


Restless Legs Syndrome and Sleep Related Movements

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Restless Legs Syndrome

Restless legs syndrome (RLS): A condition in which there is strong urge to move the legs when they are motionless. Movement of the legs provides relief of the uncomfortable feeling. This is typically only temporary and the uncomfortable sensation comes right back. It typically happens in the evening or at night when sitting or lying down.

Restless legs syndrome can begin at any age. It is also known as Willis-Ekbom disease.

CBSBoston.com

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Disease State Summary

- RLS affects approximately 10% of US adults*
- Difficulty falling asleep may frequently be associated with moderate-to-severe RLS
- RLS can be diagnosed using 4 criteria

*Includes mild, moderate, and severe RLS.

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Key Diagnostic Criteria for RLS

Key RLS Diagnostic Criteria*	Supportive Features*
✓ Urge to move the legs —usually accompanied or caused by uncomfortable leg sensations	– Sleep disturbances
✓ Temporary relief with movement —partial or total relief from discomfort by walking or stretching	– Involuntary leg movements
✓ Onset or worsening of symptoms at rest or inactivity , such as when lying or sitting	– Positive family history for RLS
✓ Worsening or onset of symptoms in the evening or at night	– Positive response to dopaminergic therapy

* Diagnostic criteria developed by the International RLS (IRLS) Study Group in collaboration with the National Institutes of Health (NIH).

Allen et al. *Sleep Med.* 2003;4:101-119.

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Supportive Criteria

- Sleep disturbances
- Normal neurologic examination
- Chronic progressive course
- Periodic limb movements of sleep (PLMS)
- Family history
- Dopamine response

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Clinical Description (Paresthesias)

- | | |
|----------------|---------------------|
| ▪ Need to move | ▪ Tension |
| ▪ Crawling | ▪ Discomfort |
| ▪ Tingling | ▪ Itching |
| ▪ Cramping | ▪ Heebie Jeebies |
| ▪ Creeping | ▪ Wriggling maggots |
| ▪ Pulling | ▪ Fidgets |
| ▪ Painful | ▪ Elvis legs |
| ▪ Electric | |

Ondo W. 1996

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Clinical Descriptions

- Usually between knees and feet
- Deep sensation (90%)
- Bilateral, unilateral or alternating
- Arms may be involved (22%-57%)
- Periodic Limb Movements of Sleep (PLMS)

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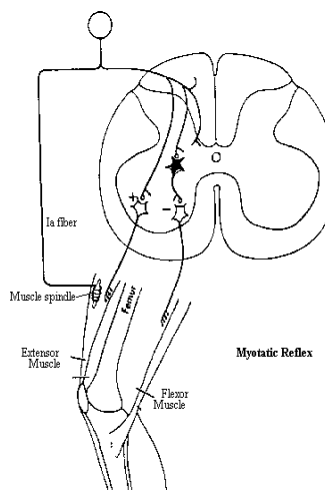


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Dopamine is involved in the modulation of the sensory/motor pathways, such as those that are part of the monosynaptic reflex arc (which is involved with deep tendon reflexes).

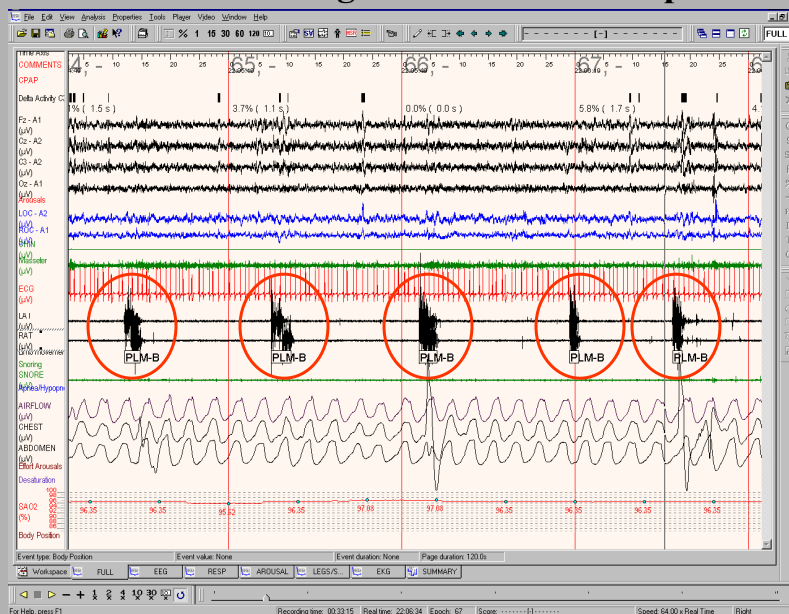
Low levels may cause a restless sensation in the limbs and may cause periodic leg movements during sleep.

