Secondary Sleep Disorders

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Sleep disorders may be secondary as a symptom of organic or psychic/psychiatric diseases. These disorders can appear as accompanying or temporary symptoms; however, in the context of chronic diseases, they contribute significantly to the morbidity and maintenance of the disease. In those cases, the treatment of the sleep disorder may have a positive effect on the course of the underlying disease. The expertise of the sleep specialist is also required when comorbid sleep disorders need to be treated in patients with organic or psychic/psychiatric diseases. Furthermore, organic or psychic/psychiatric diseases may manifest primarily as a sleep disorder. The sleep specialist is then responsible to discover the basic origin of the sleep disorder and to initiate adequate treatment approaches.

It is clear that not all organic and psychic/psychiatric diseases leading to secondary sleep disorders may be discussed in this chapter. One focus of this chapter is the presentation of the most important secondary sleep disorders that may appear as complaints of insomnia or hypersomnia. The treatment of the underlying diseases however is not included in this chapter.

10.1 Sleep Disorders Caused by Organic Diseases

Sleep disorders and sleep-related symptoms are apparent in numerous organic diseases.

On one hand, organic diseases may be the *origin* of secondary sleep disorders, and on the other hand classic symptoms of sleep disorders such as difficulties of initiating and maintaining sleep or daytime sleepiness may be seen as the *leading symptoms* of an organic disease. Thus, organic diseases have to be considered in the differential diagnosis of insomnia and hypersomnia. Finally, the relevant symptoms can even be the *result* of medical therapy of an underlying organic disease, which emphasizes the necessity of careful history taking regarding medication (▶ Chap. 2).

The most important organic diseases that should be considered in this context are these:

- Insomnia
  - Endocrine diseases (hyperthyroidism)
  - Chronic pain
  - Neurological diseases (neurodegenerative diseases)
  - Respiratory diseases (bronchial asthma)
- Hypersomnia
  - Endocrine diseases
  - Cardiovascular diseases (cardiac arrhythmia, hypotension, heart failure)
  - Respiratory diseases
  - Renal failure

The aforementioned classification is mainly based on didactic reflections. Many of those diseases may lead to complaints of insomnia as well as hypersomnia, depending on the severity of the disease and the individual patient.

10.1.1 Insomnia as a Symptom of Organic Diseases

10.1.1.1 Endocrine Diseases

Hyperthyroidism is generally associated with symptoms of psychomotor restlessness. In addition to a frequently slight tremor and increased nervousness, in general symptoms of sleeplessness with difficulties in initiating and maintaining sleep are also observed. Other clinical symptoms are goiter, which is encountered in 70% to 90% of the patients, sinus tachycardia with possibly occurring arrhythmia, weight loss, hyperhidrosis, and heat intolerance.

Those symptoms may be seen not only in the context of immunogenic hyperthyroidism (Graves' disease) or thyroid autonomy, but may also be caused by inappropriate dosage of thyroid hormones.

In the daily routine of sleep medicine, patients with the clear manifestation of hyperthyroidism do not present problems of differential diagnosis. In cases of accordingly weak symptoms, however, those patients may primarily complain about disorders of initiating and maintaining sleep as leading symptoms. Regarding the frequent occurrence of thyroid diseases, patients should undergo an appropriate history taking and in suspected cases additional laboratory testing as part of the diagnostic process in cases with insomnia.

10.1.1.2 Chronic Pain

Chronic pain is closely related to sleep disorders and regularly interferes with each other. Chronic pain is often associated with disorders of

initiating and maintaining sleep. Approximately two thirds of patients with chronic pain report symptoms of insomnia.

In particular, in the context of *tumor-related pain*, not only does the pain cause sleep disorders, but also the stress caused by the disease contributes to the persisting chronic sleep disorder.

On the other hand, chronic sleep disorders or chronic sleep deprivation may significantly influence the *perception of pain* so that an adequate treatment of the sleep disorder may decisively improve the efficacy of analgesic therapy. In addition to current therapeutic approaches in the treatment of chronic pain, sedating antidepressants are often included in the co-analgesic therapy. Hereby, sedation leads not only to an increased effect of classic analgesics but also to improved sleep.

