuterol] which may still be used for "rescue" or as-needed basis), inhaled corticosteroids may be needed. In very severe cases, oral corticosteroids (but only on alternate days, using the lowest effective dose) combined with inhaled corticosteroids may have to be used. The role of supplemental oxygen therapy is discussed below. For patients not able to use inhaled medication, oral therapy including sustained-release theophylline in addition to a β_2-agonist or anticholinergic may have to be used. Theophylline can also be useful to control nighttime symptoms; however, nighttime symptoms may cause insomnia that itself needs separate treatment consideration. Insomnia is prevalent in COPD patients and needs to be treated to improve quality of life; however, use of hypnotics in the hypercapnic patient with severe COPD might be dangerous [311, 323]. Benzodiazepines may be dangerous for elderly COPD patients, particularly those with overlap syndrome. Nonbenzodiazepine receptor drugs may be used with some benefit, but even these drugs may promote apnea, thus exacerbating hypoxemia in COPD patients. Ramelteon has been shown to be safe and efficacious in mild-to-moderate COPD and OSA patients; however, further research is needed to determine

the safety in this population [311]. In patients with overlap syndrome, treatment with CPAP or BIPAP therapy may have to be used, but such treatment in these patients may not necessarily lead to an improvement in the coexistent COPD [324]. However, more recent studies have shown that treatment of OSA with CPAP in patients with overlap syndrome improves daytime arterial blood gas abnormalities, nocturnal oxygen saturation, and daytime sleepiness as measured by ESS [325]. Furthermore, in a prospective study of overlap syndrome, it was noted that patients who used CPAP had significantly lower risk of death compared with those who did not use CPAP [326].

In summary, current guidelines for medical therapy in COPD recommend "stepping up" triple therapy (a combination of long-acting beta agonists [e.g., salmeterol], muscarinic antagonists [e.g., triotropim], and glucocorticoids for moderate–severe COPD patients [327]). However, Magnussen et al. [328] have now shown in a recent trial that "stepping down" therapy (discontinuing inhaled glucocorticoids but keeping the other two agents) did not make a significant difference in terms of risks of moderate–severe exacerbations. In very severe cases not responding adequately to medical therapy, lung volume reduction surgery or lung transplantation should be considered [320].

Treatment of Nocturnal Oxygen Desaturation

Investigators have become aware of severe nocturnal hypoxemia in many COPD patients [278–280]. This nocturnal hypoxemia may or may not be accompanied by sleep-related apnea, hypopnea, or periodic breathing and impairment of gas exchange [281–283]. It is clear that repeated or prolonged oxygen desaturation at night may cause cardiac arrhythmias and may lead to pulmonary hypertension and cor pulmonale [329]. In addition, COPD patients show changes in sleep architecture [278, 304–309, 312, 313] that may be related to the poor quality of sleep or may be secondary to nocturnal hypoxemia causing disruption of nocturnal EEG sleep stages. Oxygen desaturation during sleep in COPD patients can be identified only if PSG, using sleep staging or continuous monitoring of oxygenation, is performed. Several studies show episodes of oxygen desaturation during sleep in COPD patients. An important study by Wynne's group [281] showed that oxygen desaturation could be associated with two types of patients: those with OSA (apnea and hypopnea) and those without OSA. In patients with OSA, the desaturation typically lasts less than 1 min and is mild. In the other group, the desaturation lasts 1–30 min and is associated with a profound decrease in oxygen saturation. The maximum episodes, lasting longer than 5 min, occur during REM sleep. Similar episodes of nocturnal oxygen desaturation have been described in patients with kyphoscoliosis [330, 331], in young patients with cystic fibrosis [285, 332, 333] and in patients with interstitial lung disease [334, 335].

Modern treatment of nocturnal hypoxemia is administration of oxygen by nasal cannula at a slow flow rate, usually less than 2 L/min. The multi-center study by the Nocturnal Oxygen Therapy Trial Group [336] and the Medical Research Council Working Party study [337] showed increased longevity for patients who used continuous supplemental oxygen at home. The Thoracic Society of Australia and New Zealand has published a position statement for oxygen therapy in COPD patients [338].

Particular indications for supplemental oxygen can be summarized as follows: daytime Pa_{O_2} below 55 mm Hg (Sa_{O_2} below 88 %) and daytime Pa_{O_2} between 56 and 60 mm Hg (or Sa_{O_2} of 89 %) accompanied by signs of right-side heart failure, unexplained polycythemia, pulmonary hypertension, and cor pulmonale [316, 339, 340], as well as significant nocturnal or exercise-induced oxygen desaturation. Oxygen administration may also improve sleep architecture [309]. O'Reilly and Bailey [341] reviewed the published evidence for and against the use of long-term oxygen treatment in COPD, summarized the problems with current guidelines, and suggested important areas for future research. Earlier, Croxton and Bailey [342] published recommendations for long-term oxygen treatment for COPD for future research based on a National Heart, Lung and Blood Institute Workshop report.

The question of safety of oxygen administration has to be determined [277]. Some patients become more hypercapnic after oxygen administration [278]. Furthermore, Motta and Guilleminault [343] showed the worsening effects of administration of oxygen at night in patients with OSAS. In an earlier study, Chokroverty et al. [344] reported worsening of apnea and prolongation of apnea after administration of 100 % of oxygen in four patients with obesity-hypoventilation syndrome. Many COPD patients may have OSA (overlap syndrome) [278, 295, 296], so physicians must be careful during administration of oxygen. Kearley and colleagues [345] have shown that administration of oxygen at 2 L/min reduces the episodic desaturation. Fleetham et al. [346] confirmed this finding, but Guilleminault et al. [283] contradicted these findings in five patients with excessive sleepiness associated with chronic obstructive airflow disease. The multiple institution studies by the Nocturnal Oxygen Therapy Trial Group [336] showed the relative safety of oxygen therapy, however, including home oxygen. In COPD patients undergoing long-term oxygen therapy, it may be useful to monitor breathing and oxygen saturation by finger pulse oximetry during sleep at night [347]. The role of noninvasive intermittent positive pressure ventilation (NIPPV) to improve hypoxemia in COPD patients remains undetermined [348, 349] in the absence of adequate clinical

trials using a large number of patients. However, in a recent prospective, multicenter, randomized control trial, Kohnlein and coworkers [350] investigated the effect of long-term NIPPV in 195 patients (102 NIPPV groups and 93 control groups) in advanced stable hypercapnic COPD. The authors concluded that addition of long-term NIPPV to standard therapy improved all-cause mortality after 12 months of follow-up of hypercapnic, stable COPD patients. This positive observation was reinforced later by Windisch et al. [351] after summarizing the current literature on NIPPV in COPD. These authors stated that there is now increasing evidence to support the role of NIPPV in hypercapnic COPD patients but how to select such patients needs to be determined.

Bronchial Asthma, Including Nocturnal Asthma

The characteristic clinical trials of asthma are the paroxysm of dyspnea, wheezing, and cough [352]. The paroxysmal attacks of wheezing and breathlessness may occur at any hour of the day or night, and the nocturnal attacks are distributed at random without any relationship to a particular sleep stage. Nocturnal symptoms of wheezing and coughing at least once per week are noted in as many as 75 % of asthmatics [353]. Breathing is characterized by prolonged expiration accompanied by wheezing and unproductive cough. There may be tightness of the chest and palpitation. The attacks typically last for 1–2 h. When the attacks last hours, the disorder is called *acute severe asthma* or *status asthmaticus;* this is a life-threatening condition because of extreme respiratory distress and arterial hypoxemia.

Pulmonary function tests and radiographic examination of the chest are important for confirming the diagnosis of bronchial asthma [352]. Abnormalities of certain pulmonary function tests [i.e., FEV_1, vital capacity (VC), and peak expiratory flow (PEF)] suggest airflow obstruction. An overnight fall in PEF of over 15 % associated with characteristic history is diagnostic of nocturnal asthma [354]. Chest radiography may reveal hyperinflated lungs and emphysema.

Sleep Disturbances in Bronchial Asthma

A variety of sleep disturbances have been noted in patients with asthma [355–364]. Janson et al. [363], using questionnaires and sleep diaries, studied the prevalence of sleep complaints and sleep disturbances prospectively in 98 consecutive adult asthma patients attending an outpatient clinic in Uppsala, Sweden. Compared with 226 age- and sex-matched controls, the authors found a high incidence of sleep disturbances in asthma patients, including early morning awakening, difficulty in maintaining sleep, and EDS. Sleep disturbances in general consist of a combination of insomnia and hypersomnia. Polysomnographic studies may reveal disruption of sleep architecture as well as sleep apnea in some patients. Nocturnal exacerbation of symptoms during sleep is a frequent finding in asthma patients [287, 353, 365].

There is evidence of progressive bronchoconstriction and hypoxemia during sleep in patients with asthma [354, 356]. In an important study by Turner-Warwick [357], 94 % of 7729 asthmatics surveyed woke up at least once a night with symptoms of asthma, 74 % at least one night a week, 64 % at least three nights a week, and 39 % every night. Nocturnal asthma is a potentially serious problem, as there is a high incidence of respiratory arrest and sudden death in adult asthmatics between midnight and 8:00 AM [358, 359].

To understand the relationship between the attacks of asthma and sleep stage and time of night, Kales et al. [360] studied six men and six women aged 20–45 years with PSG, each for 2–3 consecutive nights. They observed a total of 93 asthma attacks in these patients, 73 during NREM sleep, and 18 during REM. They did not find a relationship between asthma attacks and sleep stage or time of night. Sleep pattern showed less total sleep time, frequent WASOs, early final awakenings, and reduced stage 4 sleep. Kales' group [361] observed similar findings in a PSG study of 10 asthmatic children. Montplaisir and colleagues [362] studied 12 asthmatics, eight of whom showed nocturnal attacks on sleep studies (six women and two men aged 20–51 years).

Two questionnaire surveys from the European community [363, 364] found that bronchial asthma was associated with increased daytime sleepiness and impaired subjective quality of sleep (difficulty initiating sleep and early morning awakenings). One survey also noted increased prevalence of snoring and sleep-related apneas during sleep [363]. In the same survey, associated allergic rhinitis may have been a confounding variable. Twenty-six attacks were documented. No attacks occurred in stage 3 or 4 NREM sleep, nor were attacks more frequent during REM than NREM sleep. Thus, stages 3 and 4 sleep was "protective." Sleep efficiency was decreased. The number and duration of apneas were not significantly greater in asthmatics than in controls. Episodes of oxygen desaturation occurred only in the asthmatics. In a retrospective analysis of PSG recordings from children aged 5–17 years with (n = 113) and without (n = 104) asthma from a single pediatric sleep unit in Australia, Jensen et al. [366] reported that female asthmatic children had longer sleep latency but the male asthmatic children had shorter sleep duration, thus underscoring the gender difference in sleep disturbance among asthmatic children. Sleep efficiency and waking time after sleep onset were altered in asthmatics. When there were no attacks, no difference in sleep architecture was noted between the controls and the patients, which suggested that sleep disturbances are characteristic of unstable asthma with nocturnal attacks.

A number of pathogenic mechanisms for sleep disturbances and nocturnal exacerbations of asthma have been suggested [287, 353–355, 367–370]:

- Sleep deprivation [371]
- Impaired ventilatory function in the supine posture [372]
- A decrease in circulating epinephrine at night, with an increase in histamine [373]
- Gastroesophageal reflux [374, 375]
- Marked fluctuation in airway tone during REM sleep [376]
- Theophylline, a commonly used asthma drug that may cause insomnia [377, 378] and increased episodes of gastroesophageal reflux [379, 380] (a study by Hubert's group [381] found no such increase in asthmatics taking theophylline)
- Prolonged administration of corticosteroids in some asthmatics, which may have adverse effects on sleep and daytime functioning because of increased incidence of OSA [381, 382]
- Increased cellular inflammatory response in the bronchopulmonary region at night [369, 383]
- Miscellaneous factors, including allergens (e.g., house dust); increased bronchial secretions combined with suppression of cough, especially during REM sleep; airway cooling at night; increased pulmonary resistance; altered bronchial reactivity; normal propensity for worsening of lung function during sleep; normally increased vagal tone during sleep, which may be a major cause of nocturnal bronchoconstriction as evidenced by circadian desynchronization studies and cholinergic blockade studies [384, 385]; and suppressed arousal response to bronchoconstriction in severe nocturnal asthma [369]
- Certain circadian factors [367–370].

The following evidence supports the claim that circadian factors contribute to nocturnal exacerbation of asthma:

1. PEF typically is highest at 4:00 PM and lowest at 4:00 AM [369]. The variation is ordinarily approximately 5–8 %, but if it reaches 50 %, as it can in some asthmatics, there is the danger of respiratory arrest [369]. This circadian variation in PEF is related to sleep and not to recumbency or the hour [368–370].
2. Airway resistance as measured breath by breath is not increased in normal individuals at night, but asthmatics show a circadian rhythm of increased airway resistance at night that is related to the duration of sleep and not to sleep stages [369, 386].
3. OSA is more prevalent and more severe in severe asthmatics [365, 387–391]. Asthma in turn is more prevalent in OSA [392].
4. Finally, tonsillar hypertrophy has been reported to be more frequent in children with a history of wheezing

Treatment of Bronchial Asthma

Treatment of bronchial asthma, including nocturnal asthma, can be grouped into two main components: [352] 1. Rescue agents (acute relievers) and 2. The controller treatment (agents that modify the airway environment causing less frequent occurrence of airway narrowing).

The rescue treatment includes a rapid-acting β-agonist as inhaler; this is the mainstay of bronchodilator treatment of asthma: a short-acting β2-selective inhaler (e.g., albuterol) on an as-needed basis in patients with mild intermittent asthma (by nebulizer or metered-dose inhaler). The dose consists of two "puffs" from the inhaler with a separation of 3–5 min between the first and the second puffs. The first puff dilates the narrowed airways and then the second puff has a better chance of access to the affected areas of the lungs. This treatment can be repeated every 4–6 h. Another rescue treatment is an anticholinergic agent (e.g., ipratropium bromide, an atropinic agent) which inhibits acetylcholine release promoting bronchodilation. It is given as two puffs every 4–6 h in a metered-dose inhaler.

The controller treatment includes inhaled corticosteroids (e.g., fluticasone, budesonide, and triamcinolone) to improve lung function and prevent exacerbation of asthmatic attacks. One must consider adverse effects of steroids.