Mild iron deficiency may interrupt functioning of the dopamine receptors within the spinal cord, causing the Restless Legs Syndrome symptoms and Periodic Leg Movements of sleep.

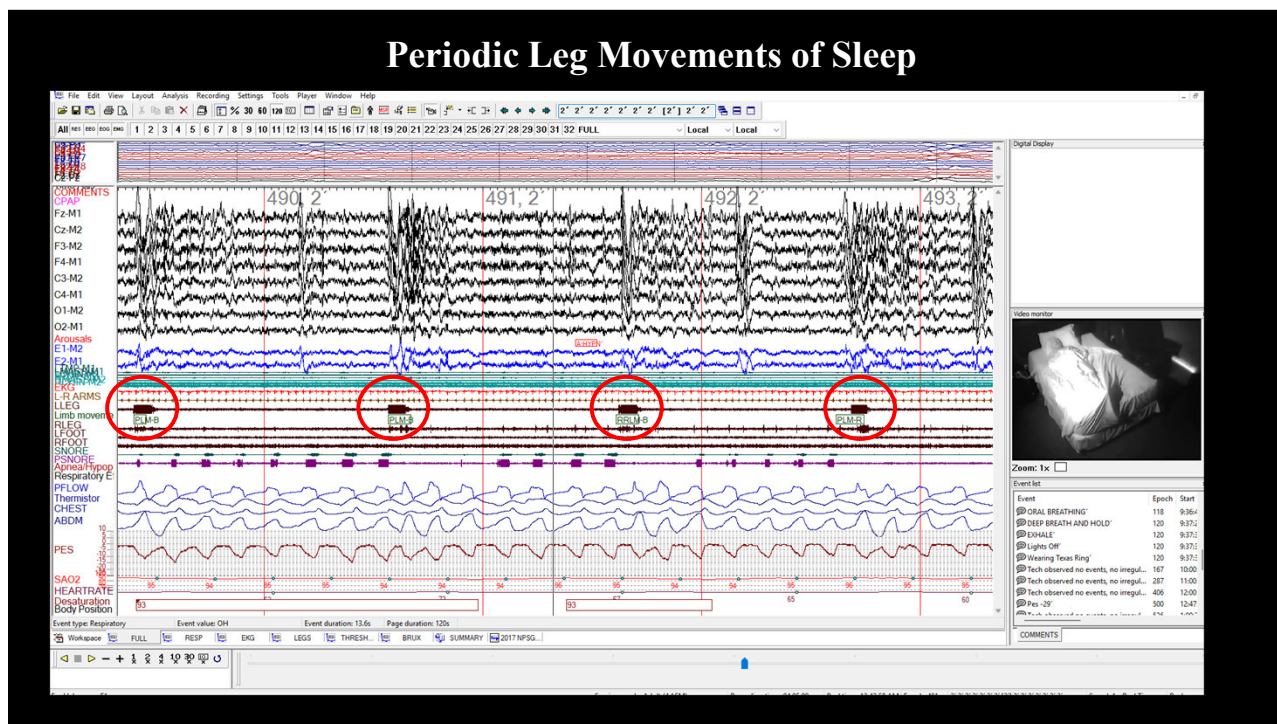


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Periodic Leg Movements of Sleep



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PLMS (Periodic Leg Movements of Sleep) vs PLMD (Periodic Leg Movements Disorder)

Whats the difference?

PLMD is when the patients PLMS occurs to a degree that is disrupts sleep to where it causes symptoms worthy of treatment.