10.1.1.3 Neurological Diseases

Neurodegenerative diseases such as Parkinson's disease or dementia of Alzheimer's type frequently lead to distinct sleep disorders up to the disintegration of the sleep–wake cycle.

In more than 50% of the cases, *dementia diseases* are associated with sleep disorders. The severity of dementia and the dispersed daytime and nighttime rhythm are closely interrelated. There may be an important discrepancy between the objectively diagnosed sleep disorder and the subjective assessment of sleep. Disorders of the sleep–wake cycle, daytime sleepiness, and daytime sleep episodes are typical symptoms. In up to 50% of the cases, central sleep apnea syndromes occur; furthermore, periodic leg movements are observed.

In those cases, generally a stabilized sleep–wake cycle may be achieved by appropriate sleep hygiene and a stable daytime rhythm that should include regular phases of physical activity. Regarding medical treatment of the difficulties of initiating and maintaining sleep of dementia patients, low-dose, slightly sedating neuroleptics or antidepressants with low anticholinergic components may be applied. Short-acting benzodiazepine receptor agonists are also available.

In the context of *Parkinson's disease*, sleep disorders represent a frequent, non-motor symptom. Neurodegenerative processes, especially in dopaminergic systems, as well as periodic leg movements during sleep, disorder of REM sleep, and secondary sleep-related respiratory disorders seem to be responsible for sleep disturbances frequently associated with Parkinson's disease.

10.1.1.4 Respiratory Diseases

Patients suffering from *bronchial* asthma often report difficulties of initiating and maintaining sleep and present with a reduced percentage of slow wave sleep. Additionally, the application of stimulating bronchodilators at nighttime may have a negative effect on nocturnal sleep.

10.1.2 Hypersomnia as a Symptom of Organic Diseases

10.1.2.1 Endocrine Diseases

In contrast to the aforementioned symptoms of hyperthyroidism, patients suffering from hypothyroid metabolism generally present with a typical activity decrease, lethargy, fatigue, and sleepiness. Other frequently observed clinical symptoms of hypothyroidism are increasing weight (also caused by a generalized myxedema), sensitivity to cold temperatures, and obstipation. In general, those symptoms are not as impressive as in the context of hyperthyroidism. Lethargy and fatigue or sleepiness may be the salient symptoms. Patients with hypersomnia complaints thus should routinely undergo history taking with regard to the described symptoms, to previous surgical interventions of the thyroid, to radioiodine therapy or medical treatment of the thyroid, and finally laboratory testing in suspected cases.

Additionally, hypothyroidism often leads to sleep-related respiratory disorders because of increased weight and tissue edema and thus to hypersomnia in a twofold respect. Even if the percentage of patients with hypothyroidism among all patients suffering from obstructive sleep apnea is rather low (1% to 3% according to the international literature), hypothyroidism seems to be accompanied by obstructive sleep apnea in 50% to 100% of cases.

Case Report

A patient presents in our medical sleep center with complaints of nonrestorative sleep and severe daytime sleepiness (ESS 16).

Besides the predominant complaints of increased tendency to fall asleep, the patient also describes a general lethargy and a clear

reduction of physical and mental activity that leads to significant problems at work and in his private life. During the previous year, he has considerably increased in weight although he has not changed his habits of nutrition and life (current BMI, 32 kg/m^2).

Sleep medical diagnosis reveals low-grade obstructive sleep apnea with an AHI of 13. Because of the severe daytime sleepiness with only low-grade sleep apnea and the described complaints, a thyroid-stimulating hormone (TSH) test is initiated that indicates hypothyroid metabolism with a value of 15.3 mU/l. Outpatient diagnostics performed by the general practitioner confirm the diagnosis of hypothyroidism; substitution treatment with thyroid hormones is initiated.

The daytime situation of the patient is significantly improved; the treatment leads to clear weight reduction. A polysomnographic control after 3 months reveals that his respiratory problems have completely disappeared.

Cushing syndrome also may be relevant for differential diagnosis. In general, the affected patients show adynamia and obesity, which is frequently associated with obstructive sleep apnea. Also in this context, the increase of pharyngeal soft tissue related to regularly occurring obesity, is responsible for the development of obstructive breathing disorders. In addition, corticosteroid-induced myopathy is discussed as a possible origin. Some of the patients with high cortisol levels during nighttime also tend to insomnia. This observation is mainly found in patients with adrenal Cushing or ectopic ACTH expression. Both symptoms are not subject to circadian regulation and lead to permanently increased cortisol levels.