Other Modalities of Treatment [352] consist of antileukotrienes (e.g., montelukast, 10 mg tablet once a day), long-acting β-agonists (e.g., salmeterol), one-to-two puffs every 12 h as controller agents, and theophylline bromide for moderate to persistent asthmatics who are also receiving other agents as described above. Systemic corticosteroids may be considered as last resort for moderate-to-severe persistent asthma. Rarely monoclonal antibody treatment (e.g., omalizumab, lebrikizumab, and mepolizumab [not FDA approved in USA]) has been prescribed for severe cases of asthma. Finally in children with tonsillar hypertrophy, adenotonsillectomy is followed by improvement in asthma symptoms [393]. Other measures include treating the reversible factors such as allergens, nasal congestion, or bronchopulmonary infections, and using a humidifier [369].

In a double-blind, placebo-controlled crossover study, Kraft et al. [394] and Wiegand et al. [395] reported that salmeterol, an inhaled β_2-agonist with a prolonged duration of action, improved the number of nocturnal awakenings with nocturnal asthma. Wiegand et al. [395] found that salmeterol was superior to theophylline in maintaining nocturnal FEV_1 levels and in improving morning and evening PEF, and in an improvement in patient perception of sleep but not in PSG measures of sleep architecture. Previously, several studies showed efficacy of salmeterol in

nocturnal asthma, primarily in combination with inhaled corticosteroids [396–400].

Sleep disturbances in asthma caused by nocturnal asthma attacks should not be treated with hypnotic medicines; rather, the best treatment is vigorous treatment of the asthmatic attacks by using oral and preferably inhaled steroids, salmeterol, and anticholinergic medications (e.g., inhaled ipratropium bromide) as stated above [322, 352, 354, 369, 395, 401, 402]. Patients with PSG evidence of OSA should be treated with CPAP, which not only is effective for OSA but also helps nocturnal asthmatic symptoms. Ciftci et al. [389] reported moderate-to-severe OSA based on an AHI of 15 in 16 of 43 asthmatic patients with nocturnal symptoms. CPAP treatment improved nocturnal symptoms but did not correct pulmonary function test abnormalities. Patients with gastroesophageal reflux disease (GERD) often have worse symptoms of the disease at night, which may worsen the nocturnal asthmatic symptoms. Treatment of GERD with proton pump inhibitors (e.g., omeprazole) at bedtime may improve nocturnal asthmatic symptoms and sleep quality [403, 404]. However, the evidence is conflicting; Coughlan et al. [405], after a systematic review, concluded that clear evidence or improvement of nocturnal asthmatic symptoms after treating GERD is lacking.

Restrictive Lung Disease

Restrictive lung disease is characterized functionally by a reduction of total lung capacity, FRC, VC, expiratory reserve volume, and diffusion capacity but preservation of the normal ratio of FEV_1 to FVC [335]. This may be due to intrapulmonary restriction (e.g., interstitial lung disease) or extrapulmonary restriction resulting from diseases of the chest wall (e.g., kyphoscoliosis) or pleura; neuromuscular diseases; obesity; or pregnancy, which may abnormally elevate the diaphragm.

Interstitial Lung Disease

Etiopathogenesis

Interstitial lung disease (ILD) may result from a variety of causes, including idiopathic pulmonary fibrosis, fibrosing alveolitis associated with connective tissue disorders, pulmonary sarcoidosis, occupational dust exposure, pulmonary damage resulting from drugs, or radiotherapy to the thorax [406–410]. The common features of all these conditions include alveolar thickening due to fibrosis, cellular exudates, or edema; increased stiffening of the lungs causing reduced compliance; and ventilation–perfusion mismatch giving rise to hypoxemia, hyperventilation, and hypocapnia.

Clinical Features

Features of interstitial lung disease include progressive exertional dyspnea, a dry cough, clubbing of the fingers, and pulmonary crackles (crepitations) on auscultation of the lungs. The diagnosis is based on a combination of characteristic clinical features, radiographic findings (e.g., diffuse pulmonary fibrosis), and pulmonary function test results.

Sleep Abnormalities

Several authors [334, 408–416] reported on sleep studies in interstitial lung disease. Sleep abnormalities consist of repeated arousals with sleep fragmentation and multiple sleep stage shifts, increased stage 1, and reduced REM sleep accompanied by oxygen desaturation during REM and NREM sleep owing to episodic hypoventilation and ventilation–perfusion mismatch, and occasionally OSA. Mermigkis et al. [412], in a retrospective study, reported OSA in 18 patients with interstitial lung disease. These authors concluded that an increased body mass index and a significant impairment in pulmonary function tests may predict the occurrence of OSA in these patients, and it is important to make the diagnosis and treat comorbid OSA to improve quality of life. Milidi et al. [40] in a review article described fatigue as a disabling symptom of ILD, and the patients show poor sleep quality and SRBD correlating with impaired sleep quality. PSG studies document frequent sleep apnea–hypopnea as well as reduced sleep efficiency, SWS, and REM sleep in addition to REM-related hypoventilation. Treatment of sleep-breathing disorders improves quality of life. Schiza et al. [413] observed an increasing prevalence of OSA in idiopathic pulmonary fibrosis (IPF). The recently published IPF guidelines recognized OSA as an important comorbidity affecting patients' survival.

There is no effective treatment for interstitial lung disease except to treat the comorbid conditions such as OSA. Corticosteroids are found to be effective in some cases. George and Kryger [335] advocated symptomatic treatment with supplemental nocturnal oxygen therapy according to the guidelines developed by the Nocturnal Oxygen Therapy Trial Group [336]. In summary, supportive care, treatment of comorbid conditions, and ultimately lung transplantation are the only therapeutic options available for these conditions.

Kyphoscoliosis

Kyphoscoliosis is a thoracic cage deformity that causes extrapulmonary restriction of the lungs and gives rise to impairment of pulmonary functions, as described earlier for restrictive lung diseases. The condition may be primary (idiopathic) or secondary to neuromuscular disease, spondylitis, or Marfan syndrome [335].

In severe cases of kyphoscoliosis, breathing disorders during sleep (e.g., central, obstructive, and mixed apneas associated with oxygen desaturation) and sleep disturbances (e.g., disrupted night sleep, reduced NREM stages 2 through 4 and REM sleep, and EDS) have been described [330, 331, 335].

The best treatment for patients with chronic respiratory failure secondary to severe kyphoscoliosis is NIPPV. This

has been described in detail in Chap. 41. Long-term NIPPV treatment improves nocturnal and daytime blood gases, respiratory muscle performance, pulmonary function, and hypoventilation-related symptoms in patients with severe kyphoscoliosis [417–419].

Lung Transplant Recipients and Sleep Dysfunction

Lung transplantation has recently become a life-saving modality and a treatment of last resort in many patients with end-stage lung disease (ESLD) (e.g., idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease or COPD, and cystic fibrosis). However, these patients are at increasing risk for poor sleep due to comorbidities and use of immunosuppressants, steroids, and other medications [420, 421]. Insomnia and sleep-disordered breathing (SDB) are the most frequently reported sleep disorders in these patients. Often the sleep disorders are unrecognized and untreated. It is important to screen such patients for sleep disorder before and after transplantation. Sommerwerck et al. [422] polysomnographically studied 77 patients (45 men) and noted a prevalence of SDB of 49.4 % (42.9 % OSA and 6.5 % CSA). The authors concluded that the prevalence of SDB is high in stable lung transplant recipients and COPD is an independent predictor of SDB. High prevalence of SDB was also noted in several other reports [420, 421, 423–425]. Some of the factors cited are weight gain, altered chemosensitivity, and central control of breathing and medication use. Reilly-Spong et al. [420] using Pittsburg Sleep Quality Index and actigraphy in patients with various organs including lung transplant recipients reported poor sleepers in 41 %. Sleeplessness is mostly related to steroids and immunosuppressive medications.

Gastrointestinal Diseases

Peptic Ulcer Disease

A peptic ulcer is an ulcer in the lower esophagus, stomach, or duodenum [426]. The prevalence of peptic ulcer in the general population is fairly high—approximately 10 % of the adult population—and men are most often affected. The most common presentation of peptic ulcer is episodic pain localized to the epigastrium that is relieved by food, antacids, or other acid suppressants. The pain has a characteristic periodicity and extends over many years. The patient generally can localize the pain to the epigastrium. Occasionally, however, it is referred to the interscapular region at the lower chest and is usually described as burning or gnawing. Duodenal pain is often described as "hunger pain" and is relieved by eating. An important feature is that the pain awakens patients 2–3 h after retiring to bed, disturbing sleep. An important physical sign is the so-called pointing sign and localized epigastric tenderness.

The natural history of the disease is episodic occurrence over a course of days or weeks, after which the pain disappears, to recur weeks or months later. Between attacks the patient feels well. Presentation may be secondary to complications of ulcer, such as an acute episode of bleeding or perforation or even an episode of gastric obstruction. The differential diagnosis of ulcer pain should include cholecystitis, angina, gastroesophageal reflux, esophagitis, and pancreatitis. Definitive diagnosis is established by barium examination of the gastroduodenal tract and, if necessary, by endoscopic examination and biopsy.

In the last two decades, it has been clearly established that the most common cause of peptic ulcer disease is *Helicobacter pylori* infection [426–429]. The second most common cause is ingestion of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) [426, 427]. *Helicobacter pylori* infection is responsible for 95 % of duodenal and more than 85 % of gastric ulcers [427].

Sleep, Nocturnal Acid Secretion, and Duodenal Ulcer (See also Chap. 11)

To understand the role of nocturnal gastric acid secretion in duodenal ulcer, Dragstedt [430] studied hourly collections of nocturnal gastric acid from patients with duodenal ulcer and from normal subjects. The study found 3–20 times greater volumes of nocturnal acid secretion in patients than in normal controls (see also Fig. 11.10). Vagotomy abolished this increased secretion and improved healing of ulcers [431]. Studies by Orr et al. [432] have shown that patients with duodenal ulcer exhibit failure of inhibition of gastric acid secretion during the first 2 h after onset of sleep. A study by Watanabe et al. [433] confirmed the findings of Orr et al. [432] and found that the intragastric pH values increased during NREM and REM sleep in healthy controls and gastric ulcer patients, but the intragastric pH of duodenal ulcer patients did not change. Schubert and Peura [434] reviewed the physiology and pathophysiology of acid secretion and its inhibition in the management of acid-related clinical conditions.

Sleep disturbances in duodenal ulcer patients characteristically result from episodes of nocturnal epigastric pain. These symptoms cause arousals and repeated awakenings, thus fragmenting and disturbing sleep considerably in these patients.

Treatment

In light of the evidence about the role of *H. pylori* infection and NSAIDs in the pathogenesis of gastroduodenal ulcers, the theory of hypersecretion of acid in peptic ulcer patients has been relegated to a secondary role [427]. The first step is to find the causes of ulcer based on the history and laboratory tests such as serology, carbon-13 urea breath test, and endoscopic biopsy and histology, particularly in patients with gastric ulcer [426, 427]. The purpose of treatment is to

relieve symptoms; heal the ulcer; and either cure the disease, in the case of *H. pylori* ulcers, or prevent recurrences, in the case of NSAID ulcers [426, 427]. To cure the ulcer, the best approach is a triple combination of antimicrobial therapy as recommended and approved by the Food and Drug Administration as follows [426, 427, 435–437]: esomeprazole, amoxicillin, clarithromycin; lansoprazole, amoxicillin, clarithromycin; omeprazole, amoxicillin, clarithromycin; or rabeprazole, amoxicillin, clarithromycin. Antimicrobial agents effective against *H. pylori* infection include amoxicillin, clarithromycin, tetracycline, and metronidazole. Most commonly a 10- to 14-day regimen may be effective. To accelerate healing, the antimicrobial agent is combined with antisecretory agents [histamine$_2$ (H_2)–receptor antagonists such as cimetidine (Tagamet), ranitidine (Zantac), nizatidine (Axid), or famotidine (Pepcid)]. The most potent antisecretory agents are the proton pump inhibitors (e.g., esomeprazole, lansoprazole, omeprazole, and rabeprazole). Because of emergence of resistant strains of *H. pylori* and failure of eradication in 20–25 % of cases, quadruple [427, 438] and sequential therapy has been suggested for eradication of *H. pylori* infection [426, 435, 436, 439–441]. Sequential therapy includes an initial 5 days of therapy with a proton pump inhibitor and amoxicillin followed by 5 days of a proton pump inhibitor plus clarithromycin and tinidazole. For treatment of NSAID ulcers, NSAID therapy should be stopped and treated with traditional antisecretory agents. Patients who require continued NSAID therapy, however, may be treated with misoprostol, a synthetic prostaglandin E_1 analog (200 mg four times a day) [426, 427]. General measures of treatment of peptic ulcer disease should consist of avoidance of tobacco and alcohol. For detailed management of uncomplicated, complicated, and resistant ulcers, the reader is referred to Feldman [427] and Kuipers et al. [426].

Gastroesophageal Reflux Disease

Clinical Features

Gastroesophageal reflux disease (GERD) is preferable to the term *reflux esophagitis* [442]. GERD frequently occurs in middle-aged and elderly women, and sometimes in younger women during pregnancy. Hiatal hernia is often associated with reflux esophagitis. The characteristic symptom is heartburn, described as retrosternal burning pain exacerbated by lifting or straining or when the patient lies down at night [442, 443]. The nocturnal burning pain causes difficulty in initiating sleep, frequent awakenings, and fragmentation of sleep [431, 444– 447]. The nocturnal pain is characteristically relieved by sitting up or ingesting food or by acid-suppressant agents. An important differential diagnosis would be angina, particularly when the pain radiates to the neck, jaws, and arms, but an important point to remember is that the esophageal pain is usually not related to exertion. Other symptoms include transient or persistent dysphagia if the patient has developed stricture and regurgitation of gastric contents associated with coughing, wheezing, and shortness of breath due to the aspiration of the gastric contents into the bronchopulmonary region [431, 442, 443]. A serious complication of repeated episodes of gastroesophageal reflux and esophagitis is Barrett's esophagus, which may be a precursor to esophageal adenocarcinoma [442, 443, 448, 449]. Another potential complication is exacerbation of nocturnal asthma.