Many patients have PLMS to a mild degree with no RLS symptoms and treatment may not be warranted. But once symptomatic (daytime sleepiness, repetitive awakenings out of sleep, possibly hypertension), then treatment should be initiated and a diagnosis of PLMS is given.

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Epidemiology and Disease Burden of RLS



14.5%

Estimated prevalence in Western populations³

50-79

Median age group of RLS patients¹

1-2 M

Estimated refractory patients in the US

2X

More common in women than men⁴

4-5%

Adults with moderate-severe disease⁴

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RLS is the second most common sleep disorder in the US

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¹ Allen RP et al, Arch Intern Med (2005) | ² Meyers J et al, Manag Care (2012) | ³ Innes KE et al, Sleep Med 2011, Aug 12 (7): 623-34 | ⁴ Allen RP et al, Arch Intern Med. 2005; 165(11): 1286-1292

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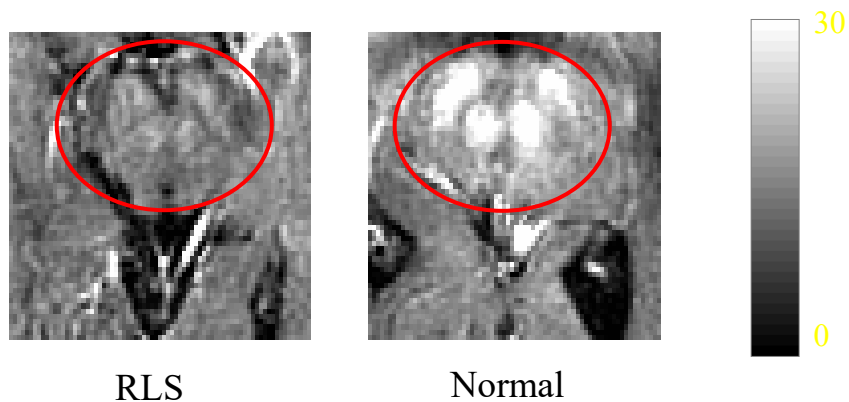
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Iron levels best measured by Ferritin (iron transport protein in the blood)

- A ferritin level below 50 µg/L (even within the "normal" lab range) is considered functionally low in RLS patients and is associated with symptom exacerbation
- Some studies by Earley et al. found that ~25% of RLS patients presenting to sleep clinics had ferritin under 50 µg/L
- Guidelines from the IRLSSG (International RLS Study Group) recommend iron supplementation when ferritin is below 75 µg/L in RLS patients — a higher threshold than general population norms
- Brain iron deficiency (particularly in the substantia nigra and putamen) can occur even when serum ferritin is in the normal range, which is why the threshold for treatment in RLS is set higher than the standard lab cutoff

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MRI Brain Iron Studies in RLS



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Ferritin levels as a marker of patients with RLS who may respond to Iron therapy: A re-evaluation of the normal range of Ferritin.

- 97 patients from the Sadler Clinic dx with RLS with PLMS had Ferritin levels drawn
- 36 had Ferritin levels less than 50 ng/dl, 3 with levels less than 11 ng/dl
- 6 had anemia and the 89 had normal cell counts, two did not have CBC drawn

Simmons, JH, Sadler Clinic Sleep Disorders Center.
Sleep, 2000 Vol 23 p106

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RLS in Children

- No definitive epidemiology (1-2%)
- Many children do not meet criteria for adult RLS
- May present with:
 - “growing pains”
 - Associated with low ferritin and PLMS
 - Attention deficit hyperactivity disorder

Picchiatti D, 2013

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RLS and ADHD

- ADHD Children have:
 - Greater PLMS
 - 26% have >5/hour
 - Worse sleep in general
 - 32% have a parent with RLS
 - Lower ferritin