In most cases, however, the Cushing syndrome is iatrogenic. In patients who undergo long-term medication with corticosteroids this fact should be included in the diagnostic and therapeutic considerations. Most corticosteroids should be taken in the morning because all preparations cause waking reactions.

Even if it occurs more rarely, *acromegaly* must be mentioned and included in the differential diagnosis. Sleep apnea syndromes are found in about 60% of the patients suffering from acromegaly; obstructive sleep apnea especially is relevant. An increase of the pharyngeal soft tissue seems to be responsible for the development of obstructive sleep apnea in the context of acromegaly. If the typical clinical symptoms of acromegaly become apparent (coarsening of the facial characteristics, increased ring and shoe size, hyperhidrosis, etc.), adequate endocrinological examination has to be performed.

Diabetes mellitus is the most frequent metabolic disease and is associated in a number of ways with sleep-related disorders, in particular with obstructive sleep apnea. Both phenomena frequently occur together in the context of metabolic syndrome. Furthermore, however, obstructive sleep apnea is currently increasingly understood as an independent risk factor for insulin resistance. There are hints that diabetic autonomous neuropathy may lead to an impairment of the breath-synchronized innervation of the muscular dilator muscles of the upper airways.

10.1.2.2 Cardiovascular Diseases

Cardiac arrhythmia may lead to insomnia not only because of tachycardia at nighttime but it can also induce consecutive deterioration of cardiac output: this mainly affects patients suffering from preexisting bradycardial arrhythmia.

An according reduction of the physical activity that may manifest as fatigue or sleepiness with morning waking difficulties is also observed in other diseases accompanied by *hypotension* (e.g., heart failure). Frequently, according symptoms are also found in the context of antihypertensive therapy when undesired low blood pressure results or the patients are not yet adapted to the changed (actually normotensive) blood pressure at the beginning of treatment.

Notwithstanding the foregoing, *heart failure* is regularly associated with sleep-related breathing disorders and may induce central as well as obstructive respiratory disorders. In this context, Cheyne-Stokes respiration represents the classic disorder (see ▶ Chap. 4).

It should be a routinely asked question in sleep-related history taking if the patient suffers from cardiovascular diseases or takes *medication* accordingly. In cases of suspected findings, blood pressure and heart rate should be measured; if necessary, a 24-h record of blood pressure should be initiated.

10.1.2.3 Respiratory Diseases

Chronic respiratory diseases such as *bronchial asthma* or *chronic obstructive pulmonary disease* are often associated with sleep-related breathing disorders. These conditions alone may lead to a sleep-related hypoventilation syndrome (► Sect. 4.1); as comorbidity, however, they frequently aggravate preexisting sleep apnea because of the low pulmonary reserve. In those cases, the diagnosis and treatment of respiratory disorders can be considered as causal therapy of a sleep-related hypoventilation syndrome; also in the context of sleep apnea syndromes, however, a concomitant respiratory disorder should be treated to achieve an optimal therapeutic outcome.

10.1.2.4 Renal Dysfunction

Patients with advanced renal dysfunction often suffer from sleep disorders regularly accompanied by symptoms of daytime sleepiness. In the context of chronic uremia and renal replacement therapy, sleep disorders are reported in as many as 80% of the cases, but they can occur in earlier stages of renal dysfunction.

Besides *disorders of initiating and maintaining sleep*, mainly the following sleep disorders are associated with renal dysfunction:

- *Restless legs syndrome* or *periodic leg movements during sleep*
- Central as well as obstructive *sleep apnea syndrome*

Among others, uremia as well as an associated iron deficiency or associated anemia seem to be responsible for concomitant complaints of restless legs.

The triggering mechanism for the development of central sleep apnea syndromes in this context is not finally clarified; however, disorders of central and peripheral chemosensitivity are increasingly discussed. Furthermore, metabolic disorders are considered responsible for central respiratory regulation disturbances.

Regarding the incidence of obstructive sleep apnea, a narrowing of the upper airway seems also to be responsible.

