Restless Legs Syndrome and Management

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Goal. The goal of this lesson is to review restless legs syndrome, with emphasis on presenting key points of information to pass along to patients.

Objectives. At the completion of this activity, the participant will be able to:

1. demonstrate knowledge of restless legs syndrome including its causes and triggers, epidemiology and prevalence, pathogenesis, and clinical impressions;
2. explain the mechanism of action and major adverse events associated with the drugs used in treating restless legs syndrome;
3. select nonpharmacologic measures that are reported to modify symptoms of restless legs syndrome; and
4. demonstrate an understanding of information relative to restless legs syndrome to convey to patients and their caregivers.

Background

Restless legs syndrome (RLS), also known as Ekbon’s syndrome, was named after Swedish neurologist/physician Karl Ekbon. In the mid-1940s, Ekbon described the condition as a common and distressing condition, but one that is readily treatable. Two to 15 percent of the general population of the United States may experience RLS symptoms, although the exact prevalence may be much higher because it is generally held that many patients fail to discuss their symptoms with healthcare providers. Patients may believe their condition is too insignificant with which to bother their physician, or they may not recognize that RLS can be symptomatic of more serious pathology that requires physician intervention. A sensorimotor (both sensory and motor) neurologic movement disorder, RLS causes patients to experience an almost irresistible urge to move their legs. Usually worse during periods of inactivity or rest, walking or other physical activity involving the legs can usually alleviate the sensations. Often associated with a sleep complaint, the inability to rest can have a negative impact on the patient’s quality of life due to agitation, discomfort, frequent waking, chronic sleep deprivation and stress. These conditions, in turn, can negatively affect job performance, social activities, and family life. Disturbed sleep and inability to tolerate sedentary activities can lead to a compromised ability to enjoy life, and serious problems maintaining relationships.

RLS hardly receives the attention it deserves. It has attracted little attention in medical textbooks until recently. A study conducted jointly in the United States and Europe suggests that the condition is not only under-reported, but also greatly under-diagnosed and under-treated. A 1996 report described the outcome of a group of patients who delayed seeking medical help for many years, but even after they did receive help, accurate diagnosis frequently took a decade or more. The Restless Legs Syndrome Foundation has taken account of these observations and often reminds its constituency that RLS is “the most common disorder you have never heard of!”

This lesson describes RLS, including its clinical features and medical management. It stresses information that will be useful not only to pharmacists, but also to patients who experience the condition.

Epidemiology and Prevalence

RLS can affect persons of any race or ethnic group, but it is more common in persons of Northern European descent. African Americans are affected significantly less often than Caucasians. Its prevalence is distinctly lower in Asian populations, ranging from 0.1 percent in
Etiology and Pathophysiology

Although RLS is a disorder of the central nervous system, it is not a psychophysiologic pathology; however, it may contribute to or be exacerbated by such conditions. RLS can generally be categorized into primary (idiopathic) and secondary forms. Primary RLS is not related to other identifiable abnormalities; secondary RLS is associated with an underlying pathology. When no specific cause can be identified for initiating RLS symptoms, it is considered a primary condition.

It is thought that RLS may be due to dysfunction of dopamine-producing cells in the nigrostriatal areas of the brain. Pharmacologic studies have shown a dramatic improvement in RLS symptoms with administration of levodopa, the precursor of dopamine, or with dopaminergic agonists that act on dopamine receptors in the brain. Conversely, dopamine antagonists will worsen symptoms in patients with RLS. Advanced brain imaging has revealed decreased dopamine D2 receptor binding in the striatum of patients with RLS. Hypoactive dopaminergic neurotransmission in RLS has recently been demonstrated and study results suggest that both striatal and extrastriatal brain regions are involved.

The high incidence (40 to 60 percent) of familial cases of RLS strongly suggests a genetic origin for primary RLS, especially if the condition onsets at an early age. Family and twin studies have proposed both autosomal-dominant as well as recessive modes of inheritance. Genetic studies suggest several chromosomal loci associated with RLS. At present, five loci have been mapped for RLS in single families, and three susceptibility loci have been identified in a genome-wide association study. Secondary causes of RLS are more common in persons who develop symptoms for the first time in later life; secondary RLS occurs in over 70 percent of persons with onset at age 65 years or more. It is important to rule out secondary RLS when attempting to control symptoms.

