Restless legs syndrome (RLS) and nocturnal leg cramps (NLCs) are common disorders affecting 7.0% and 24.1% of the population in some European countries, respectively. Patients suffering from RLS experience uncomfortable nocturnal sensations in the legs with the urge to move that dissipates while moving. NLC is characterized by abrupt muscle contraction, most often in the gastrocnemius or foot muscles, which occurs at night and may result in significant sleep disturbances. The diagnosis of these disorders has presented a challenge to health care providers because of symptom overlap with other sensory and motor disturbances with nocturnal predominance. Treatment options and approaches are lacking, partially because of our currently incomplete understanding of the pathophysiological mechanisms underlying these conditions. We reviewed the medical literature to provide a comprehensive assessment of RLS and NLC with a focus on improved diagnostic accuracy and treatment approaches.

Introduction

Restless legs syndrome (RLS) is a disorder whereby patients experience uncomfortable sensations with the urge to move that dissipates while moving. Symptoms tend to worsen later in the day and in the night. The prevalence of RLS was reported to reach 7.0% of the population among 5 European countries.1 The condition is frequently misdiagnosed, likely due to the high prevalence of lower extremity sensory complaints, the differential diagnosis of which is broad. This underscores the importance of a rigorous clinical evaluation and adherence to strict diagnostic guidelines.

The hallmark characteristic of RLS, namely, a circadian disorder of sensorimotor integration, has resulted in theories of the underlying pathophysiological mechanisms, many of which pertain to dysregulation of iron regulation and its impact on dopamine metabolism.2 However, the variability in responses to treatment regimens illustrates the incompleteness of our current understanding of the disease.

Nocturnal leg cramps (NLCs) were reported in approximately 25% of the population in Germany and the United States, and in as many as 37% of individuals over the age of 50 in the United Kingdom.3-5 The heterogeneity of symptom descriptions has contributed to its frequent misdiagnosis as RLS. Efficacious treatments are limited, partly due to an incomplete understanding of the pathophysiological mechanism.

The present review discusses RLS and NLC with a focus on improved diagnostic accuracy and treatment approaches.

Restless legs syndrome Diagnosis Updated diagnostic criteria for RLS were proposed in 2003 by the International Restless Legs Syndrome Study Group at a workshop of the National Institutes of Health.6 These diagnostic criteria outline the phenotype as uncomfortable sensations that may be associated with the urge to move and that predominantly occur at night and typically involve the legs. Movement causes these individuals to experience relief until movement ceases. An individual’s symptoms must also not be solely accounted for as symptoms primary to another condition.7

The URGES acronym has been suggested as a clever tool to help health care providers recall the diagnostic criteria.8 “U” stands for the urge to move one’s limbs. “R” stands for rest-induced, referring to symptom onset or exacerbation in the absence of movement. Similarly, “G” stands for gyration, referring to the fact that symptoms improve with movement. “E” stands for evening, referring to the circadian pattern whereby symptom presence or exacerbation occurs later in the day or at night. Finally, “S” refers to RLS being the sole
While this may be a reasonable means of assisting the diagnosis process, treatment with dopaminergic agents is associated with the risk of augmentation, which is discussed in detail in the section on treatment. Although somewhat counterintuitive, patients with RLS typically do not report daytime sleepiness. An exception to this would be in those with severe RLS. Therefore, in the absence of severe symptoms, reports of daytime sleepiness should prompt evaluation for other causes, such as primary sleep disorders or medication effect. Plazzi et al demonstrated a higher prevalence of narcolepsy with cataplexy in 184 patients with RLS (14.7%) compared with 3% in normal controls, but this relationship needs to be further validated.

**Restless legs syndrome mimics** While the 5 diagnostic criteria have increased the clinician’s ability to differentiate RLS from other conditions, it is worthwhile to briefly review the so-called mimics of RLS, as they are frequently encountered in general medical practice. Each individual aspect of RLS diagnostic criteria may apply to a number of other conditions. For this reason, it is useful to approach the differential diagnosis in a systematic fashion by assessing whether the symptoms satisfy each diagnostic criterion.