Picchiatti 1998, Picchiatti 1999, Cherven 2002

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Spectrum of RLS Causes

Deficiency in the central
Dopamine Filter

Peripheral Etiology

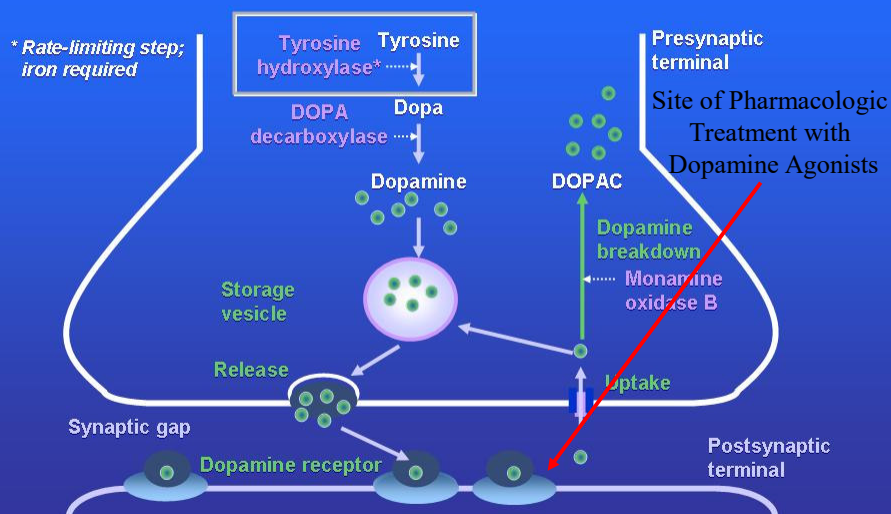
- Idiopathic (familial)
Typically develops early in life
- Iron Deficiency
- Dopamine antagonists
- Central lesion
(i.e. cervical spinal compression)

- Peripheral Neuropathy
- Radiculopathy

Most patients have a combination of a primary predisposition resulting in a mildly lowered dopamine central filter in conjunction with a peripheral etiology.

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Pharmacology of Dopamine Synthesis and Metabolism



Adapted from Standaert DG, Young AB. In: Hardman et al, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York: McGraw-Hill, 2001:553.

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Secondary Restless Legs Syndrome

William Ondo MD

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Secondary Causes of RLS

- Iron deficiency
- Renal failure
- Neuropathy
- Pregnancy
- Multiple sclerosis
- Essential Tremor
- Parkinson's Disease

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Pregnancy RLS Risk Factors

- Low folate
- Low iron
- Increased estradiol

Boetz M NEJM 1976, Lee K. J Wom Health Gen Med 2001, Fulda S J
Sleep Res 2004

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Medications That Worsen RLS

- Anti-histamines
- Dopamine blockers
- Anti-depressants

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RLS Treatments

- Dopamine Agonists
- L-dopa
- Opioids
- Benzodiazepines
- Gabapentin (Enacarbil)
- Pregabalin
- Iron (oral, IV)
- Thermal therapy

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Augmentation

- Worsening of symptoms after initial therapeutic benefit not accounted for by other factors
- Earlier onset of symptoms (<4 hours) OR,
- Earlier onset of symptoms (>2 hours) AND one
 - Shorter latency to symptoms when at rest
 - Extension to other body parts
 - Greater intensity
 - Less relief from treatment

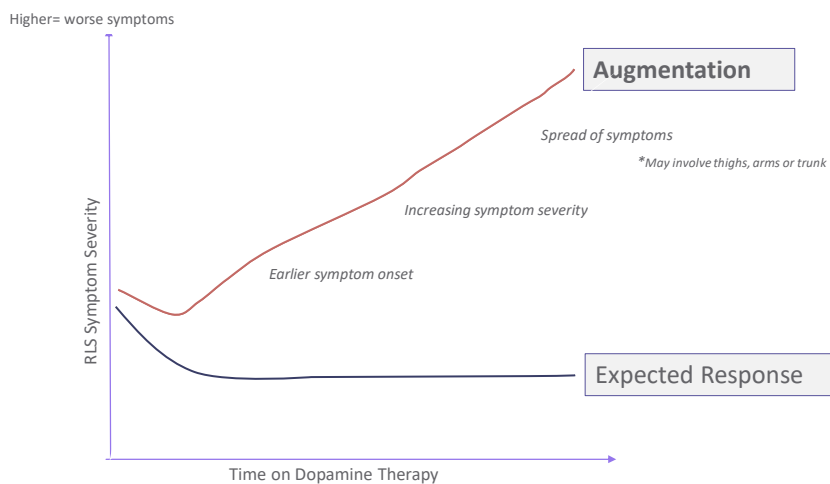
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Dopamine Agonists