Secondary Causes. A number of secondary causes of RLS have been identified. For example, symptoms of RLS may be associated with iron deficiency. A patient’s iron stores may be deficient without causing anemia. Studies have shown that decreased iron stores (i.e., ferritin levels below 50 µg/L) can exacerbate RLS symptoms. Iron is an essential cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis. Animal studies demonstrate that iron deficiency is associated with hypofunction of dopamine D2 receptors that is corrected by iron replacement. The fact that the extent of iron deficiency correlates well with symptoms and that iron is an effective therapy, at least in iron-deficient patients, provide strong support for the role of iron deficiency in the pathogenesis of some patients with RLS. Physiologists often order serum ferritin levels in patients with newly diagnosed RLS or RLS patients with a recent exacerbation of symptoms. Once iron levels are corrected (discussed subsequently), symptoms are reduced.

RLS has been reported in persons with spinal cord and peripheral nerve lesions, and in patients with vertebral disc disease. The exact pathological mechanism remains unknown.

RLS occurs in up to one-half of patients with end-stage renal failure. Symptoms may be especially bothersome during dialysis when the patient is in a forced resting position. Improvement in RLS symptoms has been shown after renal transplantation.

One in five women experience symptoms during pregnancy, especially in their last trimester. Some women, in fact, report RLS for the first time during pregnancy. Symptoms can be severe, but usually subside within four weeks postpartum.

RLS symptoms may be worsened or unmasked by a variety of medications (Table 1). As a group,
antidepressants are the drugs most commonly implicated in secondary RLS with almost all classes reported to worsen symptoms. Persons with RLS who take one or more of the listed drugs are advised to discuss with their physician the possibility of changing medications to improve symptoms.

Clinical Assessment
A diagnosis of RLS is based primarily on a careful patient history and detailed physical and neurological examination. There is no laboratory test that can confirm the presence of RLS. The patient’s physical examination is often normal, except for those who have symptomatology suggestive of a secondary form of RLS or a comorbid condition.

Symptoms may be described by patients as ranging from mild to intolerable. Due to the subjective nature of the disorder, however, patients often experience difficulty in describing their symptoms. Oftentimes their sensation defies description (Table 2). Confirmation of RLS is not easy. A population study showed that a large number of patients do not seek medical aid because of their motor condition, but rather because of the consequences of their disorder such as insomnia or decreased quality of life.

Most patients with RLS experience the feelings in their lower legs (calves); however the aggravating sensations may also occur any place in the legs or feet. They may also occur in the arms or elsewhere. The feelings seem to originate from deep within the limbs, rather than from the joints, or on the surface. The sensations are usually bilateral, but may occur in one leg, move from one leg to the other, or affect one leg more than the other. The pain is more of an ache rather than sharp, jabbing pain. Symptoms are generally worse in the evening and night, and less severe in the morning. Symptoms appear with rest, sitting or lying down. The more comfortable the patient is, the more likely it is that RLS symptoms will occur. The reverse is also true – the less comfortable the patient is, the less likely it is that symptoms will onset. As a result, some patients may prefer to sleep on a hard surface including the floor rather than in a comfortable bed. The condition should be distinguished from sleep-related disorders of the legs.

Periodic Limb Movements in Sleep. The presence of repetitive and highly stereotypic periodic limb movements in sleep (PLMS) supports, but does not confirm, a diagnosis of RLS. PLMS is also known as periodic limb movement disorder, and was formerly referred to as myoclonus. PLMS is noted as repetitive movements, typically in the lower limbs, that occur every 20 to 40 seconds. Symptoms can also occur in the arms. Hundreds of these involuntary, rhythmic muscular jerks in the lower limbs may occur, sometimes throughout the night. Affected persons are often not aware they are experiencing the movements. In a person with severe RLS, these involuntary kicking movements may also occur while awake. PLMS is common in older adults, even those without RLS, and does not always disrupt sleep. Eighty percent of persons with RLS also experience PLMS, which correlates with RLS severity, but less than half of those with PLMS also have RLS.