Several conditions present with abnormal restlessness such as akathisia, other hyperkinetic movement disorders, psychiatric disorders, orthostatic hypotensive restlessness while sitting, and leg stereotypy disorder. Akathisia may result from medications (ie, neuroleptics and dopaminergic agents), neurodegenerative disorders, or infections of the nervous system. Other hyperkinetic movement disorders may include myokymia, essential myoclonus, orthostatic tremor or myoclonus, or leg stereotypy disorder. Various psychiatric disorders may include anxiety or depression and attention-deficit or hyperactivity disorder. Fidgeting may be seen in normal individuals.

Many conditions may present with nocturnal leg discomfort. Growing pains may be a normal occurrence and should be considered in adolescents with such symptoms. Conditions such as venous insufficiency may be seen in the elderly population and in patients with other vascular risk factors. Patients with small-fiber neuropathies may also present with nocturnal pain, and this entity should be considered especially in patients with diabetes mellitus. Arthritis, myalgias, and radiculopathies are possible causes; however, a careful history taking with a thorough physical examination should differentiate these conditions from RLS. Psychiatric conditions should also be considered. One such example is Ekbom syndrome (delusional parasitosis) whereby individuals experience a delusion that bugs are attacking their bodies, evidenced by concomitant visual and tactile hallucinations.

Nocturnal movements may be seen in normal individuals as they transition from the awake state to sleep. Among these are hypnic jerks, hypnagogic foot tremor, and propriospinal myoclonus. Individuals will often not be aware of these symptoms; however, they may be severe enough to cause awakening. These movements are not the result of an uncomfortable sensation, which helps differentiate them from RLS. Sleep-related rhythmic movement disorder consists of rhythmic (0.5–2.0 Hz) and stereotyped movements such as body rocking, head banging, and head rolling and may occur in up to 60% of infants. While these movements are generally believed to be self-soothing, children tend not to remember the movements and adults typically do not report a volitional component, thus differentiating it from RLS. Periodic limb movement disorder is common and generally supportive of a diagnosis of RLS; however, this may occur in isolation without other features of RLS.

Leg discomfort or pain may be accompanied by unusual motor activity in a number of conditions. Painful legs and moving toes syndrome is characterized by pain in 1 or more limbs, most often the legs, accompanied by repetitive and nonrhythmic movement of the digits. Many of these patients will be diagnosed with peripheral neuropathy or radiculopathies. A critical distinction is that the movements do not provide relief unlike in RLS. Disorders such as muscular pain-fasciculation syndrome can generally be differentiated from RLS based on the presence of fasciculations and on the basis that discomfort typically does not consistently improve with movement. Cramp-fasciculation syndrome can be uncomfortable, resulting in leg movements; however, a thorough history and physical examination should reveal the presence of cramps or fasciculations or both. Electromyography as well as the presence of antibodies against voltage-gated potassium channels are useful to support the diagnosis of cramp-fasciculation syndrome. Causalgia-dystonia syndrome is a rare condition that shows some similarities to complex regional pain syndrome in
that it is typically precipitated by minor trauma and characterized by painful sensations including allodynia and hyperpathia. This condition can generally be differentiated from RLS based on the presence of dystonia, a history of trauma, and the lack of a strong circadian correlation. Proper history taking should screen for intermittent claudication, which is typically worse with movement rather than at rest, distinguishing it from RLS. NLC should also be considered in a differential diagnosis, and the phenotypic description of NLC is discussed further in the text.

**Pathophysiology** Responses to dopaminergic agents and iron supplementation have been the primary drivers of theories regarding the pathophysiological mechanisms underlying RLS. These theories have been developed further with the aid of improved neuroimaging and genetic testing techniques and applications.