- Ropinirole (Requip / Requip XR)
- Pramipexole (Mirapex / Mirapex ER)
- Rotigotine (Neupro patch)
- Pergolide (Permax)
- Bromocriptine (Parlodel)
- Cabergoline (Dostinex)
- Apomorphine (Apokyn injections)
- Lisuride / Sumanriole

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Augmentation in Dopaminergic Treatment of RLS

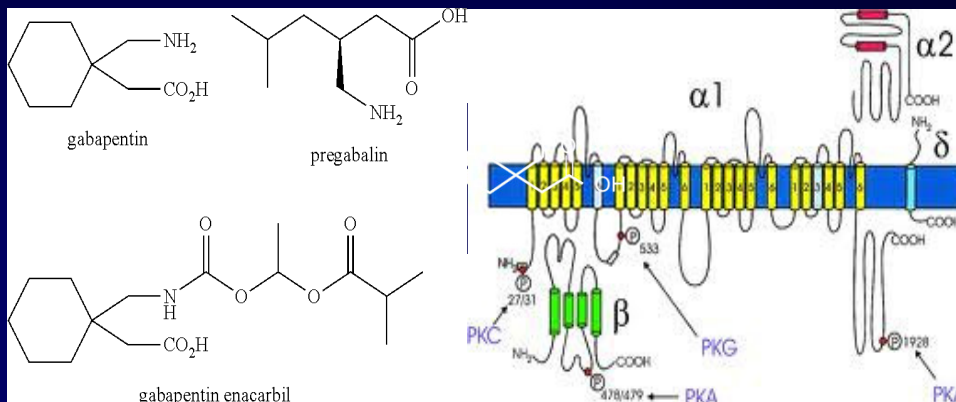


Augmentation represents a paradoxical worsening of RLS symptoms during long-term dopaminergic therapy¹

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Alpha-2delta Subunit Voltage Gated Calcium Channel

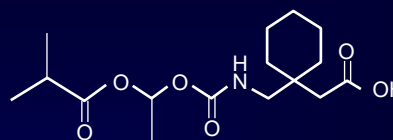
Gabapentin, Gabapentin enacarbil, Pregabalin



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Gabapentin Enacarbil (Horizant)

- Gabapentin prodrug, which is actively transported by MCT1 and SMVT
- Well absorbed throughout gastrointestinal (GI) tract
- Immediately releases gabapentin in blood
- Linear pharmacokinetics (no saturable absorption of gabapentin)
- 2 mg of Gab Enacarbil produces ~1 mg of gabapentin
- Dose: 600-1200 mg with food about 6 PM



MCT1 indicates monocarboxylate transporter type 1; SMVT, sodium-dependent multivitamin transporter.

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Horizant (gabapentin enacarbil)

Currently recommended as a first line agent because, dopamine agonists, which was previously recommended as a first line agent, frequently cause rebound (when not dosed optimally) and has a rare occurrence of impulse control issues.