### Table 2
Terms patients may use when describing RLS symptoms

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Aching</td>
<td>Flowing water</td>
</tr>
<tr>
<td>Burning</td>
<td>Numb</td>
</tr>
<tr>
<td>Buzzing</td>
<td>Painful</td>
</tr>
<tr>
<td>Cramping</td>
<td>Pulling</td>
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<tr>
<td>Crawling</td>
<td>Restless</td>
</tr>
<tr>
<td>Creeping</td>
<td>Searing</td>
</tr>
<tr>
<td>Drawing</td>
<td>Tense</td>
</tr>
<tr>
<td>Electric current-like</td>
<td>Tingling</td>
</tr>
<tr>
<td>Gnawing</td>
<td>Tugging</td>
</tr>
<tr>
<td>Indescrivable</td>
<td>Uncomfortable</td>
</tr>
<tr>
<td>Itching</td>
<td>Feeling of worms or bugs crawling under my skin</td>
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Essential Criteria that Confirm RLS. The International Restless Legs Syndrome Study Group in collaboration with the National Institutes of Health has established criteria for diagnosis of RLS

### Table 3
Criteria for diagnosis of RLS

**Diagnostic criteria**
- Compelling urge to move the limbs, usually associated with paresthesias/dyesthesias
- Motor restlessness as noted in activities such as floor pacing and rubbing the legs
- Symptoms present or worse during rest, with temporary relief by activities such as walking or stretching, at least as long as the activity continues
- Symptoms worse in evening and at night than during the day, or occur only in the evening or night

**Supportive clinical features**
- Sleep disturbance and daytime fatigue
- Normal neurological examination in primary RLS
- Involuntary, repetitive, periodic jerking limb movements during sleep or while awake
- Positive family history of RLS
- Positive response to dopaminergic therapy

**Associated features**
- Natural clinical course: Onset age is variable, in patients with earlier onset (<50 years) the symptoms are insidious, while patients with later onset have a more aggressive course. RLS is usually a chronic disease with a progressive clinical course; in the mildest forms of RLS, the clinical course can be static or intermittent.
- Sleep disturbances: disturbed sleep is usually associated with RLS.
- Medical evaluation/Physical examination: physical and neurological examination is generally normal (except for secondary RLS). Medical evaluation should be addressed to identify possible causes for secondary RLS.

*Minimal criteria for positive diagnosis of RLS
+Supportive clinical features common in RLS but not required for diagnosis
§These features may provide additional information about the patient’s diagnosis
Four essential criteria must be present to establish a positive diagnosis. A mnemonic to help remember these points is URGE: Urge to move, Rest induced, Gets better with activity, Evening and night accentuation. In the absence of the core clinical features of RLS, a positive diagnosis of RLS cannot be made, and other causes of PLMS or isolated periodic limb movement disorder must be considered. The relation between PLMS and RLS is unclear, but treatments used for RLS may also be effective in PLMS as well. The presence of supportive and associated clinical features as shown in Table 3 is not necessary for a positive diagnosis, but they are definitely helpful to the differential diagnosis.

Differential Diagnosis. RLS should be differentiated from other conditions including:

- Nocturnal Leg Cramps. These typically include painful, palpable, involuntary muscle contractions, often focal, with a sudden onset. Nocturnal leg cramps are usually unilateral.
- Akathisia. This is a closely related disorder, described as a condition of motor restlessness, ranging from a sense of inner disquiet, to inability to sit or lie quietly or to sleep, with no sensory complaints. The restlessness is generalized and internal rather than localized to the limbs and associated with paresthesias. Akathisia often does not correlate with rest or time of day, and often results as a side effect of medication such as neuroleptics or other dopamine blocking agents.
- Peripheral Neuropathy. This can cause leg symptoms that are different from RLS. Symptoms are usually neither associated with motor restlessness nor lessened by movement. The condition is not worse during the evening or nighttime. Sensory complaints include numbness, tingling or pain. Small fiber sensory neuropathies such as those seen in diabetes mellitus may be confused with RLS. Patients with neuropathies may have both neuropathic and RLS symptoms.
- Vascular Disease. Conditions such as deep vein thrombosis can be confused with RLS.

RLS in Children

Although RLS is generally discussed as a disease of adults, over the past 20 years there has been increasing recognition that it also occurs in children. Adults with the diagnosis often retrospectively recall having had symptoms during their childhood. Case series have described children as young as 18 months of age with features of RLS.

Diagnosing RLS in children is particularly difficult because clinicians rely heavily on the patient's description of symptoms. Even for adults with RLS, an accurate description of its subjective symptoms may be difficult. Children may describe RLS symptoms differently than adults, using terms such as ouchies, tickle, spiders, twitchy, jerky, boo-boos, want to run, and a lot of energy in my legs. Or, children may have at least two of the following: sleep disturbance, a biological parent or sibling with RLS, or polysomnographic-documented PLMS. Determining RLS in children can be aided using the same four criteria as for adults (see Table 3).

