Sleep Disorders: Narcolepsy (Excessive Uncontrollable Daytime Sleepiness) and Restless Legs Syndrome (RLS)

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Permanent sleepless nights are torture: Sleep disorders are accompanied by much suffering for affected individuals. Which of the disorders that mostly occur nocturnally should you know about for your practice routine and the medical exam? The following article will introduce you to the fundamentals of sleep disorders, diagnostics as well as therapeutic remedies in cases of REM sleep behavior disorders and sleep myoclonus. Particular focus is laid on narcolepsy and restless legs syndrome. This article is concisely prepared with focus on the exam and will leave no questions concerning sleep disorders in neurology unanswered.

Fundamentals of Sleep Disorders

Sleep disorders are divided into two subtypes: dyssomnias and parasomnias.

Dyssomnias

Dyssomnias are subdivided into hypersomnias and hyposomnias.

| Hypersomnias (too much sleep) | Hyposomnias (too little sleep) |
**Sleep apnea syndrome:** loud, irregular snoring leads to breaks between breathing of up to 10 seconds, particularly during REM sleep. Lack of oxygen and a slower heart rate lead to short awakenings resulting in a massive disruption of the sleep architecture. Patients are sleepy during the day and have trouble concentrating.

**Difficulty falling and staying asleep** and waking up during the night due to variable causes, i.e. depression.

**Irregular sleep-wake rhythm:** Night jobs and shift work, changes in time zones/jetlag (over time, the consequences are a weakened immune system as well as functional and psychosomatic disorders). Once the circadian rhythm has adjusted to the new environmental conditions, it is referred to as **resynchronization.**

**Narcolepsy:** sudden sleep attacks during the day that last several minutes (see below)

**Parasomnias**

Parasomnias are a group of strange phenomena that may occur during sleep. The following **REM sleep parasomnias** frequently appear at a young age:

- **Somnambulism:** sleep walking
- **Somniloquy:** sleep talking
- **Night terror (pavor nocturnus):** sleep terrors
- **Bruxism:** nocturnal teeth grinding
- **Nocturnal enuresis (enuresis nocturna):** nocturnal bedwetting

In comparison, **non-REM sleep parasomnias** such as REM sleep behavior disorder, occur more frequently in adults.

**Diagnosing Sleep Disorders**

In the study of sleep disorders and sleep research, two diagnostic tools are particularly significant: **EEG and polysomnography** showing the result of the **hypnogram** (sleep profile).

**Interpreting the EEG**

*Image: “A fictional EEG showing a sleep spindle and K-complex in stage 2 sleep.” by*
The EEG shows the different sleep stages as well as the sleep-wake rhythm via typical sleep signals. Furthermore, one can differentiate between REM sleep and non-REM sleep.

- **Paradoxical sleep**: The EEG appears “wake-like” with simultaneous complete muscle atony.
- **Sleep spindles**: Another EEG morphology that preferably occurs in stage II and presents with high frequency and low amplitude.
- **K-complexes**: K-complexes are potentials that can be triggered by abrupt and strong stimuli (i.e. lightning and thunder). They can be interpreted as a form of micro-arousals and can characteristically be seen in the EEG in stage II.

**Study tip**: You should memorize these terms very thoroughly in order to be able to describe the sleep EEG using the correct terms. Read more about the biopsychology fundamentals here. (Sleep stages, circadian rhythm and much more).

**Polysomnography** is of significant importance in diagnosing sleep disorders. During the very elaborate polysomnography process, different bodily functions are monitored throughout an entire night. The result analysis shows, among others, a **hypnogram**, the patient’s sleep profile. With some syndromes, the hypnogram alone can make a diagnosis possible.

### Example of a Hypnogram

![Hypnogram](image)

**Image**: “Hypnogram - one sleep cycle” by Schlafgut. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

### The REM Sleep Behavior Disorder

The REM sleep behavior disorder (**RBD**) represents an important differential diagnosis to epilepsy in the elderly which occurs frequently. The muscle atony typically occurring during REM sleep is absent with RBD, resulting in the patients **acting their dreams out**. They hit and kick and report violent and scary dreams.

Long-term studies indicate that REM sleep behavior disorder is strongly associated with neurodegenerative diseases: Over the course, patients acquire **Parkinson’s disease**, **Lewy body dementia** and **multiple sclerosis**.
Therapy: Symptomatic treatment consists of administering clonazepam in the evening (0.5 – 2mg).

Sleep Myoclonus: Physiological or Epileptic?

Case study: A patient comes to see you in the neurological outpatient clinic and reports twitching in his arms and legs when falling asleep. He is worried that he may have epilepsy.

Most likely, this patient is experiencing **physiological sleep myoclonus** which takes place during the transitional state from wakefulness to sleep. In order to rule out epilepsy as differential diagnosis, a sleep lab study should be conducted. In order to assure that there are no epileptic attacks occurring simultaneously with the myoclonus, several episodes should be recorded.