Differential Diagnosis, Pathogenesis, and Diagnostic Tests

Peptic ulcer disease, ischemic heart disease, sleep apnea, abnormal swallowing, and sleep choking syndromes may be mistaken for gastroesophageal reflux [442, 443, 445]. It has been shown that the fundamental mechanism of GERD is the inappropriate, transient, and frequent relaxation of the lower esophageal sphincter, causing episodes of acid reflux [431, 442, 443, 450]. The esophagitis resulting from acid reflux in the esophagus reduces the sphincter pressure and impairs esophageal contractility [431, 442, 450]. An additional mechanism is the presence of a hiatal hernia. Other factors, such as the acid clearance time, frequency of swallowing, and secretion of saliva, play an important role in the pathogenesis. The diagnosis of gastroesophageal reflux and prolonged acid secretion can be made by continuous monitoring of lower esophageal pH [431, 451]. When the pH falls below 4, gastroesophageal reflux occurs [452]. Repeated prolonged episodes of gastroesophageal reflux during sleep at night can cause esophagitis [453]. Physiologic changes during sleep consisting of suppression of saliva, decreased swallowing frequency, and prolonged mucosal contact with the gastric acid all contribute to the development of esophagitis [431, 442, 445, 454, 455]. After repeated prolonged episodes of gastroesophageal reflux at night for many years, patients may develop Barrett's esophagus, which results from replacement of the squamous epithelium of the lower esophagus by the columnar epithelium of the stomach [442, 443, 448, 449]. Documentation of spontaneous gastroesophageal reflux and prolonged acid clearance is important for diagnosis and treatment of esophagitis and of extraesophageal reflux and upper aerodigestive tract diseases resulting from repeated episodes of gastroesophageal reflux [431, 442, 454, 456–459].

Role of Gastroesophageal Reflux in Bronchopulmonary Disease

In some patients with asthma and chronic bronchitis or COPD, spontaneous gastroesophageal reflux at night plays a role in the pathogenesis of symptoms such as nocturnal wheeze, cough, or shortness of breath [431, 442, 443, 460–462]. In such patients, intraesophageal pH monitoring has shown prolonged acid clearance [461]. This is important from a therapeutic point of view, because administration of acid suppressants to such patients improves pulmonary

symptoms [443]. A study by Tan et al. [463], however, casts doubt on the relevance of gastroesophageal reflux to asthma.

The mechanisms of pulmonary symptoms in gastroesophageal reflux include aspiration of the gastric contents in the lungs causing pneumonitis and acid contact with the lower esophagus initiating reflex stimulation of the vagus nerve, causing bronchoconstriction. Actual aspiration of gastric contents into the lungs can be documented with the scintigraphic technique used by Chernow et al. [464]. These authors instilled a radionuclide into the stomach before sleep. A lung scan the next morning showed the radioactive material in the lung, suggesting nocturnal pulmonary aspiration. Children with asthma and bronchopulmonary disease may have sleep apnea, in addition to the other complications of gastroesophageal reflux [465]. Gastroesophageal reflux has been implicated in some cases of sudden infant death syndrome, possibly causing apnea and sudden death, but this has been found in only a small percentage of cases [466, 467]. The relationship between GERD and OSAS remains undetermined, although there is an increased prevalence of GERD in OSAS patients and CPAP treatment in such patients improves GERD symptoms [468–470]. These findings agree with the conclusion of Shepherd et al. [471] that the prevalence of nocturnal reflux symptoms is increased in those with or suspected of having OSA. This conclusion was based on 1116 patients with PSG-diagnosed OSA and 1999 participants of population health survey (2007 Busselton Survey). In a recent report Shepherd and Orr [472] suggested that obesity rather than airway obstruction is responsible for GERD symptoms.

Diagnostic Tests

No single test is diagnostic for GERD, but a combination of tests to assess the potential for reflux damage to the esophagus and actual presence of reflux is necessary to make the diagnosis. The diagnosis is confirmed by barium examination, and, if necessary, by endoscopic examination and biopsy [442, 443]. Measurement of lower esophageal sphincter pressure and a diagnosis of hiatal hernia may detect risk factors for reflux [442, 443]. Damage to the esophagus may be assessed by Bernstein's test (acid perfusion test), esophagography, esophagoscopy, and mucosal biopsy [442]. The actual presence of reflux may be established with the following tests: esophagography, acid reflux test, prolonged esophageal pH monitoring, and gastroesophageal scintigraphy [442]. The importance of 24-h ambulatory esophageal pH monitoring has been emphasized by Triadafilopoulos and Castillo [442].

Treatment

Treatment [442, 450] includes general measures such as avoidance of fatty foods and stooping, weight reduction, and elevation of the head of the bed to reduce reflux at night. Smoking should also be avoided. These simple measures decrease the frequency and length of reflux episodes as demonstrated by 24-h pH monitoring [452, 453]. If the patients fail to improve as a result of these simple measures, H_2-receptor antagonists (cimetidine, ranitidine, famotidine, and nizatidine) in the usual dose range as used for peptic ulcer patients (see earlier) will improve the symptoms of GERD [442, 443, 450]. For patients who are resistant to H_2-receptor antagonists, a proton pump inhibitor may be used [442, 443]. Proton pump inhibitors decrease gastric acid secretion through inhibition of the proton pump (H^+,K^+-ATPase) of the parietal cells (this is the most potent inhibitor of gastric acid secretion) and are in fact the treatment of choice for nighttime symptoms causing sleep dysfunction [442, 471–480]. Several studies have shown improvement of subjective measures of sleep without evidence of objective measurement after pharmacologic treatment for GERD [477, 479]. Other measures found to be useful are prokinetic agents (e.g., metoclopramide, 10 mg qid; cisapride, 10 mg qid; bethanechol, 10 mg qid) [346]. For patients who fail to respond to medical treatment, antireflux surgery (e.g., fundoplication) is indicated [442, 481]. Rarely, a Roux-en-Y near esophagojejunostomy is necessary for those intractable GERD patients who failed prior antireflux surgery [482].

In conclusion, an awareness of the role of sleep in the pathogenesis and treatment of peptic ulcer disease, particularly duodenal ulcer and esophageal reflux, is important for diagnosis and treatment. Facilities for all-night PSG study and 24-h esophageal pH monitoring have contributed to an understanding of the association between sleep and these diseases. These disorders are good examples of diseases that benefit from a multidisciplinary approach to patient management by a gastroenterologist, a pulmonologist, and a sleep specialist. This review also shows that sleep adversely affects patients with GERD by increasing the episodes of reflux and prolonging the acid clearance time. Furthermore, repeated spontaneous reflux episodes adversely affect sleep by causing arousals, frequent awakenings, sleep fragmentation, and excessive daytime sleepiness [444–446, 483].

Sleep in Functional Bowel Disorders

Functional bowel disorders include functional or nonulcer dyspepsia (NUD) and irritable bowel syndrome (IBS). NUD includes functional disorders of the upper gut and presents with upper abdominal pain or discomfort, nausea, gaseous distention, and early satiety [484–488]. A number of patients with functional bowel disorders have symptoms originating from the lower gut consistent with IBS, which is a common medical disorder characterized by symptoms of bowel dysfunction and abdominal pain [488]. In the last two decades, our understanding of IBS has grown considerably [488,

489], beginning with change in the classification and definition, which are the symptom-based Rome III criteria [490]. The basis for IBS symptoms is thought to be dysregulation of the brain–gut (central nervous system–enteric nervous system) relationship. The concept of IBS as a functional bowel disorder with no structural alteration has been dispelled by the functional and structural magnetic resonance imaging (MRI) findings of significant cortical thinning of the anterior cingulate cortex (ACC) and insula [491]. These findings confirm the investigators' previous observation of absent rectal pain-related functional MRI responses in the anterior insula and ACC in IBS [492]. These findings support the earlier abnormal EEG findings in IBS [493]. Davis et al. [491] also noted reduced gray matter in the anterior/medial thalamus and ACC on voxel-based morphometry in the IBS group relative to healthy controls.

Many patients with NUD and IBS have history of sleep complaints (e.g., frequent awakenings with or without pain and nonrestorative sleep) [494–496]. Such functional disorders may be associated with fibromyalgia syndrome (FMS) [489, 497–499]. Patients with FMS complain of a variety of sleep problems (see later). Jarrett et al. [500] and Eisenbruch et al. [501] reported that women with IBS associated with gastrointestinal symptoms complain of poor sleep and nonrestorative sleep more often than women without IBS. In a previous study, Eisenbruch et al. [502] reported poor sleep quality in the absence of objective sleep abnormalities (PSG findings), suggesting an altered sleep perception. In contrast to these findings, Fass et al. [503] prospectively evaluated 505 new patients with functional bowel disorders and 247 healthy controls using validated bowel symptom and sleep questionnaires. They concluded that functional dyspepsia patients, but not IBS patients, reported sleep disturbances more frequently than healthy control subjects. Another important observation is that IBS patients, compared with controls, had greater sympathetic dominance as indicated by increased LF/HF heart rate variability ratio during REM sleep because of vagal withdrawal, suggesting that autonomic functioning during REM sleep may be an useful biological marker to identify IBS patients [504]. However, in a later review of the literature, Mazurak et al. [505] concluded that most studies reported no difference in heart rate variability (HRV) when the IBS population was compared to healthy controls. Treatment of IBS patients includes an integrated pharmacologic and behavioral approach depending on the severity of symptoms and disability [488].

Miscellaneous Gastrointestinal Disorders and Sleep

There is circumstantial evidence that sleep deprivation or sleep disturbance may trigger flare-ups of two chronic autoimmune inflammatory bowel disorders: Crohn's disease or regional ileitis, and ulcerative colitis [506, 507]. Demonstration of exacerbation of colonic inflammation and tissue damage following acute and chronic sleep deprivation in a mouse model of colitis [508] supports such contention. Future research and clinical trials focusing on an improvement in the quantity or quality of sleep in patients with inflammatory bowel disorders are needed to provide definitive evidence.

Hepatic encephalopathy may cause hypersomnia, inversion of the sleep–wake rhythm, and recurrent stupor, which are most likely related to neurotransmitter alterations in the brain. There is an excessive accumulation of endozepines [benzodiazepine-like γ-aminobutyric acid (GABA) type A receptor modulators] in hepatic encephalopathy, explaining the recurrent stupor that is noted in some cases [509]. Prior hepatic encephalopathy may synergize with OSA in worsening sleep architecture and sleep disturbance in cirrhosis of liver [510] (nonrestorative sleep, reduced SWS, and increased stage N2). In a population-based cohort study from Chou et al. [511] observed that the risk of liver disease (particularly cirrhosis of liver and hepatitis c) was more than five times higher and among people with OSA compared with the control group. Previous studies [512–514] have also postulated a high prevalence of OSA in liver disease; however, a prospective study is needed to determine the factors responsible for such a high prevalence and also to evaluate the effect of CPAP therapy on the morbidity and mortality in liver disease.

Sleep disturbances have not been adequately studied in celiac disease (nontropical sprue or gluten-sensitive enteropathy) and Whipple's disease (a chronic multisystem disease due to infection with *Tropheryma whipplei*). Patients with celiac disease may have restless legs syndrome (RLS)—periodic limb movements in sleep (PLMS) [515], and Whipple's disease patients may present with insomnia or sleep–wake cycle changes.

Endocrine Diseases

Thyroid Disorders

It is important to be aware of the association between thyroid disorders, disordered breathing, and sleep disturbances. History and physical examination may direct attention to a thyroid disorder, in which case thyroid function tests should be performed to confirm the clinical diagnosis.

Hypothyroidism

The salient diagnostic features suggestive of myxedema consist of presentation in a middle-aged or elderly individual of fatigue, weight gain, decrease of physical and mental faculties, dryness and coarsening of the skin, pretibial edema, hoarse voice, cold sensitivity (sometimes presenting with hypothermia), constipation, and bradycardia or

evidence of ischemic heart disease in the ECG. Both upper airway obstructive [516] and central sleep apneas [517], which disappeared after thyroxine treatment, have been described in patients with myxedema. Mechanisms include deposition of mucopolysaccharides in the upper airways as well as central respiratory dysfunction as evidenced by impaired hypercapnic and hypoxic ventilatory response [518].

In an important study, Jha et al. [519] evaluated 50 newly diagnosed consecutive patients with primary hypothyroidism using PSG in all patients. Thyroxine replacement therapy was associated with improvement, including the findings in the repeat PSG study. This supports the previous findings of Rajagopal et al. [520]. Grunstein and Sullivan [521] recommended nasal CPAP treatment in patients with hypothyroidism and concomitant OSA while the patient is receiving thyroxine treatment. Routine screening for hypothyroidism in OSAS remains controversial [522–525]. Hashimoto's thyroiditis, an autoimmune disease diagnosed on the basis of high titers of antithyroid antibodies and histologic findings, is associated with higher prevalence of sleep-related breathing problems compared with controls [526]. A recent study [527] of 203 patients documented a total of 12.77 % of subclinical and clinical hypothyroidism in PSG proven OSAS patients.

Hyperthyroidism

Clinical features suggestive of thyrotoxicosis are presentation in a woman (female-to-male ratio, 8:1) of apparent increased energy, weight loss despite increased appetite, staring or bulging of the eyes (exophthalmos), tachycardia or atrial fibrillation, heat intolerance with excessive sweating, feelings of warmth, and a fine tremor of the outstretched fingers.

Few sleep studies have been made in patients with thyrotoxicosis. Dunleavy et al. [528] observed an increased amount of SWS, which returned to normal after treatment. In contrast, Passouant et al. [529] did not find any change in SWS but described an increase in sleep-onset latency in hyperthyroid patients. Johns and Rinsler [530] found no relationship between stages of sleep and alteration of thyroid function.

Ajlouni et al. [531] reported eight cases of patients with new-onset sleepwalking coinciding with the onset of thyrotoxicosis resulting from diffuse toxic goiter. Disappearance of sleepwalking with successful achievement of a euthyroid state supported a cause-and-effect relationship.

Diabetes Mellitus

For a discussion of sleep disturbance and sleep apnea in diabetes, see the section on autonomic neuropathy in Chap. 41.

