

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

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Permanent sleepless nights and 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 rapid eye movement (REM) sleep behavior disorders and sleep myoclonus. Particular focus is given to narcolepsy and restless legs syndrome. This article is concisely prepared with a focus on the exam and will leave no questions concerning sleep disorders in neurology unanswered.



Fundamentals of Sleep Disorders

Sleep disorders are divided into 2 subtypes: **dyssomnias** and **parasomnias**.

Dyssomnias

Dyssomnias are subdivided into hypersomnias and hyposomnias.

Hypersomnias (too much sleep)	Hyposomnias (too little sleep)
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<p>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 awakening resulting in a massive disruption of the sleep architecture. Patients are sleepy during the day and have trouble concentrating.</p>	<p>Difficulty falling and staying asleep and waking up during the night due to variable causes, i.e. depression.</p>
<p>Narcolepsy: sudden sleep attacks during the day that last several minutes (see below)</p>	<p>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.</p>

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:** sleepwalking
- **Somniloquy:** sleepwalking
- **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, 2 diagnostic tools are particularly significant: **electroencephalogram (EEG)** and **polysomnography** showing the result of the **hypnogram** (sleep profile).

Interpreting the EEG

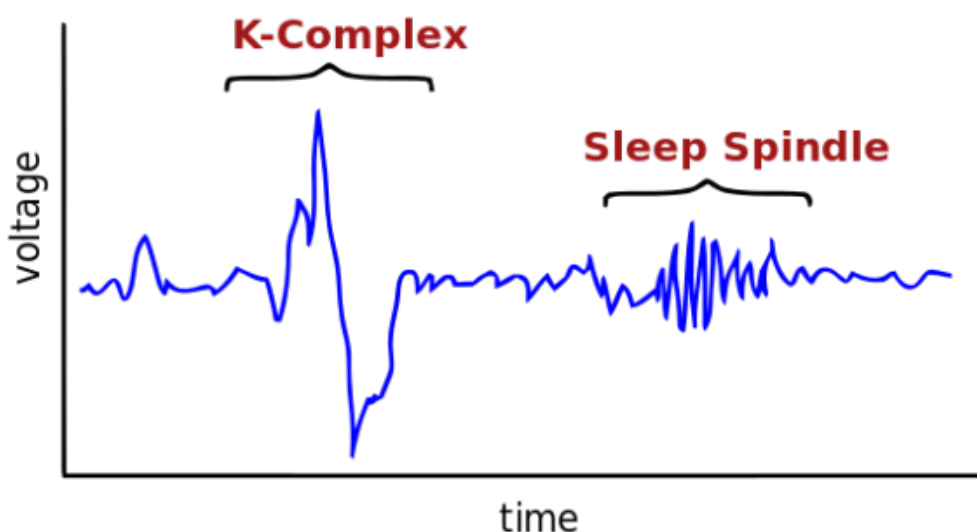


Image: 'A fictional EEG showing a sleep spindle and K-complex in stage 2 sleep' by

Neocadre. License: [Public domain](#)

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 2 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 2.

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

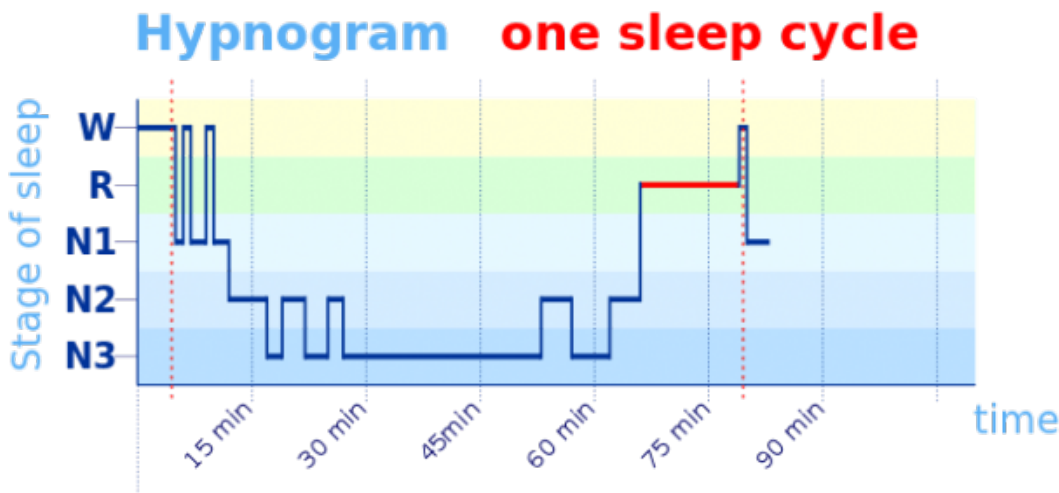


Image: "Hypnogram - one sleep cycle" by Schlafgut. License: [CC BY-SA 3.0](#)

The REM Sleep Behavior Disorder

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 of time, patients may acquire **Parkinson's disease**, **Lewy body dementia**, and **multiple sclerosis**.