While the severity of RLS increases with decreased peripheral iron levels and is more prevalent in individuals with iron-deficiency anemia, most patients do not have iron deficiency as would be detected by serum ferritin levels. A regional iron deficiency within the brain has been suggested by studies that demonstrated decreased iron levels in the substantia nigra, putamen, caudate, and thalamus, using magnetic resonance imaging. This deficiency may be the result of impaired iron transport across the blood–brain barrier and regional dysfunction of transport mechanisms responsible for importing iron into critical neuronal cells. The application of immunohistochemical and protein expression techniques has yielded evidence suggesting that RLS may result from destabilization of the transferrin receptor mRNA due to a defect within iron regulatory protein 1, ultimately causing impaired iron transport within specific brain regions, such as the neuromelanin cells of the substantia nigra. Subsequently, myelin synthesis may be impaired, as demonstrated by Connor et al. Furthermore, some studies have shown an increased propensity for hypoxia in the leg muscles of patients with RLS with a circadian correlation consistent with RLS symptoms. These symptoms may be more consistent with global dysfunc-

**Treatment** The treatment of RLS has evolved in conjunction with our increased understanding of disease mechanisms. For instance, the clinical observation of augmentation is one in which initial adequate response to dopaminergic treatments wanes and progresses to a rebound worsening of disease. Health care providers have treated this problem by steadily increasing the dose of dopaminergic agents; however, the demonstration of postsynaptic D2-receptor downregulation supports anecdotal claims that this is the wrong approach and only worsens symptoms. In 2016, the American Academy of Neurology published treatment guidelines for adults with RLS. Current treatments for RLS are listed in TABLES 1 and 2.

Once the diagnosis of RLS has been made, the clinician should determine whether the patient has idiopathic RLS or whether RLS is secondary to another condition such as pregnancy, renal dysfunction, medication effect (eg, neuroleptic agents, dopamine receptor-blocking antinausea medications), or iron deficiency. RLS affects from 2.9% to 32% of pregnant women, and pharmacological treatment should be generally avoided; however, replenishment of iron stores prior to pregnancy may be considered, given that low iron levels are associated with an increased risk of developing RLS during pregnancy.

Ekbohm reported iron deficiency in 25% of patients with RLS. A double-blind,
Treatments for restless legs syndrome that are currently not approved by the US Food and Drug Administration

**TABLE 1** Treatments for restless legs syndrome currently approved by the US Food and Drug Administration

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dose (starting, therapeutic) mg/d</th>
</tr>
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<tbody>
<tr>
<td>Ropinirole</td>
<td>0.25, 0.25–4.0</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>0.125, 0.25–0.5</td>
</tr>
<tr>
<td>Rotigotine patch</td>
<td>1.0, 1.0–3.0</td>
</tr>
<tr>
<td>Gabapentin enacarbil</td>
<td>600, 600</td>
</tr>
<tr>
<td>Relaxis (vibrational counterstimulation)</td>
<td>–</td>
</tr>
</tbody>
</table>

**TABLE 2** Treatments for restless legs syndrome that are currently not approved by the US Food and Drug Administration

<table>
<thead>
<tr>
<th>Intervention</th>
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<tbody>
<tr>
<td>Cabergoline</td>
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<tr>
<td>Levodopa</td>
</tr>
<tr>
<td>Pregabalin</td>
</tr>
<tr>
<td>Oral iron</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
</tr>
<tr>
<td>Iron sucrose</td>
</tr>
<tr>
<td>Prolonged-release oxycodone/naloxone</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Near-infrared spectroscopy</td>
</tr>
<tr>
<td>Pneumatic compression</td>
</tr>
<tr>
<td>Repetitive transcranial magnetic stimulation</td>
</tr>
<tr>
<td>Transcranial direct current stimulation</td>
</tr>
<tr>
<td>Acupuncture</td>
</tr>
<tr>
<td>Massage</td>
</tr>
<tr>
<td>Hot baths</td>
</tr>
</tbody>
</table>