Growth Hormone Disorders

Growth Hormone Deficiency and Sleep

In eight adults with isolated growth hormone (GH) deficiency (aged 18–28 years), Astrom and Lindholm [532] found a reduction of stage 4 sleep but increases in stages 1 and 2 NREM sleep, with a net result of an increase of total sleep time. In a later paper, Astrom and others [533] studied these patients after daily treatment with GH for 6 months and found a decrease in total sleep time that was due mainly to a reduction in stage 2 sleep, unchanged slow waves, and an increase in REM sleep time. In contrast to these findings, Pavel et al. [534] found no difference in sleep efficiency and daytime sleepiness in 16 GH-deficient adults (7 women and 9 men with a mean age of 36.8) after GH substitution. The subjective sleep parameters improved, however, and the authors suggested that this improvement might be caused by other indices of general well-being in this study with a small sample size. In 30 patients with GH deficiency (pituitary dysfunction in 26 and hypothalamic origin in four), Copinschi et al. [535] reported sleep dysfunction (high Pittsburgh Sleep Quality Index Scores, daytime sleepiness, and reduced QoL) compared with 30 controls. GH efficiency associated with morbid obesity, OSA, and hypogonadism is an important manifestation of Prader–Willi syndrome [536], a rare multi-system paternally inherited disorder of gene expression on chromosome 15q11–q13.

Excessive Growth Hormone Release and Sleep

Sullivan et al. [537] reported sleep apnea in association with GH release from the pituitary in patients with acromegaly. The most common explanation for sleep apnea in these patients is the enlargement of the tongue and pharyngeal wall, which causes narrowing of the upper airway. Sullivan's group [537] studied 40 patients with acromegaly and observed central sleep apnea in 30 %. Increased respiratory drive with increased hypercapnic ventilatory response is present in these patients. Sandostatin, a somatostatin analog, cured central apnea and normalized the ventilatory response.

Grunstein et al. [538] studied 53 patients with acromegaly who were consecutively referred for consultation. Sleep apnea was a reason for referral of 33 patients, whereas 20 patients were referred without any suspicion of apnea. Thirty-one patients of the group of 33 referred for apnea had sleep apnea; 12 of the 20 patients referred without suspected apnea were found to have apnea. Central apnea was predominant in 33 % of patients. The authors concluded that sleep apnea is common in individuals with acromegaly and central sleep apnea is associated with increased disease activity as reflected by biochemical measurement. They speculated that alteration of respiratory control may be a mechanism for sleep apnea in these patients. In a later study of 54 patients with acromegaly, Grunstein et al. [539] found

increased hypercapnic ventilatory responses in those patients with central sleep apnea but not in those with OSA or those without sleep apnea. These authors also found that acromegalic patients with central sleep apnea have increased GH and insulin-like growth factor-I levels compared with their counterparts with OSA. The authors concluded that increased ventilatory responsiveness and elevated hormonal parameters of disease activity contribute to the pathogenesis of central sleep apnea and acromegaly.

In contrast, later investigators found a high prevalence of sleep apnea, predominantly obstructive type and rarely central apnea [540, 541]. Suggested mechanisms for the development of OSA in acromegaly include an anatomic abnormality, especially at the base of the tongue [542]; craniofacial changes (e.g., increased vertical dolichofacial growth) causing narrowing of the posterior airway space, and displacement of the hyoid caudally [543].

Octreotide, a long-acting somatostatin analog, has been found to be an effective noninvasive treatment for sleep apnea in acromegaly [544, 545]. Sze et al. [546] reported a high prevalence of sleep apnea syndrome in acromegaly patients with resolution of SDB symptoms after transsphenoidal adenoidectomy. The relationship between sleep apnea and the GH level in active acromegaly remains unresolved [538, 541, 544]. Nonfunctional pituitary macroadenoma patients ($n = 69$) in long-term remission after trans-sphenoidal surgery on replacement therapy showed impaired sleep quality EDS and altered sleep–wake rhythmicity (decreased daytime and increased nighttime activities in actigraphic recordings) probably due to a dysfunction of the adjacent SCN [547].

Miscellaneous Endocrine Diseases and Sleep

In the only controlled study in patients with Cushing's syndrome (hyperpituitarism with corticosteroid excess), about one-third of the patients were diagnosed with sleep apnea [548]. There is one report of decreased delta sleep and increased stage 1 sleep and sleep fragmentation [549].

Addison's disease (adrenal gland insufficiency) patients may have increased sleep fragmentation and decreased REM sleep [550].

The male hormone testosterone is a risk factor for sleep apnea, as exogenous administration of testosterone induces sleep apnea in both normal and hypogonadal men [551] and worsens sleep apnea in older men [552]. Testosterone treatment transiently worsens severity of OSA [553], and serum testosterone levels are negatively correlated with severity of OSA [554]. However, CPAP therapy has no influence on testosterone level in men with OSA [555].

There is an increased prevalence of OSAS, insulin resistance, and type 2 diabetes mellitus in patients diagnosed with polycystic ovary syndrome, the most common endocrine disorder in reproductive-aged women, characterized by chronic anovulation and hyperandrogenism [556–558].

Renal Disorders

Sleep Disturbances and Chronic Renal Failure

Sleep dysfunction has been well described in cross-sectional studies of patients with chronic renal failure (CRF) on hemodialysis [559–567] and those not on hemodialysis [568–571], and even in patients with renal transplantation [572, 573]. Sleep dysfunction has been noted in up to 80 % of patients with CRF [560]. There is, however, no clear relationship noted between indices of renal failure and sleep disturbance in these studies.

Several studies have used PSG to objectively document the sleep disturbances, which consist of reduced sleep efficiency, increased sleep fragmentation, frequent awakenings with difficulty in maintenance of sleep, decreased SWS, and disorganization of the sleep cycle [559, 560]. Various studies have demonstrated a variety of sleep complaints in CRF patients that include poor-quality and nonrestorative sleep, difficulty in initiating and maintaining sleep, EDS, SDB, and sleep apnea. In a more recent study [574], Ezzat and Mobab sought to assess the prevalence of sleep dysfunction in patients with end-stage renal disease (ESRD) on hemodialysis ($n = 30$), chronic kidney disease (CKD) on conservative management ($n = 30$) comparing these two groups with normal controls ($n = 30$). In addition to standard blood biochemical studies and hemoglobin levels, all had one night of PSG study. They found a high percentage of sleep dysfunction in both patient groups. The types of sleep disorders and percentage were as follows in those on hemodialysis: insomnia (69); OSAS (24); RLS-PLMS (18); nightmares (13); EDS (12); sleepwalking (2); possible RBD (2); and possible narcolepsy (1.4). The figures in the CKD patients not on dialysis were as follows: insomnia (54); RLS (19); PLMS (12); OSAS (16); nightmares (15); EDS (1); sleepwalking (4); possible RBD (3); and possible narcolepsy (1). The authors concluded that sleep dysfunction is common in all kidney disease patients, and treatment of anemia, hyperphosphatemia, and hypoalbuminemia may improve their sleep problems.

In a prospective longitudinal study of 154 consecutive patients with CRF (78 completed the follow-up), Sabbatini et al. [575] determined sleep quality based on the Pittsburgh Sleep Quality Index (PSQI), and the data suggested that the progression of renal disease is accompanied by a progressive worsening of sleep quality. The data showed no correlation with creatinine clearance or with other indices of renal failure, but showed a correlation with age, which served as a

confounding variable. Four patients had high PSQI score at baseline and had further deteriorated at 3-year follow-up.

There are several factors which may contribute to the sleep problems in CRF patients [576]:

1. Disease-related factors (e.g., symptoms related to uremia, anemia, comorbid conditions, metabolic changes, and alterations in neurotransmitters)
2. Treatment-related factors (e.g., rapid changes in fluid, electrolyte, and acid-based balance; alterations in melatonin and thermoregulatory functions; medications; types of dialysis; alterations of cytokine metabolism in patients treated with hemodialysis causing abnormal somnolence [577] and proinflammatory cytokines (interleukin-1β), which might be associated with sleep complaints in hemodialysis patients [578])
3. Demographic factors (e.g., increasing age, male gender, and white race)
4. Psychological factors (e.g., anxiety and depression)
5. Lifestyle factors (e.g., increased intake of coffee, cigarette use, and poor sleep hygiene).

Sleep Apnea in Patients Receiving Dialysis

Sleep apnea is noted in up to 50 % of patients with renal failure [579]. Sleep apnea could be upper airway obstructive or central, but mainly an obstructive type of apnea is noted in most of the patients [577, 580–588]. This sleep apnea improves after nocturnal hemodialysis [488], which may be due to a decrease in chemosensitivity, suggesting also that, in some patients with kidney failure, increased chemoreflex responsiveness may contribute to the pathogenesis of sleep apnea. Beecroft et al. [589] studied 23 patients on hemodialysis and found decreased hypercapnic ventilatory response in sleep apnea patients who showed a significant reduction of the AHI after conversion from conventional to nocturnal hemodialysis. The authors suggested that increased chemosensitivity, by destabilizing respiratory control during sleep, may be responsible for both obstructive [590] and central sleep apnea [79, 591, 592]. An important study from the Sleep Heart Health Study identified an association between conventional hemodialysis and severe sleep apnea with nocturnal hypoxemia [593]. It should be noted that the prevalence of sleep apnea is similar in patients before and after receiving peritoneal dialysis or hemodialysis [594–596]. Although sleep problems may not be as common among transplantation patients as those on dialysis, the problems are still higher than in the general population [572, 573]. There are case reports indicating resolution of sleep apnea after renal transplantation [597]; however, many patients do not improve [584, 586, 598].

The following are the suggested mechanisms for the pathogenesis of sleep apnea in CRF:

- Upper airway edema causing partial airway obstruction coupled with decreased muscle tone during sleep [583].
- CNS depression during sleep resulting from so-called uremic toxins causing excessive reduction of upper airway muscle tone [583] (persistence of sleep apnea after dialysis speaks against this suggestion).
- Disturbance of the ventilatory control of breathing in renal failure and hemodialysis [577, 589, 597] making the respiratory control unstable, causing an imbalance between diaphragmatic and upper airway muscles. Beecroft et al. [599] reported an increased ventilatory sensitivity to hypercapnia in CRF patients with sleep apnea, suggesting an increase in respiratory control system "loop gain," which destabilizes central respiratory control and contributes to upper airway occlusion. Beecroft et al. [589] suggested that decreased chemoreflex sensitivity after conversion from conventional hemodialysis to nocturnal hemodialysis corrected sleep apnea by decreasing respiratory control system "loop gain," thus stabilizing the control of ventilation.
- CCF, which may occur in association with CRF, itself causing sleep apnea.
- Anatomic narrowing of the upper airway [600]. The same investigators also noted that there was an increase in pharyngeal size following conversion from conventional hemodialysis to nocturnal hemodialysis in those patients who previously had decreased pharyngeal cross-sectional area [601].
- Hypertension associated with CRF.
- Metabolic derangement associated with uremia. Soreide et al. [602] reported that an infusion of branched-chain amino acids stimulated nocturnal respiration and resulted in a decreased number of obstructive apneas.

Restless Legs Syndrome in Chronic Renal Failure Patients

There is an increased prevalence of RLS (20–50 % and even higher in patients with ESRD on dialysis [603–617]). Uremic RLS and idiopathic RLS resemble each other and cannot be distinguished clinically [609]. There are no specific biochemical risk factors identified with RLS associated with CKD except for low iron status as a predictor of poor outcome. Serum ferritin less than 70 μg/ml is the best cutoff for identifying possible iron deficiency which is the strongest predictor of RLS in CKD in older hospitalized patients [618]. Reports of disappearance or improvement of RLS symptoms after kidney transplantation suggest that some unknown biochemical or other factors are causing RLS symptoms in ESRD [606, 607]. Winkelmann et al. [607] investigated clinically the long-term course of 11 of 64 hemodialysis patients who underwent kidney transplantation. In all patients, RLS symptoms disappeared within 1–21 days after transplantation, and at follow-up visits up to

9 years, four patients remained free of RLS symptoms. In three other patients, RLS symptoms gradually reappeared. In 3 of 11 patients, transplantation failed and RLS symptoms reoccurred within 10 days to 2 months. In one patient, RLS symptoms reoccurred with transplant failure but disappeared after a second successful transplant. The authors concluded that kidney transplantation has a positive effect on RLS symptoms in hemodialysis patients. In an important cross-sectional study, Molnar et al. [606] assessed the prevalence of RLS in 992 kidney-transplanted patients using an RLS questionnaire. They found a prevalence rate of RLS of 4.8 % and concluded that the prevalence is significantly lower in kidney-transplanted patients than in patients with maintenance dialysis. The increasing prevalence of RLS in their series is associated with declining renal function and iron deficiency. In a preliminary study, Benz et al. [619] treated 10 hemodialysis patients having sleep complaints with recombinant human erythropoietin; in 9 of 10 patients, this therapy corrected the anemia and improved sleep quality. There is one report of MEIS1 and BTBD9 genetic association with RLS in ESRD [620]. Patients with ESRD and RLS showed an increased likelihood of cardiovascular and cerebrovascular events and mortality [621]. But a later report contradicted these findings [622].

Fibromyalgia Syndrome, Rheumatoid Arthritis, and Other Rheumatologic Disorders

All of these conditions are associated with chronic pain, and hence, some knowledge of human pain pathways is essential for understanding the pathophysiology of these disorders [623]. Pain pathways include afferent (ascending) fibers, central pain processing regions, and descending (efferent) fibers modulating these pathways. According to the current consensus, there are two central ascending pain pathways: a lateral sensory discriminative pathway and a medial affective pathway [624]. Impulses from peripheral pain-sensitive receptors are transmitted via thinly myelinated A delta and unmyelinated C fibers to the lateral pain pathway originating in the dorsal horn of the spinal cord in the region of zone of Lissauer, from where the fibers cross within one-to-three spinal segments to the contralateral spinothalamic tracts. The sensory afferent neurons in the spinothalamic tracts terminate in the ventral posterolateral nucleus of the thalamus. The third-order neurons from the thalamus terminate in the somesthetic cortex (SI and SII) for pain perception, discrimination, and central processing. Fibers also project directly both from thalamus and from SII to anterior insular cortex (the cortical pain center) [624]. The medical polysynaptic pain pathway includes spinoreticular and trigeminoreticular tracts projecting to the brain-stem reticular formation and then to the contralateral medial dorsal thalamic nucleus with upward projection to the anterior cingulate cortex which is responsible for the affective component of pain [624–629]. The other emotional pain pathway includes spinomesencephalic fibers to midbrain reticular formation with onward projection to the amygdala which is primarily responsible for the sense of fear [624]. Sensory descending pathways originating from the periaqueductal gray region, locus ceruleus, and hypothalamus [624, 630, 631, 632] modulate pain perception [633, 634]. These anatomic pathways are influenced by several neurotransmitters and neuromodulators [635–638] (e.g., noradrenalin, serotonin, and dopamine) as well as neuropeptides and their receptors. Dysregulation of ascending and descending pathways and alteration of central sensitization may be responsible for chronic pain in articular and nonarticular painful syndromes. Electrophysiologic [639–641] and functional neuroimaging [642–646], as well as SPECT and positron emission tomography (PET) [647, 648], studies have lent support to these hypotheses. This section briefly reviews sleep disturbances in FMS; rheumatoid arthritis (RA), including juvenile rheumatoid arthritis; osteoarthritis; and miscellaneous other painful conditions (e.g., ankylosing spondylitis, systemic lupus erythematosus, Sjögren's syndrome, and scleroderma) causing sleep disturbances.

