

Restless Legs Syndrome

DSM-5-TR 333.94 | ICD-10-CM G25.81

Urge to move the legs with uncomfortable sensations, worse at rest and at night and relieved by movement, chronically disrupting sleep onset.

PREVALENCE

~2-3% clinically significant

TYPICAL ONSET

Bimodal; often before 45

SEX RATIO

~2:1 female:male

FAMILY HISTORY

~40-60% of early onset

CLINICAL PICTURE

- Patients describe creeping, crawling, or electric sensations deep inside the calves that they struggle to name, plus an urge they cannot resist.
- Symptoms follow a strict circadian pattern, worsening through the evening and peaking between midnight and roughly 4 a.m.
- Relief with walking or stretching is immediate but the sensations return within minutes of sitting back down.
- Sleep-onset insomnia is the usual presenting complaint, and the leg symptoms surface only on direct questioning.
- Long flights, movie theaters, dialysis chairs, and dental visits are classic settings in which the symptoms become intolerable.
- Periodic limb movements of sleep occur in roughly 80% of patients, producing partner-reported kicking and fragmented sleep.

DIAGNOSTIC CRITERIA AT A GLANCE

- An urge to move the legs, usually accompanied by uncomfortable sensations, meeting all five essential international consensus features.
- The urge begins or worsens during periods of rest or inactivity such as sitting or lying down.
- The urge is partially or totally relieved by movement, and the relief persists for as long as the movement continues.
- Symptoms are worse in the evening or night or occur only then, and DSM-5-TR requires 3 times weekly for at least 3 months with impairment.
- Mimics including leg cramps, positional discomfort, myalgia, arthritis, and habitual foot tapping must be excluded before diagnosis.

NEUROBIOLOGY & PHYSIOLOGY

- Brain iron deficiency in the substantia nigra is central even when serum indices look normal, since iron is a cofactor for dopamine synthesis.
- Ferritin is the decisive lab: target above 75 ng/mL with transferrin saturation above 20%, and supplement whenever values fall below that.
- Dopaminergic dysfunction is presynaptic with altered D2 receptor signaling, which explains both the drug response and the phenomenon of augmentation.
- MEIS1, BTBD9, and PTPRD variants confer risk, and heritability of early-onset disease approaches 50% in twin studies.
- Secondary causes include third-trimester pregnancy, end-stage renal disease, iron deficiency anemia, and peripheral neuropathy.
- Glutamatergic hyperarousal contributes, which explains why patients sleep far worse than the time lost to leg movements alone would predict.

PSYCHOLOGICAL MECHANISMS

- The sensation is genuinely hard to verbalize, so patients are often dismissed as anxious or drug-seeking for years before diagnosis.
- Chronic delay of sleep onset produces conditioned insomnia that persists even after the leg symptoms are pharmacologically controlled.
- Depression and anxiety rates run roughly two to three times general population levels and amplify subjective symptom intensity.
- Impulse control disorders including pathological gambling, compulsive shopping, and hypersexuality emerge in 6% to 17% on dopamine agonists.
- Bedtime catastrophizing heightens sensory attention to the legs, so cognitive strategies add meaningfully to pharmacologic control.

DIFFERENTIAL & COMORBIDITY

- Peripheral neuropathy, akathisia, nocturnal leg cramps, and vascular claudication all mimic the syndrome but lack the circadian and movement-relief pattern.
- Antidepressants, antipsychotics, sedating antihistamines, and dopamine antagonists commonly unmask or aggravate symptoms.
- Check ferritin, transferrin saturation, renal function, and pregnancy status in every new presentation before starting any drug.
- ADHD, chronic insomnia, depression, and cardiovascular disease are consistently overrepresented comorbidities in restless legs cohorts.
- Augmentation from dopamine agonists causes earlier daily onset, spread to the arms, and greater intensity, and is treated by taper rather than dose escalation.

Treatment EVIDENCE-BASED MANAGEMENT

PHARMACOLOGIC

- Iron repletion comes first: **ferrous sulfate 325 mg** with vitamin C on alternate days whenever ferritin is below 75 ng/mL.
- Intravenous **ferric carboxymaltose** is preferred for malabsorption, renal disease, intolerance, or failure of an adequate oral trial.
- Alpha-2-delta ligands are now the preferred drug class: **gabapentin enacarbil 600 mg**, **pregabalin 150-300 mg**, or gabapentin at bedtime.
- Dopamine agonists **pramipexole** and **ropinirole** have fallen out of first-line use because augmentation accumulates at roughly 7% per year.
- Low-dose opioids such as **methadone 5-10 mg** are reserved for refractory or augmented disease with close monitoring and a controlled substance agreement.

PSYCHOTHERAPY

- CBT-I** treats the conditioned insomnia layered on top of the syndrome and improves sleep beyond what medication alone achieves.
- Psychoeducation about augmentation warning signs enables early reporting instead of escalating patient requests for higher doses.
- Mindfulness-based approaches and relaxation training reduce distress and bedtime catastrophizing though not the underlying sensory urge.
- Screen at every visit for impulse control behaviors, which patients conceal and almost never spontaneously link to their medication.
- Behavioral counterstimulation strategies, from stretching routines to pneumatic compression, give patients agency at bedtime.

ADJUNCT & SUPPORTIVE

- Eliminate evening caffeine, alcohol, and nicotine, and review every medication for dopamine-blocking, antihistaminic, or serotonergic properties.
- Regular moderate daytime exercise improves symptoms, whereas intense late-evening exercise reliably worsens them.
- Pneumatic compression devices, counterstrain stretching, and near-infrared light have modest supportive evidence in mild disease.
- Recheck ferritin every 3 to 6 months during repletion and separate oral iron from tea, calcium, and proton pump inhibitors.
- Track severity with the **IRLS Rating Scale**, where a drop of 6 or more points marks a clinically meaningful treatment response.

CLINICAL PEARLS

- Check ferritin in every case; under 75 ng/mL, give iron before any other drug.
- Dopamine agonists cause augmentation; alpha-2-delta ligands are now preferred.
- Worsening on a dopamine agonist means taper, not a dose increase.

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NOTE

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