A placebo-controlled study of patients with RLS with low to normal serum ferritin levels (15–75 ng/ml) demonstrated symptomatic improvement with oral iron therapy. Oral iron therapy with ferrous sulfate (325 mg/d) taken with vitamin C (for improved absorption) is generally recommended for patients whose serum ferritin concentration is lower than 75 ng/ml. Some patients may require intravenous iron administration for various reasons, including intolerance to oral formulations or idiopathic RLS that is refractory to other pharmacological agents. Intravenous iron administration is associated with anaphylaxis and should be used conservatively.

Treatment of idiopathic RLS should aim to minimize exposure to dopaminergic agents in order to avoid augmentation. A survey-based study of 266 patients with dopamine-treated RLS identified 20% of responses consistent with “definitive or highly suggestive of augmentation” and only 25% reporting no indicators of augmentation. Therefore, a reasonable first-line treatment is with a dopamine agonist such as gabapentin enacarbil (600 mg in the evening with food) or pregabalin (300 mg/d in the evening). If treatment with these agents is unsuccessful, then adjunct therapy with a dopamine agonist is warranted. While a combination therapy of levodopa with a decarboxylase inhibitor (eg, carbidopa or benserazide hydrochloride) provides the most rapid benefit to patients with RLS, it is associated with a high risk of augmentation. In a study by Allen and Earley, augmentation occurred in 82% of the patients, resulting in levodopa discontinuation in 50%. While levodopa may have a role in patients with infrequent symptoms, it should generally be avoided in chronic treatment plans. If monotherapy with a dopamine agonist or a combination therapy proves ineffective, opioids may be considered. Trenkwalder et al demonstrated short-term efficacy with prolonged release oxycodone–naloxone. Methadone is a long-acting opioid antagonist that has shown sustained therapeutic benefit.

There are several nonpharmacological treatment options that may be beneficial and carry minimal risk of adverse effects. These include near-infrared spectroscopy and pneumatic compression, which have been demonstrated to be efficacious in small randomized control trials. A recent survey reported cramps related to sleep disturbances in 31% of French patients. Large-scale studies are needed to determine the efficacy and safety profile of intrathecal morphine.

**Nocturnal leg cramps** NLCs, also known as sleep-related leg cramps, have been reported in roughly 25% of the population in the United States, with 6% reporting moderate to severe NLCs. A recent survey reported cramps related to sleep disturbance in 31% of French patients. NLCs can occur at any age but are more common and severe with increasing age. They are associated with a reduced quality of sleep and a subsequent lower health-related quality of life.

**Diagnosis** The diagnosis of NLCs is relatively straightforward, as evidenced by the simplicity of the diagnostic criteria, which include painful muscle contractions occurring at night that are relieved by stretching of the affected muscles. As mentioned previously, there is a number of conditions that may present with nocturnal discomfort or cramp-like sensations or both. Although our understanding of the underlying pathophysiological mechanisms of NLCs is incomplete, several commonly associated factors have been identified. Activity-related factors, such as vigorous exercise and prolonged standing,
have been associated with NLCs. Multiple studies have been unable to demonstrate an association between NLCs and hypovolemia or electrolyte disturbances. Nevertheless, disturbances such as hypocalcemia, hypomagnesemia, hypoglycemia, hyperkalemia or hypokalemia, and hyponatremia, as well as endocrine conditions such as hypothyroidism or hyperthyroidism, diabetes mellitus, and Addison disease are considered predisposing factors. Conditions that may lead to these abnormalities, such as diarrhea, dialysis, and cirrhosis, should be considered when evaluating a patient with NLC. Many neurological conditions may predispose an individual to developing NLC, including nerve root compression, neuropathy, motor neuron disease, disorders of neuromuscular hyperexcitability, multiple sclerosis, dystonia, and Parkinson disease. Vascular etiologies, including peripheral vascular disease and Raynaud syndrome, have also been implicated.