Fibromyalgia Syndrome

FMS is a common but poorly understood syndrome characterized by chronic diffuse soft tissue pain and tenderness accompanied by a variety of somatic symptoms, including sleep dysfunction, in the absence of any structural lesion and without a single laboratory diagnostic test [649]. The condition has a prevalence rate of 1.3–4.7 % in the general population, with a female-to-male ratio of about 9:1, and onset typically occurs in the middle-aged and older women [650, 651]. The most common symptoms included morning stiffness, fatigue, nonrestorative sleep, pain, low back pain, impaired concentration, and memory "fog." Yunus et al. [652] originally listed specific diagnostic criteria for FMS, and this was followed by a description by Goldenberg [653] of an emerging but controversial condition. The American College of Rheumatology (ACR) in 1990 published the formal diagnostic criteria for FMS [654]. According to these criteria, the diagnosis is based on the presence of widespread diffuse pain affecting both upper and lower extremities lasting for at least 3 months and present in a symmetric fashion accompanied by 11 of 18 "tender points" when applying pressure of about 4 kg/cm^2 by digital palpation using the thumb or two fingers. The original ACR criteria are superseded by the 2010 ACR preliminary diagnostic criteria for FMS in which there was more emphasis on patient's symptoms [655] (Table 47.4). These criteria were later modified based on a self-report questionnaire (Fibromyalgia survey questionnaire [FSQ]) for improved specificity and sensitivity

Table 47.4 Diagnostic criteria for fibromyalgia

• Widespread diffuse pain lasting for at least 3 months
• Tender points in at least 11 of 18 anatomically defined sites (9 pairs of tender spots as listed below) after applying digital pressure of approximately 4 kg of force
– Second rib at the costochondral junctions
– Lateral epicondyle 2-cm distal to the epicondyle
– Suboccipital region
– Midpoint of the upper border of the trapezius
– Low cervical region
– Supraspinatus above the medial border of the scapular spine
– Gluteal region
– Greater trochanteric region posteriorly
– Medial fat pad at the knee joint proximal to the joint line

[656]. Based on a cutoff score ≥ 12, the modified ACR criteria had a sensitivity of 90.2 % and a specificity of 89.5 %; however, the modified ACR 2010 criteria questionnaire had a sensitivity of 97.4 % and a specificity of 85.2 %. Using a score of ≥ 13, the sensitivity was 93.1 % but the specificity increased to 91.7 %. The pathophysiology of the condition remains undetermined. However, based on the evidence that patients with fibromyalgia have dysfunctional pain processing in the CNS and perceive pain differently from the general population (see electrophysiologic, functional neuroimaging, SPECT, and PET studies cited above), suggested mechanisms included central sensitization, alterations in neurotransmitters, blunting of inhibitory pain pathways, genetic factors, neuroinflammation including viral infections, psychological stress, physical trauma, oxidative stress, and associated psychiatric comorbid conditions [623, 657]. A positive family history of fibromyalgia is found in some studies, and this is supported by the findings of a specific polymorphism in the 5-hydroxytryptamine$_{2A}$ receptor gene [658, 659], the serotonin transporter gene [660], and catechol-0-methyltransferese (COMT) gene [661, 662] which may predispose these patients to have psychiatric symptoms. Finally, genome-wide linkage of FMS to chromosome 17p supports a genetic factor in FMS [663].

An important item in the differential diagnosis is polymyalgia rheumatica, which is also characterized by diffuse muscle aches and pains but is often associated with accelerated erythrocyte sedimentation rate and evidence of temporal arteritis. Other differential diagnostic considerations include chronic fatigue syndrome (see later) and other myofascial pain syndromes. Sleep disturbance is very common in FMS [657, 665–671]. The characteristic PSG finding is intermittent alpha activity during NREM sleep giving rise to the characteristic alpha-delta or alpha-NREM sleep pattern in the recording (Fig. 47.2). It should be noted that although alpha-delta sleep is seen in this condition, this variant is not specific for the syndrome. Alpha-NREM sleep has also been reported in other rheumatic disorders [672], febrile illness, post-viral fatigue syndrome [673], psychiatric patients [674], and even normal individuals [675]. Nonrestorative sleep associated with nonspecific PSG abnormalities of sleep fragmentation, increased awakenings, decreased sleep efficiency, and alpha-NREM sleep is the most prominent complaint in these patients [665, 666]. In two retrospective reviews of PSG records and medical charts, there is a high prevalence of sleep apnea and RLS in addition to the other sleep complaints noted previously [669, 670]. Gold et al. [676] reported that, following CPAP treatment in women with FMS and upper airway resistance syndrome, the patients obtained considerable relief from fatigue, pain, and gastrointestinal symptoms. The most prominent feature in all of these studies is the subjective perception of poor sleep, which is out of proportion to objective measures of sleep [665, 666, 677]. Another objective measurement of sleep is actigraphy, which gave inconsistent results in FMS [678–681]. In summary, patients with FMS have a high prevalence of sleep difficulty, with up to 99 % reporting poor sleep quality [665, 666, 682]. The most common sleep difficulties reported are EDS, fatigue, and insomnia [665, 666, 683]. The observation of disassociation of subjective sleep complaints with objective sleep measures is strengthened by a pilot study showing high levels of dysfunctional beliefs and attitudes about sleep and perceived stress associated with poor sleep quality in FMS patients [684].

Treatment of FMS remains unsatisfactory. Treatment options should include both pharmacologic and nonpharmacologic therapies [657, 666, 686–688]. The nonpharmacologic treatment should include an exercise program [689] (more recent studies [690, 691] did not find exercise programs in FMS to be beneficial) good sleep hygiene measures, education and reassurance, and cognitive behavioral therapy [692–695]. Pharmacologic treatment [657, 665–677, 696] found to be useful includes tricyclic antidepressants (e.g., amitriptyline), nonbenzodiazepine hypnotic drugs, selective serotonin reuptake inhibitors (e.g., fluoxetine),

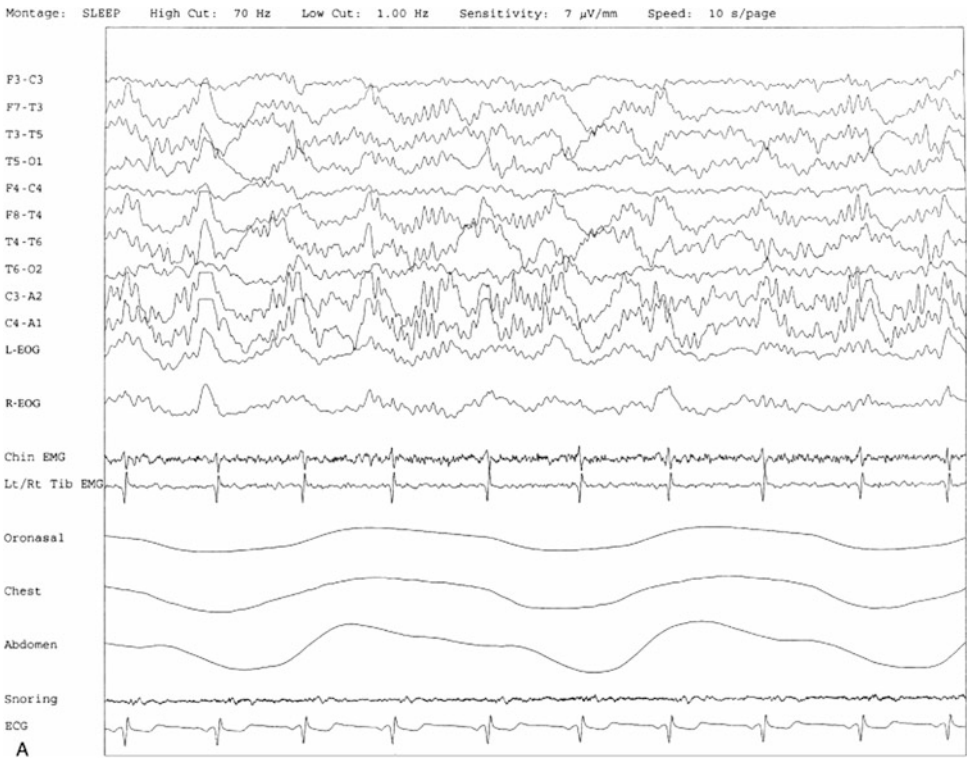

Fig. 47.2 Ten- (a) and 30 s (b) excerpts from a nocturnal PSG showing alpha-delta sleep in a 30-year-old man with history of snoring for many years. He denied any history of joint or muscle aches and pains. The alpha frequency is intermixed with and superimposed on underlying delta activity. Alpha-delta sleep denotes a nonspecific sleep architectural change noted in many patients with complaints of muscle aches and fibromyalgia. It is also seen in other conditions and in many normal individuals. (EEG, top 10 channels; Lt. and Rt. EOG, left and right electro-oculograms; chin EMG, EMG of chin; Lt./Rt. Tib. EMG, left/right tibialis anterior EMG; oronasal thermistor; chest and abdomen effort channels; snore monitor; EKG, electrocardiography) (From Ref. [685])

serotonin/norepinephrine reuptake inhibitors (e.g., venlafaxine, duloxetine, and milnacipran), gabapentin [657, 697], and pregabalin [698–700]. Pregabalin, a centrally acting drug used to treat neuropathic pain and adults with partial epilepsy, is the only drug approved by the Food and Drug Administration for treating and managing fibromyalgia. The recommended dose of pregabalin is 300–400 mg/day in two divided doses beginning with smaller doses of 75 mg twice a day and gradually increasing. Patients should also be treated for comorbid conditions (e.g., depression and sleep apnea). In a meta-analysis of five randomized placebo-controlled trials consisting of 2918 FMS patients (four with pregabalin and one with gabapentin), Hauser et al. [701] reported an improvement of sleep with reduction of pain in the patients. In a later Cochrane review, however, Moore et al. [702] reported that gabapentin 1200 mg or more per day reduced pain by 50 % in only 37 % of patients compared with 21 % on placebo.

Rheumatoid Arthritis and Other Rheumatologic Disorders

Arthritis, including rheumatoid and nonrheumatoid types, is the leading cause of disability in the USA, affecting approximately 70 million individuals. These conditions include RA (including juvenile RA), osteoarthritis, seronegative spondyloarthritis (e.g., ankylosing spondylitis, a reactive arthritis that was formerly known as Reiter's syndrome; and psoriatic arthritis, arthritis associated with ulcerative colitis, Crohn's disease, and Whipple's disease), systemic lupus erythematosis, Sjögen's syndrome, scleroderma, gouty arthritis, and polymyalgia rheumatica. Osteoarthritis is the most common type of arthritis, followed by RA. A systematic approach encompassing history, physical examination, and appropriate laboratory tests will help differentiate these conditions [703]. For appropriate diagnosis and differential diagnosis of these conditions, readers are referred to a standard text in internal medicine. Many of these patients suffer from sleep dysfunction, and in particular insomnia, fatigue, and depression; however, adequate scientific data correlating subjective with objective measures in a large number of such patients are lacking [683, 684].

In limited studies, sleep disturbances in osteoarthritis are commonly noted, consisting of sleep onset and maintenance insomnia (including early morning awakenings), correlating with the severity of joint pain, physical function, and

depression [686, 687]. Polysomnographic findings are not specific but correlate with sleep complaints, showing increased stage 1 sleep and repeated awakenings and arousals [688]. Sleep disturbances in adult RA patients consisting of difficulty in sleep onset and maintenance and fragmentation of sleep associated with EDS and fatigue are noted [689]. In a large percentage of patients [690], PSG studies show normal sleep architecture associated with alpha intrusions and increased PLMS [691, 692]. Studies generally show a positive correlation between sleep complaints and severity of the disease activity [694–696]. There is an increased prevalence of RLS in patients with RA [691, 697, 698]. There is also an increased prevalence of sleep apnea in these patients [691, 699, 700]. Similar sleep disturbances are also noted in juvenile RA [701, 702]. Similar sleep disturbances, particularly insomnia and daytime sleepiness, are also noted in systemic lupus erythematosis, Sjögren's syndrome, and seronegative spondylotic arthritis [411, 667, 703–728]. Comorbid upper airway OSA and PLMS are noted in systemic lupus erythematosis and ankylosing spondylitis. Gastroesophageal reflux, pulmonary fibrosis, and RLS are additional comorbid conditions disrupting sleep in scleroderma patients. Treatment of these conditions includes treatment of the primary diseases and associated sleep dysfunction following the general lines of management for insomnia, hypersomnia, and sleep apnea. Currently, there are no adequate studies describing the prevalence of and appropriate guidelines for treating sleep disturbances in these conditions.