Concomitant sleep disorders frequently lead to an additional impairment of the patients' quality of life and the clinical course of the underlying disorder. In this context, especially, sleep apnea syndromes are significant, not only because of their incidence but also because of the already described negative effects on cardiovascular morbidity and mortality. Even if concomitant sleep disorders regularly improve after transplantation, the incidence of sleep disorders in transplanted patients remains increased compared to healthy individuals.

Often, associated clinical symptoms such as daytime sleepiness, concentration problems, difficulties of initiating and maintaining sleep, fatigue, and impaired activity are only considered as accompanying symptoms of renal dysfunction. Because effective therapeutic options are available, however, possibly coexisting sleep disorders should be taken into account and adequately diagnosed. Appropriate treatment often improves the quality of life of the affected patients.

10.2 Sleep Disorders and Mental Disorders

In a major portion of the patients, mental disorders such as depression, schizophrenia, or anxiety are associated with sleep disorders. This fact is taken into account in the current version of the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (DSM-5) by including not only insomnia, circadian rhythm sleep–wake disorders, and hypersomnia in the chapter about sleep disorders but also narcolepsy, sleep apnea syndrome, and restless legs syndrome, explicitly indicating that sleep disorders should be diagnosed in addition to the underlying mental disorder. Because those mental disorders are highly important for the differential diagnosis of insomnia and hypersomnia disorders, they are discussed in this chapter according to their manifestation (insomnia versus hypersomnia complaints).

The close correlation between mental disorders and sleep disorders implies that the question regarding current or previous mental disorders must be included in the sleep history. In particular, the presence of current depressive symptoms and the intake of psychotropic drugs must be clarified. On the other hand, research clearly shows that mood disorders, for example, are more

often found in patients with restless legs syndrome and sleep apnea syndrome than in the normal population. Thus, screening with regard to mental disorders is highly important for patients presenting in a sleep center with the main complaint of sleep problems. After therapy of the sleep disorder, those patients should then possibly be referred to an appropriate specialist.

In this context, the following disorders are of major relevance:

- *Insomnia* complaints:
  - Affective disorders
  - Anxiety disorders
  - Posttraumatic stress disorder (PTSD)
- *Hypersomnia* complaints:
  - Atypical or seasonal affective disorder
  - Chronic schizophrenia

It must be taken into account that patients present to sleep centers who might still suffer from significant insomnia or hypersomnia complaints even though the underlying mental disorder has been treated successfully. In those cases, additional diagnostic procedures are required to assess comorbid sleep disorders.

10.2.1 Insomnia Complaints as Symptom of Mental Disorders

10.2.1.1 Affective Disorders

Affective disorders are very common. Depending on the study, the lifetime prevalence of depression amounts to 10% to 25% in females and 5% to 12% in males. Three major subgroups are classified:

- Unipolar depression (episode(s) corresponding to the criteria of major depression)
- Bipolar affective disorder
- Dysthymia

According to the DSM-5 (*Diagnostic and Statistical Manual of Mental Disorders*), an episode of *major depression* is characterized by depressed mood observed on nearly all days and for most of the day as well as a clearly reduced interest or significantly reduced pleasure in all or nearly all activities (also across most situations similar to depressive mood). This criterion of permanence is important for clinical evaluation to clearly differentiate between normal emotional changes or mood swings and depressive symptomatology.

Practical Tip

Important question for history taking:
"Do you sometimes experience sad or depressive moods?"

Unipolar depressions are affective disorders wherein the patients do not experience manic phases. They represent the main category of affective disorders.

Patients experiencing depressive and manic phases are classified as *bipolar*. Manic phases are characterized by high moods; often increased activity and a reduced need of sleep are observed. Patients may lose social inhibitions; they have inflated self-esteem or grandiosity and carelessly spend large amounts of money.

Dysthymia is a less severe mood disorder. According to diagnostic criteria, it has to persist for at least 2 years.

The key symptoms of affective disorders, sleeplessness or increased sleep nearly all days/nights, are often explicitly mentioned in the diagnostic criteria of affective disorders. Hypersomnia complaints, which are mainly present in atypical or seasonal affective disorder, are discussed in the following paragraph.