According to a recent survey of more than 10,000 families in the United States and the United Kingdom, RLS affects about 2 percent of children. A pediatric RLS prevalence of 5.9 percent was noted at one pediatric sleep disorders clinic. Another study found a prevalence of 1.3 percent in 12 pediatric practices, and another reported its occurrence in 6.1 percent of Canadian children ages 11 to 13 years. The U.S./U.K. study found a strong genetic component to RLS. More than 70 percent of children with RLS had at least one parent with the condition. There is also evidence suggesting that children with attention deficit hyperactivity disorder (ADHD) and a family history of RLS are at risk for more severe ADHD.

Most children with RLS do not require pharmacologic treatment and indeed, there are no FDA-approved drugs for use in children with RLS. Case histories and anecdotal reports suggest it is best to begin with good sleep hygiene measures, cognitive behavioral therapy and caffeine restriction (including restriction of caffeinated soft drinks). If these measures are ineffective, screening for anemia and checking the patient's serum ferritin level makes sense. For children, elemental iron in doses of 3 mg/kg/day given for three months was shown to improve PLMS and clinical symptoms, but more data are needed to determine effectiveness in pediatric RLS. Dopaminergic drugs used "off-label" in children have been shown to improve RLS symptoms. In cases of associated ADHD, dopaminergics may benefit ADHD symptoms as well.

Treatment in Adults

There is no cure for primary RLS. Both nonpharmacologic measures and pharmacotherapy, however, are helpful in relieving symptoms in many patients. It is important to note that both severity and frequency of RLS are variable; therefore, nonpharmacologic therapies alone may be appropriate for milder forms of RLS and indeed, these measures should be considered first in all but the most severe cases. It is also important to note that many pharmacologic agents are used in an "off-label" basis. Successful treatment for secondary RLS requires treating the underlying cause. Goals of treatment are to prevent or relieve symptoms, increase the amount and improve the quality of sleep, and treat or correct any underlying condition that may trigger or worsen RLS.

Lifestyle and Behavioral Changes. For those with mild-to-moderate symptoms, prevention is key to their control. In general, simple lifestyle changes that promote good health can play an important role in alleviating symptoms of RLS. The measures listed in Table 4 may help reduce the discomfort and excessive leg movements. The websites listed in Table
Drugs will work predictably for all patients. Treatment must therefore be individualized. Selection of pharmacologic agents is influenced by a number of factors, including:

- **Patient Age.** Benzodiazepines, for example, may cause cognitive impairment in elderly patients.
- **Symptom Severity.** Patients with mild symptoms may elect to forgo using medications due to cost, adverse effects or other reasons. Others may benefit from a dopaminergic agent or a dopamine agonist. Severe symptoms may require a strong opioid.
- **Symptom Frequency.** Persons with infrequent symptoms may benefit greatly from a single dose of medication given on an as-needed basis, such as an opioid or levodopa.
- **Pregnancy.** Neither safety nor efficacy of medications for RLS has been assessed in clinical trials involving pregnant women.
- **Renal Failure.** Most pharmacologic agents are generally safe in patients with renal failure, although dose frequency and quantity may be modified if the drugs are excreted via the kidney. Moreover, for dialysis patients, some medications are dialyzable (e.g., gabapentin) while others are not.

**Dopaminergic Agents.**

Discovery that levodopa was effective in RLS revolutionized its management. Every dopaminergic agent tested has been shown to be effective against RLS and PLMS. Levodopa/carbidopa (Sinemet® and others) provides near-immediate relief from RLS. The response is so characteristic that a brief course of therapy may be considered in patients whose diagnosis of RLS is in doubt. Levodopa is also effective in hemodialysis patients with RLS. In general, the drug is very well tolerated. Levodopa-induced dyskinesias have not been reported in RLS patients.