Hematologic Disorders

The hematologic disorders that may cause sleep disturbance or be adversely affected by sleep include paroxysmal nocturnal hemoglobinuria (PNH), sickle cell anemia, hereditary hemorrhagic telangiectasia, and iron-deficiency anemia. Hansen [729] noted increased levels of plasma hemoglobin in five of seven patients with PNH, and the maximum values were found at midnight or at 4:00 AM. However, the author did not record EEGs or electro-oculograms to document any relationship with different sleep stages. Sleep impairment in the form of reduced total sleep time and REM sleep percentage and increased number of awakenings and sleep stage shifts is noted in patients with clinically stable sickle cell anemia, and these findings are probably due to hemoglobin desaturation [730, 731]. OSA and sleep disturbances resulting from reduced Sao_2 can occur in patients with sickle cell anemias and the prevalence of OSA in SCD is higher than in the general pediatric population [732]; when these diagnoses are suspected, overnight PSG recording should be obtained to confirm the diagnosis so that appropriate treatment with CPAP titration can be instituted [733]. Progressive somnolence accompanied by confusion has been described in a patient with hereditary hemorrhagic telangiectasia [734]. Iron-deficiency anemia in infancy is reported to be associated with altered temporal organization of sleep states and stages in childhood [735, 736]. Sleep alterations may persist for years after correction of anemia with iron treatment [736]. Furthermore, iron-deficiency anemia with low ferritin level may be combined with RLS. Zilberman et al. [728, 737] reported an improvement of anemia in congestive heart failure following administration of erythropoietin and intravenous iron, along with an improvement of sleep-related breathing disorder and daytime sleepiness. Finally, sleep deprivation in healthy individuals may cause a hypercoagulable state as evidenced by increased levels of prothrombotic hemostasis factors, which are risk factors for cerebrovascular and cardiovascular diseases [738, 739].

Dermatologic Disorders

Dermatologic disorders may cause sleep disruption because of pruritus and painful skin diseases [740, 741]. Patients may have sleep initiation and maintenance insomnia. In many dermatologic disorders, patients may have recurrent episodes of pruritus, which is most frequently noted during stages 1 and 2 NREM and least frequently noted in SWS; the intensity of symptoms is intermediate in REM sleep [741]. Patel et al. [740] reviewed the question of the high prevalence of nocturnal pruritus in many systemic and dermatologic diseases, causing sleep disturbance and diminished quality of life. Singareddy et al. [742] reported skin picking or pathologic excoriation in nearly 2 % of patients attending the dermatologic clinic in a mid-Western region of the USA. They found a significant correlation between skin picking and poor sleep as well as high anxiety. Nocturnal scratching may occasionally present as a parasomnia not associated with dermatological disorders [743, 744]. Mouzas et al. [745] reported a significantly higher occurrence of sleepwalking, sleep terrors, nightmares, and nocturnal enuresis in 116 patients suffering from vitiligo compared with 52 patients with other dermatologic diseases and 48 healthy controls.

Atopic dermatitis (AD), a common skin disorder beginning in infancy, may also cause disturbance of sleep in children because of nocturnal itching and scratching [746–748]. This can be documented by questionnaire and actigraphic recording [747]. There is a report of patients with OSA especially male younger patients with an increased risk for AD later in life [749]. Lichen simplex chronicus is another common pruritic disorder in which nighttime pruritus is a common feature disturbing sleep. This was documented by overnight PSG

study and the Epworth Sleepiness Scale in 15 patients with lichen simplex chronicus and 15 age-matched controls [750]. Polysomnographic findings in patients demonstrated increased arousals and awakenings associated with scratching bouts during sleep. PSG study and parental report of sleep quality (sleep disturbance scale of children) in 21 children with eczema and 20 healthy controls (ages 6-16 years) documented worse sleep quality on both PSG (increased nocturnal awakening and stage shifts) and parental report in addition to significant neurocognitive deficits [751].

Miscellaneous Disorders

Acquired Immunodeficiency Syndrome

Acquired immunodeficiency syndrome (AIDS) is a multisystem disorder caused by infection with human immunodeficiency virus (HIV). Its manifestations are protean. Neurologic manifestations include both CNS and peripheral neuromuscular dysfunction. Encephalitis, due to either opportunistic infection or direct invasion by the virus, may cause a variety of disorders such as memory impairment, seizures, and pyramidal or extrapyramidal manifestations. Some patients have sleep disturbances, but adequate studies utilizing PSG recordings and validated sleep scales have not been performed in a large number of these patients.

Norman et al. [752–754] found alterations in sleep architecture in groups of asymptomatic HIV-positive men that progressed as the disease became symptomatic in 17 of the initial group of patients followed for 19–63 months. Several other authors [755–758] also reported sleep architectural abnormalities after PSG recordings in asymptomatic HIV-positive patients. Darko et al. [757, 758] also suggested that there is evidence to support a role for the somnogenic immune peptides tumor necrosis factor-α and interleukin-1β in the sleep changes and fatigue commonly seen in HIV infection. These authors [757] stated that these peptides were elevated in the blood of HIV-infected individuals and are somnogenic in clinical use and animal models.

A more recent study utilizing the PSQI and the Medical Outcome Short-Form Health Survey in a sample of 144 HIV-infected African American women recruited from 12 health clinics and AIDS service organizations in three southern states in the USA showed a high prevalence of poor sleep quality associated with an impairment of health-related quality-of-life index in these patients [759]. Moyle et al. [760] also reported sleep disturbances and alterations of sleep architecture following initiation of efavirenz-containing triple antiretroviral therapy in HIV-positive individuals.

HIV infection can cause SDB. Epstein et al. [761] identified three HIV patients with OSA due to adenotonsillar hypertrophy. They also surveyed 134 patients with asymptomatic HIV disease with a self-administered questionnaire designed to detect OSA and EDS. Those patients whose responses suggested possible OSA were studied by overnight PSG recording. Twelve HIV-positive patients with OSA were identified. The consistent risk factor in this young and non-obese population was the presence of adenotonsillar hypertrophy, which was found in 11 of 12 patients with OSA. In a previous paper, these authors [762] reported the first cases of severe OSA in HIV-infected men. Garrigo et al. [763] obtained PSG recording in asymptomatic HIV-positive men and reported an elevated apnea index in 7 of 24 patients who did not have symptoms related to SDB. In a more recent retrospective review of the medical records of consecutively identified HIV-infected subjects, there was a high prevalence of SDB on PSG recordings. The authors suggested that clinicians caring for HIV patients should inquire about risk factors for OSA because overnight PSG study can aid the diagnosis of sleep disturbances in such patients [764]. This is important for treatment and improvement of quality of life.

Whether PSG can document significant and specific abnormalities in asymptomatic individuals or warn of the development of encephalopathy remains to be determined. A systematic study of a large number of cases needs to be done to answer these questions.

There are several recent reports documenting sleep dysfunction and the factors responsible for this in HIV/AIDS patients [765–769]. A recent meta-analysis [770] covering 9246 HIV-positive subjects documented a prevalence of 58 %. Sleep problems may have potential impact on antiretroviral therapy outcome.

Lyme Disease

Lyme disease [771–778] is a multisystem disease caused by the spirochete *Borrelia burgdorferi* and transmitted to humans by tick bite. The clinical manifestations may be divided into three stages:

1. Initially, there is a characteristic skin lesion, erythema migrans, which is followed in the course of time by a febrile illness (acute stage or stage I).
2. In the subacute stage or stage II, which occurs in several weeks to months after the onset of the illness, approximately 12–15 % of patients may develop neurologic manifestations and approximately 4–10 % may have cardiac involvement (conduction disturbance or cardiomyopathy) [771, 776]. Neurologic manifestations may present as axonal polyneuropathy, radiculoneuropathy, cranial neuropathy (particularly affecting the facial nerve), lymphocytic meningitis, encephalitis, or encephalopathy. Encephalitis is rare. Patients with CNS manifestations may have sleep disturbances.
3. In the chronic stage or stage III, which occurs weeks to as long as 2 years after the onset of illness, approximately 60 % of patients develop arthritis [771, 776].

Sleep complaints are common in Lyme disease [771], but no large-scale study using PSG is available to characterize the sleep disturbances in this condition. Greenberg et al. [779] obtained 2 nights of PSG in 11 patients meeting Centers for Disease Control and Prevention (CDC) criteria for late Lyme disease with serologic confirmation and 10 age-matched controls. In addition, the authors performed the Multiple Sleep Latency Test (MSLT) in the Lyme disease patients. All patients had complaints of difficulty initiating sleep, frequent nocturnal awakenings, and EDS; a small percentage had restless legs or nocturnal leg jerking. Polysomnographic findings included decreased sleep efficiency, increased arousal index with sleep fragmentation, and alpha intrusion into NREM sleep. These authors concluded that these sleep abnormalities may have contributed to the sleep complaints and fatigue that are commonly present in this disease.

Because Lyme disease is treatable, every attempt should be made to diagnose it accurately. Diagnosis depends on the serologic detection of antibodies against *B. burgdorferi* in the serum (or, in the case of CNS infection, in cerebrospinal fluid samples) [777]. The usual method of testing is the enzyme-linked immunosorbent assay [777], but antibodies usually are not detectable until 4–6 weeks after the initial infection. Diagnosis may be complicated by false-positive results and lack of a standardized technique to assay for antibodies. Polymerase chain reaction has been shown to be useful in demonstrating *B. burgdorferi* DNA in clinical material [777]. Recently developed serodiagnostic tools, such as the C6 assay, and appropriate use of Western blotting show considerable promise in improving the diagnostic accuracy [780].

In most patients, oral antibiotics are efficient, but in severe cases, 2- to 4-week parenteral therapy is needed. Practice parameters are available for treatment of nervous system Lyme disease developed by the American Academy of Neurology and Clinical Infectious Diseases Society of America [775, 781]. The most effective oral antibiotics include amoxicillin 500 mg three times a day, doxycycline 100 mg twice a day, and cefuroxime 500 mg twice a day given for 2–3 weeks. Treatment of more than 4 weeks' duration is not needed and carries substantial risk but minimal benefit [773, 782, 783].

Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is a complex, ill-defined heterogeneous debilitating condition. Patients complain of profound fatigue, functioning below their usual level of energy, that is not improved by bed rest. CFS affects 836,000 to 2.5 million in the USA and is more common in women than men. The diagnostic criteria for CFS were established from a consensus among international experts [784]. Diagnosis of CFS depends on the patient's history and the information obtained by physical examination as well as exclusion of other causes of the fatigue after extensive laboratory investigations. There is controversy in this case definition as the condition overlaps with many other disorders and because it is based on a consensus of experts without availability of any laboratory diagnostic test [785]. The concept of CFS has evolved over the years and has been modified since the original diagnostic criteria [784] were established. In view of the evidence in later research of widespread inflammation and multisystem involvement, the term myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) [786] was thought to be appropriate to call this condition. The proposed new evidence-based diagnostic criteria by the Institute of Medicine (IOM) [664] focused on the central symptoms and one of two additional symptoms (Table 47.5). These symptoms should persist for at least six months at a moderate, substantial, or severe intensity at least half of the time. The IOM committee [664] noted that evidence of other manifestations of ME/CFS seen less frequently but these may support the diagnosis (Table 47.6). ME/CFS is thus a chronic multisystem debilitation condition manifested by chronic disability fatigue, post-exertional malaise and unrefreshing sleep associated with cognitive impairment or orthostatic intolerance [664, 787]. There are no diagnostic laboratory tests but all three national agencies [IOM, Agency for Healthcare Research and Quality (AHRQ) and National Institute of Health (NIH)] concluded that there are biological abnormalities [788]. A Positron Emission Tomographic (PET) scan showed evidence of neuroinflammation (activated microglia or astrocytes) [789], functional magnetic resonance imaging (fMRI) studies documented distinctive abnormalities when challenged with working memory tasks, and the NIH report gave evidence of neurotransmitter signaling disruption [788, 789]. There is, however, no conclusive evidence of any biomarker sensitive or specific enough to serve as a diagnostic test [788]. The cause and pathogenesis remain uncertain. Viral causes have been incriminated but no specific virus or other infectious agent has been indentified [787, 790]. There has been a suggestion of an external agent triggering an immune response leading to immune and neuroendocrine dysregulation [790, 791].

The clinical course of CFS follows a randomly cyclical pattern, and studies conducted by the CDC [792, 793] have found that 40–60 % of the people with CFS report partial or total recovery, particularly those who have received early treatment. Certain comorbid conditions with CFS include IBS, fibromyalgia, depression, Gulf War syndrome, and interstitial cystitis. There is some suggestion of increased familial aggregation of CFS because of increased concordance rates in monozygotic compared with dizygotic twins [794]. Several patients with CFS had orthostatic hypotension on tilt-table study, which was thought to be responsible for some of the

Table 47.5 Proposed IOM diagnostic criteria for ME/CFS [664]

Diagnosis requires for the patient to have the following three symptoms (core symptoms)
1. A substantial reduction or impairment in the ability to engage in preillness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
2. Post-exertional malaise, and
3. Unrefreshing sleep
At least one of the two following manifestations is also required
1. Cognitive impairment
2. Orthostatic intolerance

Table 47.6 Additional symptoms of ME/CFS

• Pain which is variable and may manifest as myalgia, arthralgia, or headache
• Evidence of immune dysfunction
• Evidence of infection
• Gastrointestinal or genitourinary symptoms
• Sore throat
• Painful or tender cervical or axillary lymph nodes
• Sensitivity to food, drugs, or other chemical agents

symptoms [795]. It is notable that orthostatic intolerance is listed as one of the five symptoms in the proposed IOM diagnostic criteria [664] (see Table 47.5).

Sleep disturbances (e.g., disturbed unrefreshing and poor quality of nighttime sleep, insomnia, and EDS) are very common in ME/CFS patients, but in many cases these have not been adequately characterized by PSG studies. PSG abnormalities have been found in a few studies [796–801]. Fischler et al. [796], in a PSG study in 49 CFS patients and 20 healthy controls, found more sleep initiation and maintenance disturbances and a significantly lower percentage of stage 4 NREM sleep in the CFS patients than in the control group. However, they did not find any association between sleep disorders and the degree of functional impairment. Similarly, in a population-based study of CFS patients and nonfatigued controls from Wichita, Kansas, utilizing overnight PSG and MSLT tests, Reeves et al. [798] did not provide evidence that altered sleep architecture is a critical factor in CFS. Guilleminault et al. [799] reported that complaints of unrefreshing sleep and chronic fatigue were associated with an abnormal EEG cyclic alternating pattern and an increase in respiratory effort and nasal flow limitation, suggesting subtle undiagnosed SDB. Togo et al. [800] compared PSG findings and subjective scores for sleepiness and fatigue (visual analog scales) in 26 CFS patients (12 with and 14 without coexisting fibromyalgia) with 26 healthy subjects. Compared with controls, CFS patients had reduced total sleep duration and decreased sleep efficiency, which positively correlated with subjective sleepiness and fatigue. The authors suggested that this sleep disruption may explain the overwhelming fatigue and unrefreshing sleep. In conclusion, the entity of ME/CFS remains ill-defined and the treatment, at present, should be symptomatic, using both pharmacologic and nonpharmacological treatment. Nonpharmacologic treatment includes sleep hygiene measures and cognitive behavioral therapy (CBT). Symptomatic treatment for depression using appropriate antidepressants and nonsteroidal medications for pain is suggested. In a meta-analysis evaluating 35 treatment trials, the benefits of therapy remain inconclusive [787]. Limited evidence was seen with the immune modulator, rintatolimod along with counseling behavior therapies and graded exercise therapy (GET) in some patients with ME/CFS [802]. However, the ME Association [803] came out with a report contradicting some of the above conclusions. Their report showed no benefit from CBT and GET but Pacing courses (containing elements of CBT and "learning coping strategies" but not GET) have consistently shown to be the most effective, safe, acceptable, and preferred form of active management for ME/CFS.