Therapy: Symptomatic treatment consists of administering clonazepam in the evening (0.5–2 mg).

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 a 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 2 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 her glasses on numerous occasions when she laughed about a joke (via [Pharmazeutische Zeitung](#)).

The etiology and epidemiology of narcolepsy

Due to its association with the human leukocyte antigen (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 the 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 25–50 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

atonic 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, and circadian rhythm disorder
- **Psychiatric and neurological disorders:** depression, alcohol and drug dependency, dementia, and neurodegenerative disorders
- **Other disorders:** shift work, sleep disorder, post-traumatic hypersomnia, and chronic fatigue syndrome

Differential diagnoses for cataplectic attacks:

- **Neurological disorders:** epilepsy, muscular disorders, drop attacks, balance disorders, and tremor
- **Internal diseases:** syncope, falls associated with polyneuropathy
- **Other disorders:** psychogenic attacks and 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 fulltime. With regard to REM-dissociated symptoms, cataplexies should be avoided.

The narcolepsy treatment approach with medications involves 2 basic types of efficacy: stimuli and medications for the treatment of REM symptoms. The use of **gamma-hydroxybutyrate** (GHB), which is supposed to improve daytime sleepiness, as well as the REM symptoms at the same time, is a new approach.

Medications for the treatment of narcolepsy			
Substance	Symptoms:	Daily dose	Side effects and special features
Modafinil	Daytime fatigue	200 - 400 mg	—
Methylphenidate	Daytime fatigue	10 - 60 mg	Schedule 2 drug under the Convention on Psychotropic Substances
Clomipramine	REM symptoms (i.e. cataplexy)	10 - 150 mg	Anticholinergic syndrome
SSRIs: Fluoxetine, reboxetine, venlafaxine	REM symptoms	Depending on the substance	Serotonin syndrome

Gamma-hydroxybutyrate	Daytime fatigue, REM symptoms and fragmented nighttime sleep	6 - 9 g	Schedule 4 of the Convention on Psychotropic Substances; short half-life - second dose must be taken in the middle of the night
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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 and recreational activities; dangerous situations such 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 2 years ago. The 'restless legs' grew steadily worse over time. During the evening hours, a very unpleasant urge to move has developed. During the night, he wakes up 2 or 3 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 RLS

RLS is 1 of the **movement disorders** that primarily occur at night. Due to these **nocturnal** symptoms, RLS is also considered a sleep disorder. Approx. 2 percent of the population is affected by a severe form of RLS. Approx. 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.