Early morning awakening (at least 2 h before the usual time to get up) is one main sleep problem in depressive patients with melancholia (also show very low mood in the morning). However, depressive patients also suffer from disorders of initiating and maintaining sleep that are comparable to complaints of insomnia patients. Because chronic insomnia may lead to affective disorders for example, dysthymia, it is necessary to evaluate which symptoms had occurred first. Simultaneous occurring of the symptoms indicates that the sleep problems are part of the affective disorder. However, in this context, it should be kept in mind that the sleep disorder may persist after cessation of the depressive complaints.

With regard to the treatment of depression, presenting the symptom of sleep problems is important in selecting the *medication*. Often a combined treatment with an activating medication, for example, a selective serotonin reuptake inhibitor, in the morning and a sedating antide-

pressant, such as mirtazapine or trimipramine, in the evening is prescribed for patients with severe sleep disorders. In patients with long-term medication, it must be also taken into consideration that many antidepressants can increase periodic leg movements during sleep and cause restless legs complaints. As a consequence, patients might report nonrestorative sleep despite improvement of the depressive symptoms.

10.2.1.2 Anxiety Disorders

Anxiety disorders may also be associated with insomnia complaints. Up to 40% of patients with anxiety disorders also report sleep problems. Anxiety disorders are classified into these diagnostic groups:

- Panic disorder with or without agoraphobia
- Social phobia
- Specific phobias (e.g., arachnophobia)
- Generalized anxiety disorder

With regard to differential diagnosis of sleep disorders, the panic *disorder* must be taken into consideration especially when panic attacks occur solely at night. Although most patients experience panic attacks during the day (with occasional panic attacks at night), some patients only suffer from panic attacks at night during sleep. In this context, it is important to differentiate from the *nightmare* disorder or *night terrors* (pavor nocturnus). It is currently not clear which sleep stage precede those nocturnal panic attacks. Although sleep lab studies indicated that non-REM sleep might precede panic attacks, one study showed that panic attacks in the home setting may also occur after negative dreams, i.e., out of REM sleep.

Practical Tip

The major fear of the panic attack is experienced in the waking stage (dyspnea, sensation of suffocation, nausea, vertigo, or fear to lose control, to go crazy, or to die). In cases of night terror and nightmares, this fear usually ceases rapidly after waking up.

Interestingly, patients with nocturnal panic attacks often show a more severe anxiety disorder than patients who suffer solely from daytime panic attacks.

In general, *therapy of the underlying disorder* is of prime importance. A sedating antidepressant such as mirtazapine or trimipramine may help these patients in addition to psychotherapeutic treatment of the anxiety disorder.

10.2.1.3 Posttraumatic Stress Disorder

Posttraumatic stress disorder is mental disorder that has a strong connection to sleep medicine. Population surveys indicate a lifetime PTSD prevalence of 1% to 14%. For high-risk populations (war veterans, or victims of natural disasters, rape, abuse, or road accidents), the percentages are higher.

It is crucial for the diagnosis of this disorder to assess the occurrence of the traumatic experience(s) with impending death, severe injury, or danger for the physical integrity of oneself or another person. The impact of the trauma is seen in such effects as these:

- Recurring stressful memories
- Avoiding behavior regarding situations that might trigger flashbacks
- Reduced affect
- Negative view of the future

Two common symptoms relate to sleep. First, there are *recurrent dreams*. About 50% of these reflect the traumatic experience more or less exactly. Recent findings indicate show that non-trauma-related nightmares can also cause severe disstress. Although the etiology is different from that of idiopathic nightmares (▶ Sect. 7.3.2), *imagery rehearsal therapy* can be helpful for patients suffering from posttraumatic nightmares (▶ Sect. 7.3.8). Because the dropout rate of women after sexual abuse was very high in a large clinical trial, it is recommended to use nightmare-related interventions as add-ons to standard psychotherapeuty of posttraumatic stress disorder.

Second is the *hyperarousal complex* (e.g., hypervigilance, excessive shock reaction, irritability) includes explicitly disorders of initiating and maintaining sleep. A few studies indicate that sleep-related breathing disorders and periodic leg movements during sleep occur more frequently in patients with posttraumatic stress disorder compared to the general population, i.e., it is recommended that these patients undergo careful sleep anamnesis and if needed also polygraphy and/or polysomnography (PSG).