Sleep of Intensive Care Unit Patients (Medical and Surgical)

Generally, patients are admitted to the medical ICU because of acute respiratory failure resulting from COPD, bronchial asthma, sleep apnea syndrome, restrictive lung disease, acute cardiovascular disorders (e.g., ischemic heart disease with or without myocardial infarction, cardiac arrhythmias, CCF),

acute neurologic disorders causing respiratory disturbances (e.g., brain-stem lesion, status epilepticus, high cervical cord lesions, neuromuscular disorders), renal failure, or gastroesophageal reflux causing acute respiratory tract symptoms. All of these conditions can be associated with sleep disturbances (insomnia, hypersomnia, and sleep-related respiratory dysrhythmia), which become intense in severely ill patients admitted to the ICU who require life-saving cardiorespiratory support [804–821].

Sleep disruption is very common in ICU patients; a figure of more than 50 % incidence has been quoted [811]. The causes of the sleep disruption include a variety of factors: (1) the ICU environment; (2) comorbid medical or surgical illnesses; (3) effects of many medications used to treat these critically ill patients; (4) individual factors, e.g., anxiety, psychological stress, pain resulting from the surgical procedures, and therapeutic interventions (e.g., use of ventilators, noise generated by the monitors) [804–821]. The ICU environment itself is deleterious to normal sleep and conducive to sleep deprivation with its attendant complications, such as ICU psychosis. In addition to sleep deprivation, physiologic and physical factors contribute to ICU psychosis. Noise, bright light, and constant activity on the part of the ICU personnel for monitoring and drug administration play significant roles in disturbing the sleep of ICU patients.

The ICU syndrome or ICU psychosis describes a cluster of psychiatric symptoms and is a characteristic mental state defined as a reversible confusional state developing 3–7 days after ICU admission secondary to sleep deprivation [812–814, 817, 821]. ICU psychosis is more common in surgical than in medical ICUs, and the prevalence has been estimated to be between 12.5 % and 38.0 % of patients admitted to the ICU [812–814]. Sleep deprivation has been cited as the major cause of the ICU syndrome [795, 822]. In a study by Helton et al. [812], 10 % of patients with moderate sleep deprivation and 33 % with severe sleep deprivation developed the ICU syndrome. There is evidence to suggest that the ICU syndrome is similar to delirium [785]. The question remains whether sleep deprivation is the cause of the delirium [823, 824]. There is evidence that higher morbidity and mortality increases the length of stay and cognitive impairment associated with ICU delirium [825, 826].

An important cause of sleep disruption in the ICU is noise [810, 811, 816, 817, 827–832]. Technological advances in the ICU setting (e.g., monitors and meters, ventilator alarms, television, phones, and beepers) have been cited as the major culprits for contributing to ICU noise and sleep disruption. The role of the noise in contributing to sleep disruption has been documented objectively by continuous sleep monitoring and recording of the environmental peak sound levels [831, 833].

In the surgical ICU, patients are usually admitted in the postoperative period because they are recovering from anesthesia, are beginning to suffer from pain, are experiencing metabolic disturbances, or have an infection related to surgical care. All these factors may cause severe disturbance of sleep and breathing.

Another condition noted in many patients admitted to the ICU is REM sleep behavior disorder. Schenck and Mahowald [834] evaluated over 200 adults with injurious, sleep-related behaviors during 8 years of clinical practice, and 20 of these had ICU admissions. Polysomnography with audio–video recordings documented REM sleep behavior disorder in 17 of these 20 patients.

Several authors have studied ICU patients using PSG to document disruption of sleep structure [827, 835–841]. These disturbances consist of marked diminution of SWS and REM sleep, frequent awakenings, sleep fragmentation, and reduced total night sleep time. The total sleep over a 24-h period appears to remain normal. Because of night sleep disturbances, ICU patients often have EDS [835, 837]. PSG recording in ICU patients has been a challenge. For one thing sleep of ICU patients is severely fragmented, especially those on mechanical ventilators [821, 835], and distributed in short segments throughout 24 h without any consolidated period of sleep containing atypical sleep prompting new scoring guidelines for ICU patients [840, 841].

Some studies have suggested that an impairment of the melatonin rhythm may play a role in explaining sleep disturbances and delirium in ICU patients [818, 819, 840–842]. The questions of ultimate outcome and functional status of patients in the ICU and the impact of improving poor sleep in ICU patients are not clearly known, and further research is needed in this direction [843]. It is stated that, overall, physical recovery is more complete than psychosocial recovery [844]. There have been reports of post-traumatic stress disorder following ICU admission for critical illnesses [845]. Roberts et al. [846] reported experiencing vivid dreams, hallucinations, or delusions associated with a longer ICU stay among 41 participants in three ICUs 24 months of post-discharge. The authors suggested that, because these dreams are disturbing, the patients should have information and counseling about delirium, particularly for those who remain in ICU for longer periods. Another factor known to play a role for sleep disturbance in ICU patients is sepsis which accounts for about 20–40 % of admissions to a medical ICU [817, 847]. Septic encephalopathy may show a characteristic EEG pattern (low-voltage mixed frequency

theta-delta waves) which has been reported to appear before the clinical manifestations of sepsis [827] along with reduced REM sleep and loss of circadian melatonin rhythm [817].

Treatment

The physicians and paramedical personnel who take care of ICU patients must be aware of the various ICU factors contributing to the problem of sleep disturbances, so that correct diagnosis and management of secondary complications (in addition to treatment of the primary disorders) can be effected promptly. The treatment for sleep disturbance in the ICU environment consists of nonpharmacologic and pharmacologic intervention. Nonpharmacologic treatment includes measures to decrease or eliminate many of the factors (noise, light, and others as described previously) causing sleep deprivation in ICU patients. Other nonpharmacologic measures include sleep hygiene rules, cognitive behavioral therapy, counseling the patients after discharge from the ICU, and adjusting ventilator settings to prevent dys-synchronous breathing and central apneas in those using mechanical ventilation [804, 817, 848]. Clinical practice guidelines to improve sleep in critically ill adults have been suggested [849]. These guidelines suggest an integrative approach to improve sleep in these patients, combining pharmacologic and nonpharmacologic measures. The suggested pharmacologic measures include hypnotics and benzodiazepine drugs (short and intermediate acting, such as alprazolam, lorazepam, and temazepam). These drugs should be used with caution because of adverse effects. Nonbenzodiazepine receptor agonists (e.g., zolpidem, eszopiclone, and ramelteon) are preferable to benzodiazepine drugs because of the lesser side effect profiles. The newer antipsychotic drugs (e.g., olanzapine, risperidone, and quetiapine) may be useful to treat delirium, but adequate studies have not been undertaken yet. Opiates and NSAIDs should be used for pain. In a report using a small sample size, significant improvement in postoperative delirium after surgery for esophageal cancer was noted following bright light therapy [850]. There is currently no standardized protocol to improve sleep of ICU patients [817]. Kamdar et al. [851] recently suggested controlling noise and light and increasing daytime activities.

In addition to treating the primary disorder, it is important to treat secondary sleep-related respiratory problems. If a sleep disturbance persists after the patient leaves the ICU, a primary sleep disorder may be suspected and appropriate investigations, such as PSG study and MSLT, should be performed.

African Sleeping Sickness (Trypanosomiasis)

African sleeping sickness is caused by *Trypanosoma gambiense* or *Trypanosoma rhodesiense* and is transmitted to humans by the bite of tsetse flies. The clinical features are characterized by lymphadenopathy, fever, and later (after several months or years) excessive sleepiness due to encephalopathy or encephalitis. In stage 1 of the disease, the parasites proliferate in the hemolymphatic system (hemolymphatic stage). In stage 2, the parasites invade the central nervous system, causing progressive neurologic dysfunction with disruption of sleep–wake patterns (meningoencephalitic stage) [824–856]. The clinical manifestations in the type caused by *T. rhodesiense* (Rhodesian sleeping sickness) are more rapidly progressive, resulting in cardiac failure and acute neurologic manifestations [853, 855]. Gambian sleeping sickness, caused by *T. gambiense,* is a more chronic illness with predominant neurologic manifestations [852]. Within 6 months to several years after the onset of the first symptoms, the Gambian type progresses into a late meningoencephalitic stage. CNS involvement is initially characterized by personality changes followed by delusions, hallucinations, and reversal of sleep–wake rhythm [852, 856]. The patient remains somnolent in the daytime and progresses gradually into the stage of stupor and coma. The cerebrospinal fluid examination shows increased cells and protein.

Several PSG studies lasting for at least 24 h and correlating with several plasma hormone levels have been conducted in patients with human African trypanosomiasis [854–865]. These studies documented disruption of the circadian sleep–wake rhythm, which is proportional to the severity of the illness. In less severely affected patients, the relationship between hormonal pulses (cortisol, prolactin, and plasma renin activity) and specific sleep stages persists. Sleep–wake rhythms are severely disturbed consisting mainly of circadian disruption and occurrence of sleep bouts lasting for 80–90 min throughout 24 h [856]. In addition, sleep-onset REM periods (SOREMP) are noted during many of these episodes which have been proposed to be a diagnostic marker and Buguet et al. [857] confirmed the usefulness of SOREMP in a five-year study of patients in Congo, particularly for diagnosing relapses following treatment. Circadian disruption of plasma cortisol, prolactin, and sleep–wake rhythms is noted in the most advanced patients, but not in patients with less severe illness [861–864]. These findings of circadian disruption suggest selective changes in the suprachiasmatic nucleus (SCN), resulting in circadian rhythm changes in the advanced stage of the illness. The association between SWS and GH secretion persisted in the patients, even in the presence of disrupted circadian rhythms [859]. In one study, circadian periodicity of the sleep–wake cycle was disturbed proportional to the severity of the illness, but the patients' melatonin rhythm was similar to that in normal individuals, suggesting additional control for melatonin beside the SCN [860]. In three advanced patients, the cytokine interferon-γ levels were increased 7- to 12-fold [862]. In an experimental study, rats infected with the

parasite *Trypanosoma brucei brucei* showed selective changes in c-*fos* expression in the SCN, supporting the hypothesis that, in human trypanosomiasis, changes in the SCN are responsible for circadian rhythm dysregulation and changes in the sleep–wake pattern [862]. Lundkvist et al. [866] suggested that the parasites target circumventricular organs in the brain, causing inflammatory responses in hypothalamic structures that may lead to dysfunction of the circadian timing and sleep-regulatory systems in patients with African trypanosomisis.

The possible role of hypothalamic hypocretin was evaluated by measuring cerebrospinal fluid hypocretin 1 levels in 25 untreated patients with human African trypanosomisis [867]. The authors observed that the cerebrospinal fluid hypocretin 1 levels were significantly higher in these patients than in narcoleptic patients but lower than in neurologic controls. The authors observed undetectable hypocretin levels in only one stage 1 patient and intermediate levels in one stage 2 patient. These results do not suggest a unique implication of the hypocretin system in African sleeping sickness, but the authors proposed that a dysfunction of the hypothalamic hypocretin region may participate in sleeping disturbances observed in African trypanosomisis. The diagnosis of trypanosomiasis is based on history as well as confirmation that the organism is in the blood, bone marrow, cerebrospinal fluid, lymph node aspirates, or a scraping from the chancre [852, 856]. The treatment of choice for patients in the meningoencephalitic stage is arsenical melarsoprol [852, 853, 856, 868, 869]. It is divided to have follow-up of these patients every 6 months for 18 months after treatment to diagnose relapse [856]. Actigraphic recording in a pilot study of none of the patients with human African sleeping sickness documented sleep–wake alterations correlating with PSG findings [870]. In a follow-up study, actigraphy showed improvement of sleep dysfunction and could be used for monitoring progress and treatment [870]. Because of growing resistance to melarsoprol, the World Health Organization (WHO) recommended the nifurtimox–eflornithine combination therapy [856, 869, 871]. However, because of adverse effects, lack of adequate synergistic effects, and possible resistance [872], there is ongoing research evaluating two new molecules [873, 874].

Sleep and Cancer

Sleep disturbance, although very common in patients with cancer, has not been systematically studied adequately in such patients as this complaint has been overshadowed by other major problems related to cancer [875]. A prominent complaint in the patient is fatigue [876–878], which may be secondary to insomnia in many of these patients. It is important to differentiate primary fatigue from that secondary to insomnia. Given the opportunity for sleep (e.g., relaxing on a couch or lying in bed during the daytime), a patient whose primary complaint is fatigue will not be able to fall asleep and will not complain of heaviness or drooping of the eyelids or head nodding. These patients remain alert and do not doze off. In contrast, patients with secondary fatigue will doze off under these circumstances. The most common sleep complaints in cancer include sleep initiation or maintenance insomnia, nonrestorative sleep, and impaired daytime function as a result of nighttime sleep dysfunction. Almost two-thirds of cancer patients and survivors have sleep problems [878–884]. Savard and Morin [885] quoted a figure of 30–50 % of patients with insomnia in newly diagnosed or recently treated cancer patients. This figure is much higher in patients with metastasis associated with pain.

The cause of sleep disturbance in cancer patients is multifactorial [878, 882, 886], including severe anxiety and depression related to cancer, cancer chemotherapy (e.g., tamoxifen in breast cancer), corticosteroids given to such patients to alleviate the medication side effects, environmental factors (e.g., hospitalization for surgical intervention), severe pain in patients with bone metastasis or compression of nerves or nerve routes, and radiation therapy. In addition to insomnia [875, 884, 887], which is the most common sleep complaint in cancer patients, some patients may have upper airway OSA after head and neck surgery as a result of edema in the pharyngeal space and reduction of upper airway dilator muscle tone [878, 888]. Sleep dysfunction in cancer patients adds to the burden of impaired quality of life and may also cause EDS in many of these patients. Most of the studies have involved breast and lung cancer patients, but there are scattered reports in patients with cancers in other sites causing sleep disturbances [822, 878, 882, 887, 889].