Narcolepsy: Excessive Uncontrollable Daytime Sleepiness

Case study: A 36-year-old mother of two small children is referred to the sleep lab by her family physician. She complains of having been very tired during the day for the last few months and also fell asleep frequently. She also states that she is unable to control falling asleep. In addition, she is frequently unable to differentiate between dream and reality when waking up. Sometimes she wakes up but is unable to move. When questioned, she states that she had dropped glasses on numerous occasions when she laughed about a joke. (via Pharmazeutische Zeitung)

The Etiology and Epidemiology of Narcolepsy

Due to its association with HLA alleles, **immunological components** are suspected with narcolepsy (similar to multiple sclerosis). Environmental influences most likely lead to autoimmunological processes that damage the centers regulating sleep. One assumes the destruction of hypothalamic neurons, which are important for the sleep-wake rhythm, producing the protein hypocretin. From a certain level of function loss, narcolepsy manifests itself clinically.

The suspected prevalence of narcolepsy is between 25 and 50 affected individuals in 100,000 residents.

*The frequency of narcolepsy can be compared with multiple sclerosis.*

Clinical Signs of Narcolepsy

The typical symptoms of narcolepsy are:

- Excessive daytime sleepiness with sudden imperative sleep attacks
- Fragmented nighttime sleep, disrupted nighttime sleep
- Cataplectic attacks triggered by strong emotions (i.e. laughter)
- Hypnagogic (when waking up) and hypnopompic (when falling asleep) hallucinations
- Changes in REM sleep: Patients with narcolepsy enter the REM sleep phase right after falling asleep (usually occurs at the end of the nightly sleep cycle).
- **Sleep paralysis:** Patients feel as if they are awake but the muscles are still
ataxic as if in REM sleep. This short paralysis can be very frightening for the patients.

**Caution: Cataplexy** = acute, reversible loss of muscle tone not to be confused with the term **catatonia**. Catatonic schizophrenia is a psychomotor form of schizophrenia, which can develop into a catatonic stupor. Another similar term is **catalepsy**: Fixed posture in which limbs remain in whatever position for an overly extended period of time.

**Diagnosing Narcolepsy and Differential Diagnoses**

A purely clinical diagnosis is possible in cases with cataplexy and excessive daytime sleepiness. This diagnosis can be confirmed by a **sleep lab study**. The typical picture of narcolepsy would be entering into the REM sleep phase right after falling asleep, during the day as well as at night.

**Narcolepsy differential diagnoses**

Differential diagnoses for excessive daytime sleepiness:

- **Sleep disorders**: sleep apnea syndrome, idiopathic hypersomnia, restless legs syndrome, circadian rhythm disorder
- **Psychiatric and neurological disorders**: depression, alcohol and drug dependency, dementia, neurodegenerative disorders
- **Other disorders**: shift work, sleep disorder, posttraumatic hypersomnia, chronic fatigue syndrome

Differential diagnoses for cataplectic attacks:

- **Neurological disorders**: epilepsy, muscular disorders, drop attacks, balance disorders, tremor
- **Internal diseases**: syncopy, falls associated with polyneuropathy
- **Other disorders**: psychogenic attacks, orthopedic disorders

**Narcolepsy Therapy**

Narcolepsy is currently **not curable**, meaning therapy is purely geared toward the symptoms. The goal of therapy is to **reduce symptoms** as much as possible. In cases of daytime sleepiness, this would mean, for instance, that patients can return to their professions full time. With regard to REM-dissociated symptoms, cataplexies should be avoided.

The narcolepsy treatment approach with medications involves two basic types of efficacy: Stimuli and medications for the treatment of REM symptoms. Using **gamma-hydroxybutyrate** (GHB), which is supposed to improve daytime sleepiness as well as the REM symptoms at the same time, is a new approach.

<table>
<thead>
<tr>
<th>Medications for the treatment of narcolepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Substance</strong></td>
</tr>
<tr>
<td>Modafinil</td>
</tr>
<tr>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Clomipramine</td>
</tr>
<tr>
<td>SSRIs: Fluoxetine, reboxetine, venlafaxine</td>
</tr>
</tbody>
</table>
**Gamma-hydroxybutyrate**

| Gamma-hydroxybutyrate | Daytime fatigue, REM symptoms, fragmented nighttime sleep | 6 – 9 g | Schedule IV of the Convention on Psychotropic Substances, short half-life, second dose must be taken in the middle of the night |

Source: A. Bender et al.: mediscript Kurzlehrbuch Neurologie. Elsevier Verlag 2013. S. 174, Tab.5.6

The treatment approach without medications consists of **short naps**. These short naps should not exceed 30 minutes and may enable the patient to drive a car again, for instance. It is very important to provide the patient with a thorough consultation regarding work environment, recreational activities, and dangerous situations as sudden cataplexy attacks can lead to severe falls.

**Future therapies:** Medications are being developed that facilitate the replacement of the destroyed hypocretin-producing cells.

### Restless Legs Syndrome (RLS)

**Case study:** A patient (52 years old) states to have noticed the first symptoms two years ago. The “restless legs” grew steadily worse over time. Especially during the evening hours, a very unpleasant urge to move develops. During the night, he wakes up two or three times and is then awake in bed for an extended period of time without being able to go back to sleep. In addition, he developed increased daytime sleepiness over the past several months. Aside from slight hypertension, no other illnesses are known.