10.2.2 Hypersomnia Complaints as Symptom of Mental Disorders

10.2.2.1 Atypical or Seasonal Affective Disorder

In cases of *depressive disorders with atypical characteristics*, hypersomnia complaints are often reported. Other symptoms of depressive disorders with atypical characteristics are these:

- Increased appetite or weight gain
- Hypersensitive to rejection

The atypical symptoms (hypersomnia complaints, increased appetite) occur in addition to the symptoms that are typical for depression (mood swings, loss of interest, etc.). Young depressive patients are more often affected by atypical depression than older patients. However, in total, the atypical syndromes are rare, with an incidence of less than 10% of all depressive patients.

The atypical symptoms are quite frequent seasonal affective disorders. Seasonal affective disorders can only be diagnosed if at least two phases occur clearly in relationship to a season (most often fall/winter).

Depression with atypical symptoms is an important differential diagnosis for primary hypersomnia, i.e., patients should be asked about the possible presence of depressive (typical and atypical) symptoms. In addition, the MSLT may provide further diagnostic evidence because patients with atypical depression spend much time in bed but do not sleep much during this time. Long sleep latencies in the MSLT may indicate atypical depression and explain the subjectively hypersomnia complaints of the patient.

With regard to therapy, it must be considered that a significant percentage of patients with seasonal affective depression (between 30% and 60%) respond positively to *light therapy* (30 min in the morning and 30 min in the evening with a light intensity of 10,000 lux).

10.2.2.2 Schizophrenia

Although schizophrenic patients often suffer from problems of initiating and maintaining sleep in the prodromal phase or during an acute productive phase (in these phases the treatment of schizophrenia is in the prime focus so that sleep-related diagnostic and therapeutic interventions can only be appropriately performed after positive symptoms have subsided), hypersomnia complaints may found in chronic schizophrenic patients with long-term medication with neuroleptics.

Often, those complaints are explained by the sedating effect of the medication and are not properly evaluated. However, experiences from our practice show that sleep-related diagnostic procedures should be initiated in cases of severe daytime sleepiness in patients with schizophrenia.

Case Report

A young schizophrenic patient presented in the sleep clinic because he sometimes fell asleep during occupational therapy sessions.

Because of neuroleptic medication, he has significantly gained weight (which is a frequent side effect), and being asked, he reported increasing daytime sleepiness in the previous weeks. He was not able to provide information about possible snoring at nighttime or the occurrence of nocturnal sleep apnea episodes because he slept alone. Subsequent polygraphy showed a moderate obstructive sleep apnea and daytime sleepiness was significantly improved after starting CPAP therapy.

In addition to developing a sleep-related breathing disorder due to weight gain during treatment with neuroleptics, there is the problem that those substances affect the dopaminergic system. Side effects due to the occurrence of periodic leg movements during sleep causing sleep problems and nonrestorative sleep may result. If possible, reduction of the neuroleptic dose is recommended. As compensation, up to 600 mg valproic acid may be applied at night. Positive effects are reported in the literature about low-dose dopamine antagonists (ropinirole or pramipexole) without re-occurrence of positive symptoms (delusion, hallucinations) in those patients. By increasing the cerebral dopamine concentration, this might be a possible complication in the treatment of schizophrenic patients.

Case Report

A young female patient with borderline personality disorder was presented in the sleep laboratory with disorders of initiating and maintaining sleep. Treatment with a benzodiazepine receptor antagonist (zopiclone) could not improve the complaints, so the patient was treated with a

neuroleptic (Pipamperone) at night. Despite subjective improvement of sleep, the patient reports significant hypersomnia complaints.

Polysomnographic measurements indicated a very high index of periodic leg movements during sleep that subsided after discontinuing of the neuroleptic. That is, the hypersomnia complaint has occurred as a side effect of the neuroleptic medication that was originally applied as sleeping aid.

Treatment with trimipramine led to a positive effect on sleep quality and restorative sleep.

Because of possible side effects of many psychopharmaceuticals (gain in weight, periodic leg movements during sleep), it is necessary that patients who receive long-term medication and report hypersomnia complaints undergo sleep diagnostics.

10.3 Questions

1. Please indicate the most important organic diseases that must be taken into consideration in the differential diagnosis of sleep disorders.
2. What are the most important mental disorders that play a major role in the differential diagnosis of insomnia, hypersomnia, and parasomnias?