It is important to diagnose sleep dysfunction in both early and advances stages of cancer to improve the quality of life. The important first step is a history obtained from patients and the caregivers. Laboratory tests are not needed in most of the patients [885], but if upper airway OSAS is suspected (e.g., if the patient complains of snoring and EDS and has witnessed apneas), an overnight PSG study is recommended so that this patient can be adequately treated to improve quality of life in advanced stages of cancer and to prevent long-term adverse consequences of OSAS in early stages of cancer with long-term good prognosis

The relationship between hypnotic medication use and cancer remains contentious. A few studies linked sleep

Table 47.7 Medications causing sleep–wake disorders

Drugs used to treat general medical disorders
• Analgesics, including opioids
• Antiemetics
• Antihistamines
• Cardiovascular medications, including angiotensin-converting enzyme inhibitors and β-blockers
• Bronchodilators
• Appetite suppressants
• Sleeping medications
Drugs used to treat psychiatric disorders
• Antidepressants (e.g., tri- and tetracyclics, MAO inhibitors, SSRIs, trazodone, nefazodone, bupropion, mirtazapine, venlafaxine, duloxetine, and lithium)
• Antipsychotic drugs (e.g., haloperidol, phenothiazines, thioridazine, clozapine, olanzapine, and quetiapine)
Drugs used to treat neurologic disorders
• Antiepileptic agents
• Antiparkinsonian medications
• Drugs used to treat RLS and narcolepsy-cataplexy
Miscellaneous agents (including drugs of abuse and alcohol)
• Amphetamines
• Cocaine
• Marijuana
• Methylenedioxymethamphetamine (MDMA; ecstasy)
• Lysergic acid diethylamide (LSD)
• Phencyclidine (PCP or "angel dust")
• Testosterone
Over-the-counter (OTC) medications
• Nasal Decongestants
• Appetite suppressants
• Caffeine
• Sleeping medications

MAO Monoamine oxidase; *SSRIs* Selective serotonin reuptake inhibitors

medication to an increased risk of cancer [890–892]. A case-control study from Finland [882] observed that sleep medication use (both the yearly dosage and the years of use of hypnotic medications) was associated with increased cancer risk of the respiratory system. These findings should be interpreted with caution as some confounding factors (e.g., smoking and BMI) could not be addressed in this study. Further research is needed to resolve the controversial relationship between cancer and hypnotic medications and the mechanism for such association.

Management of sleep disturbance in cancer patients will follow the same general principles of management of insomnia and sleep apnea as outlined in other chapters of this book. Adequate hypnotic therapy [878, 887], preferably with non-benzodiazepine GABA agonists, should be tried first; for insomnia associated with pain in advanced stages of cancer, stronger hypnotics, including opiates, should be liberally used. Pharmacotherapy should always be combined with nonpharmacologic treatment (e.g., sleep hygiene and cognitive behavioral measures). It is important for physicians to be perceptive of sleep disturbance in cancer patients as treatment will largely improve the quality of life. Another important point to remember is that the patient's caregiver or spouse may also need treatment for insomnia as that individual's sleep is also disturbed as a result of a combination of psychological factors and sleep deprivation [875, 878, 883, 885].

Medication-Related Sleep–Wake Disturbances

Medications causing sleep–wake disturbances can be divided into five groups [893–907] (Table 47.7): (1) drugs used to treat general medical disorders; (2) drugs used to treat psychiatric disorders; (3) drugs used to treat neurologic disorders; (4) miscellaneous agents (drugs of abuse and alcohol); and (5) over-the-counter (OTC) medications. The importance of chronobiology, chronophysiology, and chronopharmacology should be kept in mind when discussing medication effects because biological responses to medications may depend on the circadian timing of administration of the drugs (see also Chap. 2). Responses of antibiotics to bacteria or cancer cells to chemotherapy may depend on the time of administration because pharmacokinetic or pharmacodynamic interactions vary depending on time of day.

Drugs for General Medical Disorders

Antihistamines (histamine$_1$ blockers), used to treat allergies, cause EDS as proven by the MSLT. These agents, however, are not recommended as hypnotics because of inadequate knowledge about their safety and efficacy as well as their daytime sedation and anticholinergic effects.

Narcotics (e.g., morphine, codeine, and other opioids), which are used to relieve severe pain and to induce sleep, can cause CNS sedation and respiratory depression. Other analgesic medications such as anti-inflammatory and antipyretic agents (e.g., acetaminophen and aspirin) have not been adequately studied to understand their effects on sleep, but they may have a mild hypnotic effect. It is shown in healthy individuals that the narcotics may increase wake time and reduce the amount of REM sleep and SWS. Antiemetics (e.g., metoclopramide, domperidone, phenothiazines, and the anticholinergic scopolamine) may produce drowsiness as a common side effect. Scopolamine may increase stage 2 NREM but decrease total REM sleep. Domperidone has the least side effects.

Cardiovascular drugs include ACE inhibitors, β-blockers, and clonidine. ACE inhibitors, used to treat hypertension, may affect sleep adversely, causing impairment of performance and mood. The β-blockers (e.g., propranolol, metoprolol, and pindolol), which are used to treat hypertension, cardiac arrhythmias, and angina pectoris, may cause difficulty initiating and maintaining sleep with frequent nightmares. They may also cause insomnia by suppressing the production of melatonin. Clonidine, a centrally acting α-adrenergic receptor agonist used to treat hypertension, may disrupt the quality of sleep by inducing shift changes to stage 1 or wakefulness and by suppressing REM sleep. Clonidine, like the β-blockers, may increase daytime sleep and sleepiness.

Bronchodilators used to treat COPD and bronchial asthma may cause insomnia. Theophylline may cause sleep fragmentation and increased awakenings during sleep.

Anorectics or appetite suppressants may act as CNS stimulants by increasing catecholaminergic activity, causing insomnia.

Sleeping medications such as benzodiazepine and nonbenzodiazepine (e.g., zolpidem and eszopiclone) receptor agonists may have the opposite effect after prolonged use, and an abrupt withdrawal may disrupt sleep due to severe withdrawal effects. There is individual variation and susceptibility to the withdrawal effects. Transient disruption of sleep after cessation of hypnotic medication is common. All sleeping medications, particularly long-acting ones, may affect daytime functioning. The short-acting drugs may cause rebound insomnia, daytime anxiety, and amnesia. Although benzodiazepines affect cognition and memory, these drugs are relatively safe and have low risk of abuse, and the side effect profiles are predictable. All sleeping medications may have respiratory depressant effect, particularly in COPD patients, bronchial asthma, and OSA. Sleeping medications should be used cautiously in the elderly as these may easily induce side effects because of alterations of metabolism and drug absorption in the elderly. All benzodiazepine agonists improve sleep quality by reducing latency to persistent sleep onset, reducing WASO, and increasing sleep efficiency and total sleep time. Benzodiazepine drugs may suppress SWS, but nonbenzodiazepine agonists do not do so.

Drugs Used to Treat Psychiatric Disorders

Antidepressant medications such as tri- and tetracyclics, monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitors (SSRIs), and others (e.g., trazodone, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, and lithium) may disrupt sleep, alter sleep architecture, and suppress REM sleep. Some of the tricyclics and MAO inhibitors are sedating, whereas others are stimulating, but most of the SSRIs are stimulating drugs. These antidepressants suppress REM sleep, may increase latency to REM sleep, and reduce percentage of REM sleep. Sedative antidepressants (e.g., amitriptyline, doxepine, and trazodone) may be used to treat insomnia, especially associated with depression. Most tricyclic antidepressants may cause daytime sedation. MAO inhibitors have alerting properties, so they are best used in the morning or early afternoon. Trazodone, a sedative antidepressant, increases SWS but is a weak REM suppressant. Fluoxetine has an alerting effect and can suppress REM sleep at high doses. Lithium increases

SWS and has a mild REM suppressant effect. Sudden withdrawal of these REM suppressant medications may cause REM rebound. Anxiolytics (e.g., buspirone and alprazolam) may cause sedation.

Antipsychotic drugs such as haloperidol, the phenothiazines, thioridazine, and the newer antipsychotic agents (e.g., clozapine, olanzapine, risperidone, and quetiapine) are used to treat psychotic conditions, including schizophrenia. Some of these drugs, particularly the phenothiazines, may cause drowsiness and impairment of performance. All neuroleptic drugs may produce serious side effects in combination with hypnotics, alcohol, or antihistamines. The newer antipsychotics have a better side effect profile.

Drugs Used to Treat Neurologic Disorders

Antiepileptic drugs (AEDs), especially benzodiazepines and barbiturates, cause sedation. Newer generation of AEDs is in general less sedating. However, well-controlled studies documenting the effects of antiepileptic agents and sleep architecture are lacking (see also Chap. 44). Effective control of seizures following treatment with antiepileptic agents results in the reduction of sleep disturbance due to the reduction of seizures and not due to any specific effect of antiepileptic agents on sleep architecture.

Drugs to treat RLS mainly include dopamine agonists (e.g., Pramipexole, Ropinirole, Rotigotine patch, α-2-delta ligands [Gabapentin, Gabapentin Enacarbil, Pregabalin], and opiates in refractory or intractable cases and those with augmentation). In addition to these short-term adverse effects of daytime sleepiness with these agents, especially α-2-delta ligands, the long-term vexing complication of dopamine agonists in dopamine-induced augmentation (DIA) [908] causing also severe sleep disturbance seen in a large percentage of patients, notably with Pramipexole and Ropinole. A rare side effect with long-term opiate use is opioid-induced hyperalgesia (OIH) resembling DIA [909]. The most serious effect of opiate besides addiction is its adverse effect on breathing causing or aggravating coexisting sleep apnea [898].

Stimulants used in narcolepsy-cataplexy (e.g., Provigil, Nuvigil, methylphenidate, and amphetamines) may adversely affect night sleep if taken late in the afternoon with reduction of SWS and REM sleep [898, 907]. Sodium oxybate, indicated mainly for cataplexy but also for consolidating night time sleep, is a CNS sedative and has an increased risk of sleep apnea [903–905].

Antiparkinsonian medications such as L-dopa may cause nocturnal hallucinations and agitated confusion during sleep at night. Some of the dopaminergic agonists (e.g., pergolide, pramipexole, ropinirole, and cabergoline) may cause nightmares.

Miscellaneous Agents

Drugs of abuse and alcohol (although not a drug, alcohol can be considered a social drug) have potentially deleterious effects on sleep. Stimulant drugs of abuse (e.g., amphetamines and cocaine) may cause insomnia. Amphetamines increase wakefulness, suppress REM sleep, and delay sleep onset. Cocaine reduces REM sleep and increases sleep latency and REM latency. On cessation, these may cause REM rebound. Hallucinogens such as lysergic acid diethylamide (LSD) and mescaline may cause a state resembling dreaming. Marijuana, through its active ingredient tetrahydrocannabinol (THC), may cause sedation at lower doses and hallucinations at higher doses. THC increases SWS and reduces REM sleep. Drugs of abuse mostly alter the amount and timing of REM sleep and produce REM rebound on discontinuation.

Alcohol has profound effects on sleep/wakefulness. Acute alcohol administration, by acting as a CNS sedative, will cause shortening of sleep onset, increase SWS, and reduce REM sleep. However, after the initial sedative effects lessen and as the blood alcohol level falls, the patient will have repeated awakenings causing sleep fragmentation and REM rebound. REM rebound is also noted on discontinuation after several nights of alcohol consumption. The sedative action of alcohol may be due to facilitation of GABA function and inhibition of glutamate. Alcohol, barbiturates, tricyclic antidepressants, and SSRIs may produce REM sleep behavior disorder and other complex phenomena such as status dissociatus.

Testosterone levels in men with sleep apnea have been reported to be low which improved after CPAP therapy, but testosterone administration may worsen sleep apnea by adversely affecting neuromuscular control of upper airway potency [898].

Over-the-Counter Medications

OTC medications include nasal decongestants and anorectics, which are stimulants (e.g., pseudoephedrine and phenylpropanolamine) and will cause insomnia. Caffeine, which is present in coffee, tea, colas, and chocolates, also is a stimulant and may promote wakefulness by blocking adenosine A_{2a} receptors. As little as 150 mg of caffeine, which is the equivalent of 1–2 cups of coffee, may disturb sleep quality by increasing sleep latency and reducing total sleep time. During sleep deprivation, high doses of caffeine reduce total sleep time, increase stage 1 NREM sleep, and reduce SWS but do not affect neurocognitive functions.

OTC sleeping medications are widely used for the induction of sleep. The active ingredients in these agents are antihistamines (diphenhydramine and doxylamine), and

these drugs represent the most common use of antihistamines in OTC preparations. These histamine$_1$ blockers have undesirable anticholinergic effects (e.g., dryness of the mouth, palpitations, dilation of pupils, tachycardia, and difficulty in urination) and cause daytime sedation.

Summary and Conclusions

There has been explosive growth in sleep medicine and increasing awareness about the importance of sleep in everyday life. It is therefore important for sleep specialists, general internists, and family physicians to have adequate knowledge about sleep dysfunction in general medical disorders to practice their trade effectively. This chapter attempts to summarize in a comprehensive manner general medical disorders that may account for a variety of sleep complaints (e.g., insomnia, hypersomnia, parasomnias, sleep-related breathing disorders, and circadian rhythm sleep–wake dysfunction) or may be comorbid with sleep disorders. General medical disorders may affect sleep–wake neurons by indirect mechanisms through metabolic, toxic, or anoxic disturbances. The possibility of medically induced sleep disturbance should always be kept in mind because the natural history of medical illness may be altered by this comorbidity. It is unfortunate that the ICSD-2 eliminated medical disorders as a separate category of classification and introduced these conditions in a scattered manner throughout the eight major categories and appendices.

All major categories of general medical disorders were addressed in this chapter, and some conditions were addressed in greater details than others because of the importance of sleep complaints affecting quality of life and because of long-term adverse consequences of sleep-related breathing disorders in many of these medical conditions. In the final section, a brief description was also given of a variety of medications used to treat general medical, neurologic, and psychiatric illnesses that may affect sleep and breathing, causing acute and emergent events during the course of the practice of sleep medicine.

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