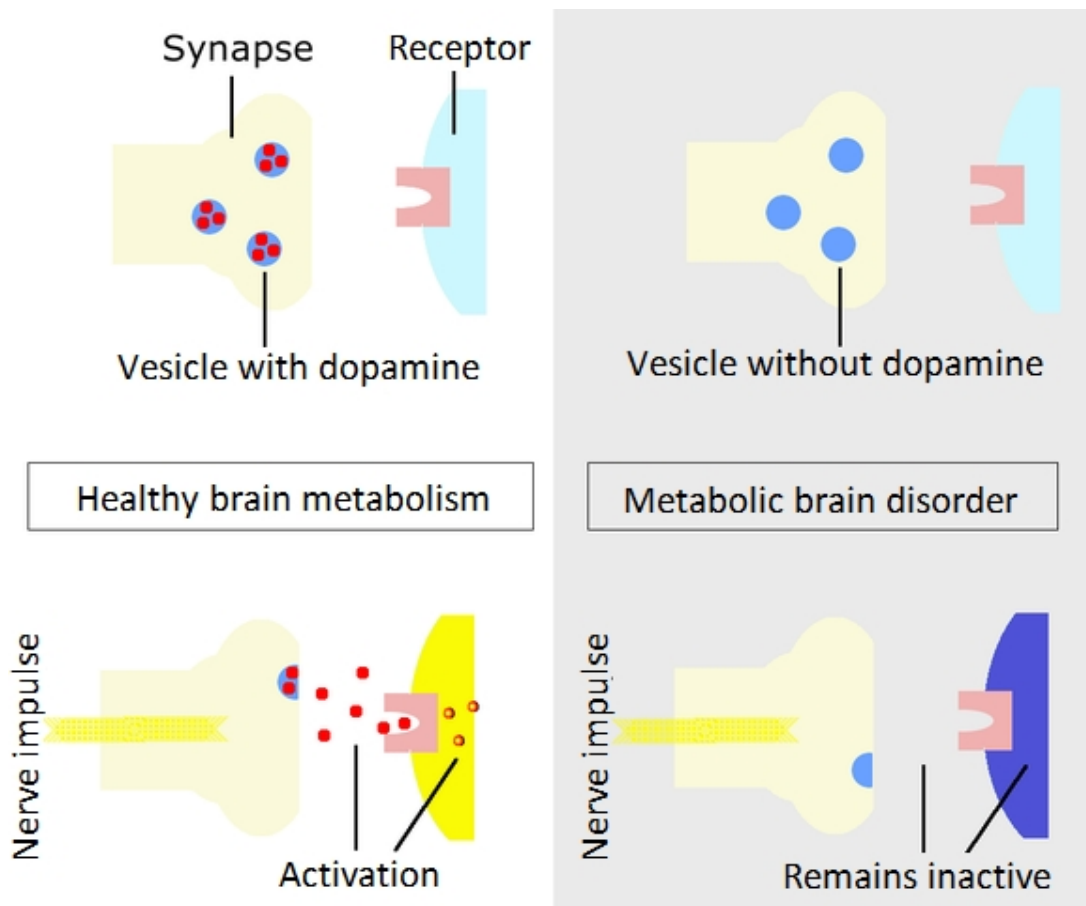


Image: 'Normally functioning and disturbed activation in dopamine metabolism' by Markus Mueller. License: [CC-SA BY 3.0](https://creativecommons.org/licenses/by/3.0/)

RLS symptoms

The 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, and 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 is the resulting sleep disorders that are characterized by **trouble falling/staying asleep** as well as **waking up numerous times**.

Diagnosing RLS

RLS is usually diagnosed clinically.

Clinical and medical history criteria

- The urge to move, usually associated with sensory symptoms (feelings in extremities on either 1 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, and exhaustion)
- Involuntary movements
- Possible positive family history ([autosomal dominant inheritance](#))

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

Secondary causes of RLS, diagnostics, and therapy

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

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

RLS therapy

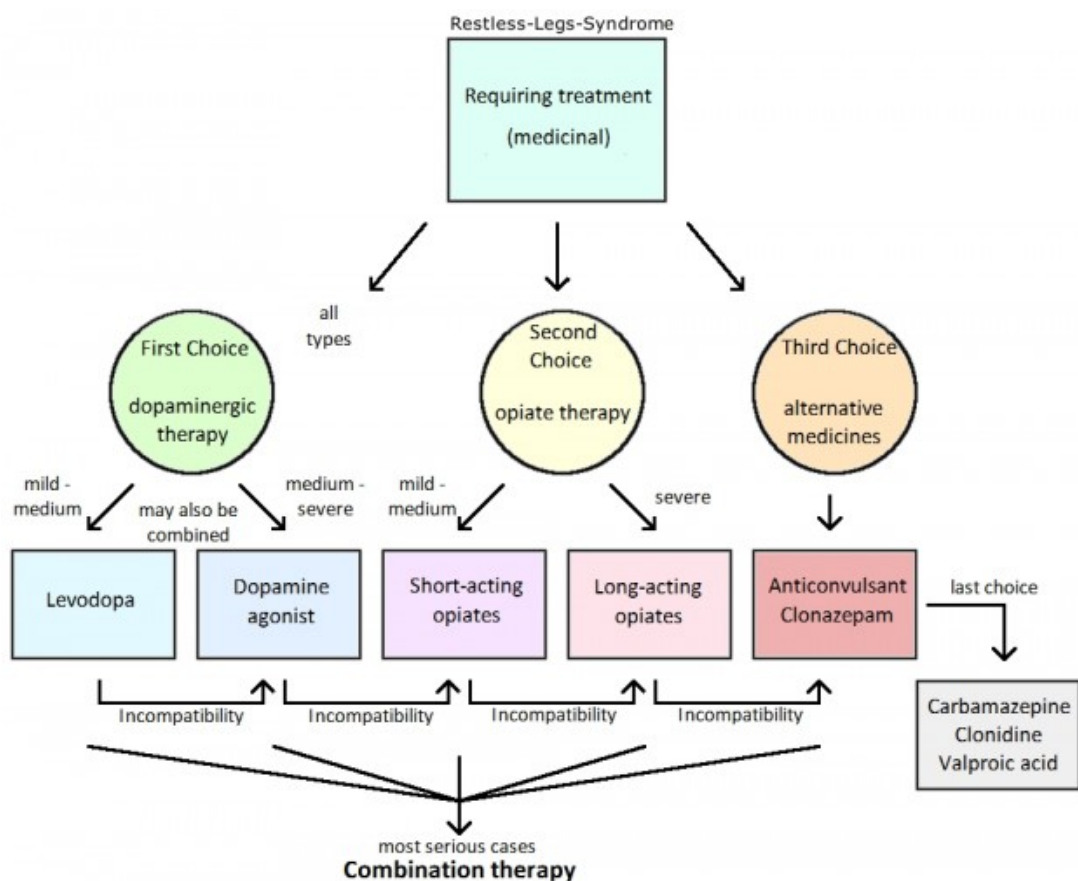


Image: 'Treatment scheme for Restless Legs Syndrome' by Markus Mueller. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

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.

RLS therapy schedule

Severity of RLS	Drug class	Substances
Mild	L-DOPA	L-DOPA decarboxylase inhibitor
Moderate to severe	Dopamine agonists	Pramipexole, rotigotine, and ropinirole
Augmentation while on L-DOPA		
Augmentation while on dopamine agonists	Opiates	Tilidine and tramadol
	Anticonvulsants	Gabapentin, pregabalin, carbamazepine, and valproate

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