**Etiology and Epidemiology of Restless Legs Syndrome**

Restless legs syndrome is among the **movement disorders** that primarily occur at night. Due to these **nocturnal** symptoms, RLS is also considered a sleep disorder. Approximately two percent of the population is affected by a severe form of RLS, approximately 20% deal with a milder form.

The pathophysiology has not been determined yet. Most likely, a **disturbance of the transmitter metabolism** in the brain is present. This disturbance seems to particularly affect the **dopaminergic system** as affected individuals almost always respond to dopamine medication. Secondary RLS develops from other underlying illnesses such as renal insufficiency, iron deficiency, rheumatoid arthritis, and intervertebral disc disorder.
Restless Legs Syndrome Symptoms

Central symptoms are „creepy crawly“ feelings in both legs. In most cases, the lower legs and also the thighs, the arms and the trunk are affected. When taking the patients’ history into account, they often have difficulty to put the symptoms into words: Burning, crawling, an unpleasant urge to move.

The symptoms occur at rest, mostly at night. When moving, while receiving massages or when taking baths, etc., these feelings almost completely disappear. A hallmark of the disease are the resulting sleep disorders that are characterized by trouble falling/staying asleep as well as waking up numerous times.

Diagnosing Restless Legs Syndrome

RLS is usually diagnosed clinically.

Clinical and medical history criteria

- Urge to move, usually associated with sensory symptoms (feelings in extremities on either one or both sides such as crawling, pulling, tearing, itching, burning, cramps or pain)
- Motor restlessness (restlessness, stretching or moving of legs, walking around, tossing and turning in bed, rubbing or massaging of legs)
- Symptoms appear or grow worse at rest (movement temporarily reduces the symptoms)
Symptoms grow worse toward the evening or overnight

Other criteria

- Sleep disorders (trouble falling and/or staying asleep, daytime fatigue, exhaustion)
- Involuntary movements
- Possible positive family history (autosomal dominant inheritance).

It is particularly important, however, to rule out secondary causes of RLS. Please refer to the following table.

### Secondary Causes of RLS, Diagnostics and Therapy

<table>
<thead>
<tr>
<th>Secondary cause</th>
<th>Diagnostics</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Levels of ferritin (goal &gt; 50 μg/l or better &gt; 80 μg/l)</td>
<td>Substituting oral ferrous sulfate</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>Clinical examination, EMG/NLG</td>
<td>Improving the underlying polyneuropathy cause, treatment of symptoms</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Lab test (uremia)</td>
<td>Treating the renal insufficiency</td>
</tr>
<tr>
<td>Hypothyreosis</td>
<td>Lab test (thyroid function)</td>
<td>Substitution, treating the thyroid disorder</td>
</tr>
<tr>
<td>Vitamin deficiency</td>
<td>Lab test (vitamin B12 and folic acid)</td>
<td>Substitution, possibly treating malabsorption</td>
</tr>
</tbody>
</table>

Source: A. Bender et al.: mediscript Kurzlehrbuch Neurologie. Elsevier Verlag 2013. S. 175, Tab. 5.7

The severity of RLS is evaluated using the RLS severity score. In cases of unclear diagnoses, polysomnography should be performed in order to rule out other sleep disorders. A vascular cause for a differential diagnosis may be peripheral arterial occlusive disease. The symptoms of intermittent claudication (claudicatio intermittens), however, improve with rest and not when moving.

### Restless Legs Syndrome Therapy
If the patient suffers from secondary RLS, the underlying disease should obviously be treated (refer to table). When only mild symptoms are present, even a slight change in lifestyle may be helpful, such as eliminating caffeine, physical activity, and a regular sleep pattern.

In severe cases of RLS (daily symptoms), therapy with dopamine may help.

**Restless legs syndrome therapy schedule**

<table>
<thead>
<tr>
<th>Severity of RLS</th>
<th>Drug class</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>L-DOPA</td>
<td>L-DOPA decarboxylase inhibitor</td>
</tr>
<tr>
<td>Moderate to severe Augmentation</td>
<td>Dopamine agonists</td>
<td>Pramipexole, rotigotine, ropinirole</td>
</tr>
<tr>
<td>Augmentation while on L-DOPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augmentation while on dopamine</td>
<td>Opiates</td>
<td>Tildine, tramadol</td>
</tr>
<tr>
<td>agonists Augmentation while on</td>
<td>Anticonvulsants</td>
<td>Gabapentin, pregabalin, carbamazepine, valproate</td>
</tr>
<tr>
<td>dopamine agonists Augmentation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. The pathophysiological cause of restless legs syndrome most likely appears to be in which transmitter system? In the...

   A. cholinergic system
   B. dopaminergic system
   C. noradrenergic system
   D. glutamatergic system
   E. serotonergic system

3. Which medication treats REM-associated symptoms as well as the daytime sleepiness associated with narcolepsy?

   A. Modafinil
   B. Methylphenidate
   C. Gamma-hydroxybutyrate
   D. Clomipramine
   E. Venlafaxine

References


Correct answers: 1E, 2B, 3C

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