NLC is associated with the use of numerous medications such as intravenous iron sucrose, conjugated estrogens, raloxifene, naproxen, and teriparatide. Garrison et al demonstrated that NLC was more likely to occur in the year following introduction of long-acting β2-agonists. NLC is more common with increasing age and several predisposing factors tend to occur as the patient ages. These include normal age-related loss of motor neurons, which is more pronounced in the legs than in the arms. Other factors that may increase nerve terminal hyperexcitability include tendon shortening, dystonia consists of involuntary cocontraction of agonist and antagonist muscles and patients will commonly assume abnormal postures as a result. It is generally accepted that cramps are a neurogenic process; however, their origin remains a topic of debate. Studies aimed at answering this question have used several methods to illicit cramps, such as direct electrical stimulation of nerves, which has demonstrated a lower threshold of intensity necessary to trigger cramps in cramp-prone individuals compared with those with no history of cramps. This suggests that there may be a physiological predisposition to cramps. Fasciculations, a classic “lower motor neuron” sign, may be seen during a cramp discharge, supporting a peripheral origin of cramps.

NLC is more common with increasing age and several predisposing factors tend to occur as the patient ages. These include normal age-related loss of motor neurons, which is more pronounced in the legs than in the arms. Other factors that may increase nerve terminal hyperexcitability include tendon shortening, ischemic disease due to diabetes mellitus and other vascular risk factors, as well as prolonged immobility. Currently, there have been no identifiable risk loci or causative genes associated with NLC.

Pathophysiology The pathophysiological mechanisms underlying cramps and secondarily NLC are poorly understood, and this has been the focus of numerous clinical electrophysiological studies. Electromyography demonstrates cramp discharges during muscle cramps. However, a variability in firing rates has been reported in various studies, with most of them suggesting 40 to 60 Hz and some suggesting higher rates, in a sputtering fashion with an abrupt onset and cessation. This distinguishes them from other similar motor phenomena, such as voluntary activity or dystonia, which appear similar except that dystonia consists of involuntary cocontraction of agonist and antagonist muscles and patients will commonly assume abnormal postures as a result.

TABLE 3 Well-studied treatments for the prevention of nocturnal leg cramps (NLCs)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dose</th>
<th>Study type</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine sulfate</td>
<td>150–450 mg/d (average, 300 mg/d)</td>
<td>Cochrane review</td>
<td>El-Tawil et al</td>
</tr>
<tr>
<td>Vitamin B complex</td>
<td>Vitamin B complex capsules (fursultiamine, 50 mg; hydroxocobalamin, 250 mg; pyridoxal phosphate, 30 mg; niacinamide, 5 mg) 3 times daily</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Chan et al</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>30 mg/d</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Voon and Sheu</td>
</tr>
<tr>
<td>Naftidrofuryl oxalate</td>
<td>300 mg twice daily</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Young and Connolly</td>
</tr>
<tr>
<td>Verapamil</td>
<td>120 mg/d at bedtime</td>
<td>Open-label prospective study of 8 patients with NLC</td>
<td>Baltodano et al</td>
</tr>
<tr>
<td>Ineffective treatments</td>
<td>Various</td>
<td>Cochrane review</td>
<td>Garrison et al</td>
</tr>
<tr>
<td>Magnesium citrate</td>
<td>Magnesium oxide and magnesium oxide monohydrate 865 mg/d (520 mg/d of free elemental magnesium)</td>
<td>Randomized, double-blind, placebo-controlled trial of 166 patients with NLC</td>
<td>Roguin Maor et al</td>
</tr>
</tbody>
</table>

a US Food and Drug Administration recommendation against off-label use of quinine for leg cramps

Treatment Adequate treatment of NLC can be very challenging for physicians. Several nonpharmacological strategies may help prevent cramps. These include passive stretching and deep tissue massage. Acute cramp treatment includes stretching the antagonist of the cramping muscle (e.g., dorsiflexion of the ankle for cramps of the gastrocnemius muscle).