Two troublesome and common problems develop with prolonged use of levodopa, which limits the value of this otherwise almost ideal agent for RLS: rebound and augmentation. Rebound is an outcome of the drug’s short half-life; after a while, patients start to awaken early in the morning with recurrence of their RLS. Sustained-release formulations can delay onset of rebound until later in the morning, although the long-term efficacy of this approach remains unknown. Augmentation is more serious. It may shorten symptom-free periods at rest. Also, symptoms develop earlier in the day (morning or afternoon instead of evening or night) and may become more severe; and symptoms may develop in parts of the body that were not previously involved. Augmentation occurs in up to 80 percent of patients treated with levodopa as early as four weeks into treatment. Approximately one-third have sufficiently severe symptoms that warrant a change in therapy. The precise mechanisms contributing to augmentation are unknown. The need for higher doses of levodopa and development of more severe RLS may predict development of this complication. Levodopa is, therefore, no longer the treatment of choice for RLS, although it remains a therapy of choice for persons with only intermittently severe symptoms.

**Dopamine Receptor Agonists.** These are now regarded as the first-line treatment for RLS.
The non-ergot agonists ropinirole and pramipexole have been shown to benefit RLS in randomized controlled trials. There is no indication based on the numerous comparative clinical trials reported for the dopamine receptor agonists that efficacy of one agent is better than another. The drugs are chemically distinct from dopamine, but their mechanism of action in the central nervous system is similar to that of the endogenous neurotransmitter.

Studies suggest that the drugs are well tolerated in patients with severe RLS who have failed other therapies and in those with augmentation. Augmentation and tolerance have been reported, although at a much lower incidence than seen with levodopa, and they seem more likely to occur in patients who previously developed similar problems with levodopa. Dose reduction may be required if augmentation or tolerance develop, but, unlike with levodopa, a change in medication is rarely needed. Several reports of unusual compulsive behaviors occurring in persons taking dopamine receptor agonists include pathological gambling and increased sexuality.

**Other Medications.** The therapeutic effect of opioids is well known. Intermittent use of low-potency opioids or opioid receptor agonists, usually taken before bedtime, can be effective. Studies have shown positive short-term and long-term responses of various opioids. In severe disease, opioids may be considered a second-choice treatment after dopaminergic agents. There is a chance for dependence, and these drugs should be used with caution in persons with a history of addiction.

**Benzodiazepines or benzo-diazepine receptor agonists,** taken before sleep, may be useful. This is especially relevant if the patient has another cause of poor sleep in addition to RLS, such as psychophysiologic insomnia. Most data have been derived with clonazepam (Klonopin®), and others. Some investigators have shown this drug to be well tolerated in older patients; however, its long duration of action may result in more adverse effects, such as an unsteadiness leading to falls during the night and drowsiness or cognitive impairment in the morning.

**Antiepileptics** including carbamazepine (Tegretol®), and others and gabapentin (Neurontin®), and others, have been reported to be efficacious in treating RLS, but are not commonly used in clinical practice due to their high incidence of adverse effects. Antiepileptics may be effective in patients with RLS who also suffer from painful paresthesias or underlying neuropathy. The most recently approved drug for RLS, gabapentin enacarbil (Horizant®) is a prodrug of gabapentin and accordingly, its therapeutic effects in RLS are attributable to gabapentin.

The management of RLS continues to evolve as new drugs become available. Cabergoline (Dostinex®, and others), a dopamine agonist, is of interest because of its long half-life (65 hours). This theoretically might produce less augmentation. Magnesium has been reported in a small open-label trial to be an effective therapy for RLS.

**Selecting the Best Treatment for a Particular Patient.** This usually proceeds in a “hit or miss” manner. Drugs should be used at their lowest effective dose, and only when necessary should the dose be slowly titrated upward. Medication should be taken early enough to permit absorption and action before the onset of sleep. Divided doses may be needed, often provided with the evening meal and later at night. If the first drug does not work, then a second agent with a different mode of action should be substituted. Sometimes a combination of medications works better than any single agent.

**Iron Replacement in Secondary RLS.** As noted earlier, a serum ferritin concentration below 45 to 50 µg/L has been associated with increased severity of RLS.

A common treatment regimen is 325 mg ferrous sulfate three times daily along with 100 to 200 mg vitamin C with each dose to enhance absorption. Oral iron can cause constipation and abdominal discomfort, and the dose may need to be reduced in some patients. Oral iron should ideally be taken on an empty stomach to enhance absorption. If gastrointestinal symptoms develop, it should be taken with food. Follow-up ferritin determinations are indicated, initially after three to four months and then every three to six months until the serum ferritin level is greater than 50 µg/L. Iron therapy can then be discontinued. For patients with severe iron deficiency (ferritin ≤10 µg/L) and oral iron intolerance, intravenously administered iron can be considered. Of note is that RLS does not always respond to an increasing serum ferritin concentration, even if it was low initially.