Pharmacological treatment and prevention of NLC have been unsatisfactory. Quinine and its
derivatives have been used to prevent cramps for decades. A meta-analysis of 8 randomized, double-blind, placebo-controlled trials demonstrated that quinine is efficacious in the prevention of NLCs.\textsuperscript{77} One limitation to this study was that 4 of the included studies were unpublished, giving rise to publication bias. Beyond this, most of the quality studies have looked at prevention of muscle cramps in general. This includes a 2015 Cochrane review that assessed quinine at doses ranging from 200 to 500 mg/d (most commonly, 300 mg/d). The authors concluded that there was low-quality evidence that quinine significantly reduces cramp number or cramp days but moderate quality evidence for a reduction in cramp intensity.\textsuperscript{78} Quinine has been associated with serious adverse effects; however, the authors demonstrated moderate quality evidence that its use for up to 60 days is not associated with more serious adverse events compared with placebo, although minor side effects, most commonly gastrointestinal symptoms, occurred more often.\textsuperscript{78} Quinine has previously been associated with serious and potentially fatal immune-mediated reactions, such as thrombocytopenia, with an incidence rate of 1.7/1000 person-years.\textsuperscript{79} These reactions generally occur within 3 weeks of starting quinine. While they are not dose dependent, other complications of quinine are dose-related, including chronic visual impairment or blindness and death secondary to cardiac dysfunction.\textsuperscript{80,81} In 2006, the FDA strongly advised against the off-label use of quinine for leg cramps.\textsuperscript{82} The treatments that have been systematically studied to determine their effectiveness in specifically preventing NLC are listed in Table 3.

Magnesium supplementation is marketed for muscle cramp prophylaxis despite numerous studies that have failed to demonstrate its efficacy, with the exception of a double-blind, randomized, placebo-controlled study of pregnant women.\textsuperscript{83} Other trials and a Cochrane review looking at the efficacy of magnesium citrate failed to show a significant benefit.\textsuperscript{84,85} Most recently, in a randomized, double-blind, placebo-controlled clinical trial, Roguin Maor et al\textsuperscript{86} demonstrated that oral magnesium oxide was not superior to placebo for older adults experiencing NLC. They also showed a reduction in the weekly occurrence of NLC of 3.41 and 3.03 in the treatment and placebo groups, respectively. The authors concluded that the improvement on placebo is likely contributing to the ubiquitous marketing and use of magnesium to treat NLC.

Conclusions RLS and NLC are 2 common conditions that constitute unique challenges for health care providers with regards to diagnosis and treatment. This is partially due to our incomplete understanding of the pathophysiological mechanisms underlying these conditions. Genome-wide association studies have been instrumental in providing new genetic loci suggesting that impaired neurodevelopment may play a role in the pathophysiology of RLS. Treatments for RLS are numerous, and providers should take caution to avoid augmentation that commonly occurs with dopaminergic treatments.

NLC represents a subset of muscle cramps that are very common. Many treatments, such as the use of quinine and magnesium, have been applied despite unsatisfactory efficacy and the presence of adverse effects. The FDA has strongly advised against the use of quinine for the treatment of leg cramps due to the risk of adverse events. Other pharmacological approaches have been demonstrated to be modestly effective and may be tried with caution; however, nonpharmacological approaches such as stretching before and after exercise, adequate hydration, and correction of electrolyte disturbances may be an effective and safe means of prophylaxis. Acute treatment of muscle cramps is generally limited to lengthening the involved muscle by stretching the antagonist, which for calf cramps may be achieved by dorsiflexion of the ankle.

The high prevalence of RLS and NLC, along with their subsequent impact on the quality of life, has been and will likely continue to be a driving force for clinicians and researchers to investigate their pathophysiological mechanisms in the hope of developing more effective treatments.

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