**Prognosis**

RLS is usually a lifelong condition that has no cure. Although it has a variable course, symptoms may gradually worsen with age, albeit more slowly for those with the primary form of RLS than for patients who also suffer from an associated medical condition. Nonetheless, current therapies can control RLS, minimizing symptoms and maximizing periods of restful sleep. Some patients experience remissions, periods during which symptoms decrease or disappear for days, weeks or months; however, symptoms usually reappear. A diagnosis of RLS that onsets during adulthood does not indicate the onset of another neurologic disease. Individuals with RLS secondary to an underlying condition may note resolution of symptoms when their underlying condition is treated. Medication, when needed, usually provides relief of symptoms.

**Summary and Conclusions**

RLS is a common but under-recognized disorder associated with discomfort in the legs that is hard to describe and a distressing urge to
move them. It increases in frequency with aging, but is also found in children. Sleep disruption in RLS may impact daytime functioning and quality of life. For patients with mild symptoms, no drug treatment may be necessary; nonpharmacologic measures may be all that is needed. In patients with moderate to severe, troublesome symptoms, a dopamine receptor agonist is the current treatment of choice, although it should be noted that there have been few satisfactory studies comparing different pharmacotherapies. If dopamine agonists are poorly tolerated or ineffective, levodopa may be a satisfactory option for many people, especially for those with intermittent symptoms, such as during a long trip or sitting through a boring lecture! It takes only 15 to 30 minutes to become effective, and augmentation is not a risk with intermittent use.
Restless Legs Syndrome and Management

1. Restless Legs Syndrome (RLS) is:
   a. a motor disorder.
   b. a sensory disorder.
   c. both a motor and a sensory disorder.
   d. neither a motor nor a sensory disorder.

2. RLS is more common in which of the following groups of people?
   a. African Americans   c. Asian Americans
   b. Northern Europeans   d. Southern Europeans

3. RLS is NOT a psychophysiologic pathology.
   a. True   b. False

4. An essential cofactor for tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis, is:
   a. magnesium.   c. calcium.
   b. iodine.   d. iron.

5. The group of drugs most commonly implicated in secondary RLS is the:
   a. antidepressants.   c. antipsychotics.
   b. antiepileptics.   d. antirheumatics.

6. Diagnosis of RLS can be easily determined by a specific laboratory test.
   a. True   b. False

7. Periodic limb movement disorder was formerly referred to as:
   a. dyskinesia.   c. myoclonus.
   b. intermittent claudication.   d. Raynaud’s disorder.

8. The condition characterized by symptoms that are usually neither associated with motor restlessness nor lessened by movement is:
   a. akathisia.
   b. intermittent claudication.
   c. nocturnal cramps.
   d. peripheral neuropathy.

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]   6. [a] [b]   11. [a] [b] [c] [d]
2. [a] [b] [c] [d]   7. [a] [b] [c] [d]   12. [a] [b] [c] [d]
3. [a] [b]   8. [a] [b] [c] [d]   13. [a] [b]
4. [a] [b] [c] [d]   9. [a] [b]   14. [a] [b] [c] [d]
5. [a] [b] [c] [d]   10. [a] [b] [c] [d]   15. [a] [b] [c] [d]

   a. True   b. False

10. All of the following are considered to be good sleep hygiene management EXCEPT:
    a. avoid bright lights in late evening or night.
    b. establish regular sleep and wake times.
    c. avoid perturbing activities immediately before sleep.
    d. do not eat anything after the evening meal.

11. All of the following drugs have been approved for treating RLS EXCEPT:
    a. gabapentin.   c. quinine.
    b. pramipexole.   d. ropinirole.

12. Which of the following drugs is dialyzable?
    a. Gabapentin   c. Quinine
    b. Pramipexole   d. Ropinirole

13. The troublesome and common problem that develops with prolonged use of levodopa that is more serious is:
    a. augmentation.   b. rebound.

14. Which of the following is regarded as first-line treatment for RLS?
    a. Benzodiazepines
    b. Dopamine receptor agonists
    c. Dopaminergic agents
    d. Opioids

15. Most data on the use of benzodiazepines to treat RLS have been derived with:
    a. alprazolam.   c. clonazepam.
    b. clordiazepoxide.   d. diazepam.

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