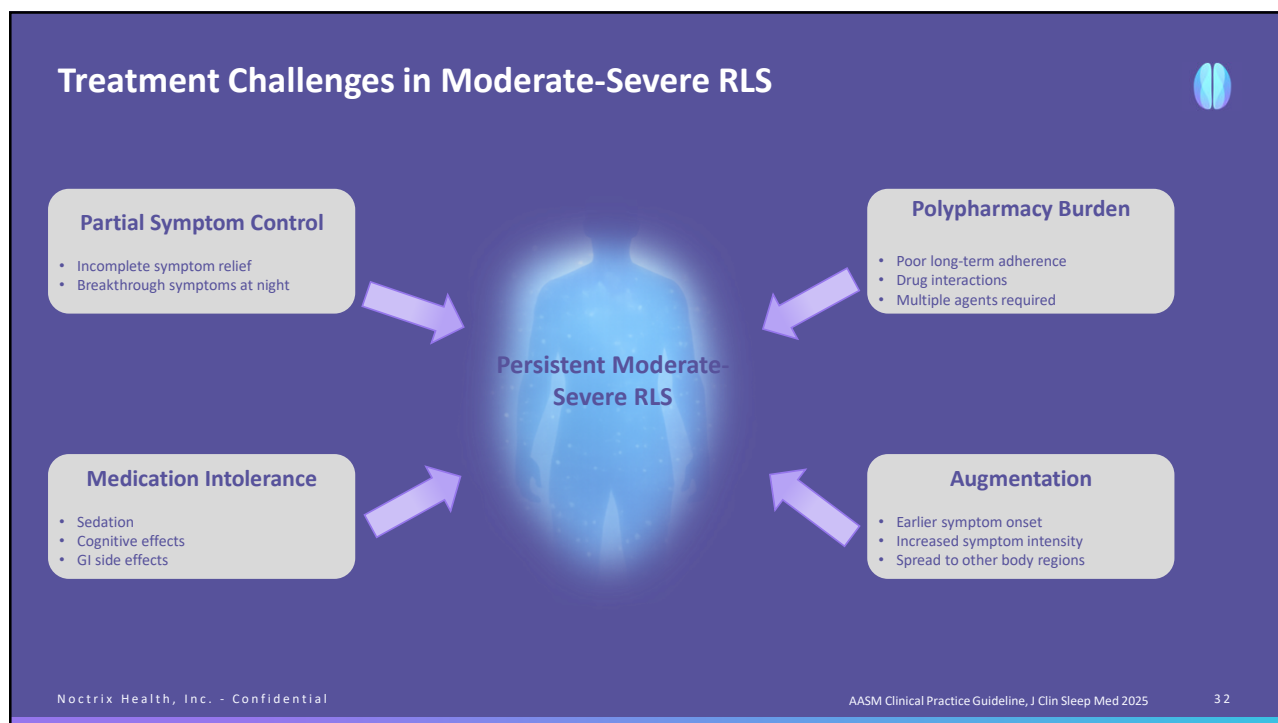
Common Side Effects:

Somnolence/sedation (up to 27–30% of patients)

Dizziness (up to 22%)

Headache (up to 15%)

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Tonic Motor Activation (TOMAC) Clinical and Mechanistic Rationale

WHAT IT IS

- Non-invasive, wearable neuromodulation therapy
- Applied below the knee to stimulate the common peroneal nerve
- Designed for on-demand (PRN) use during rest of sleep

HOW IT WORKS

- High-frequency stimulation activates low-threshold motor afferents
- Induces tonic-activation of the tibialis anterior
- Provides structured afferent input to central sensorimotor networks
- Mimics physiologic motor signaling (e.g., walking)

HOW IT IS USED

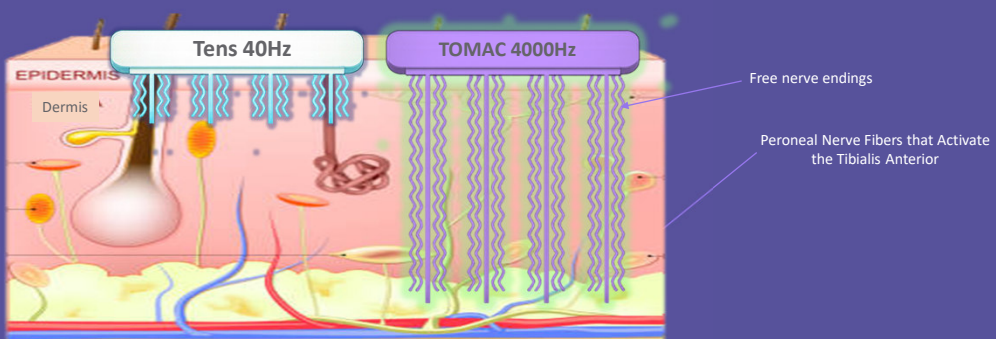
- 30-min therapy session
- Can be used day or night, based on symptom onset
- Delivers predictable, repeatable symptom relief
- Non-pharmacologic, therapy independent of dopaminergic and iron pathways



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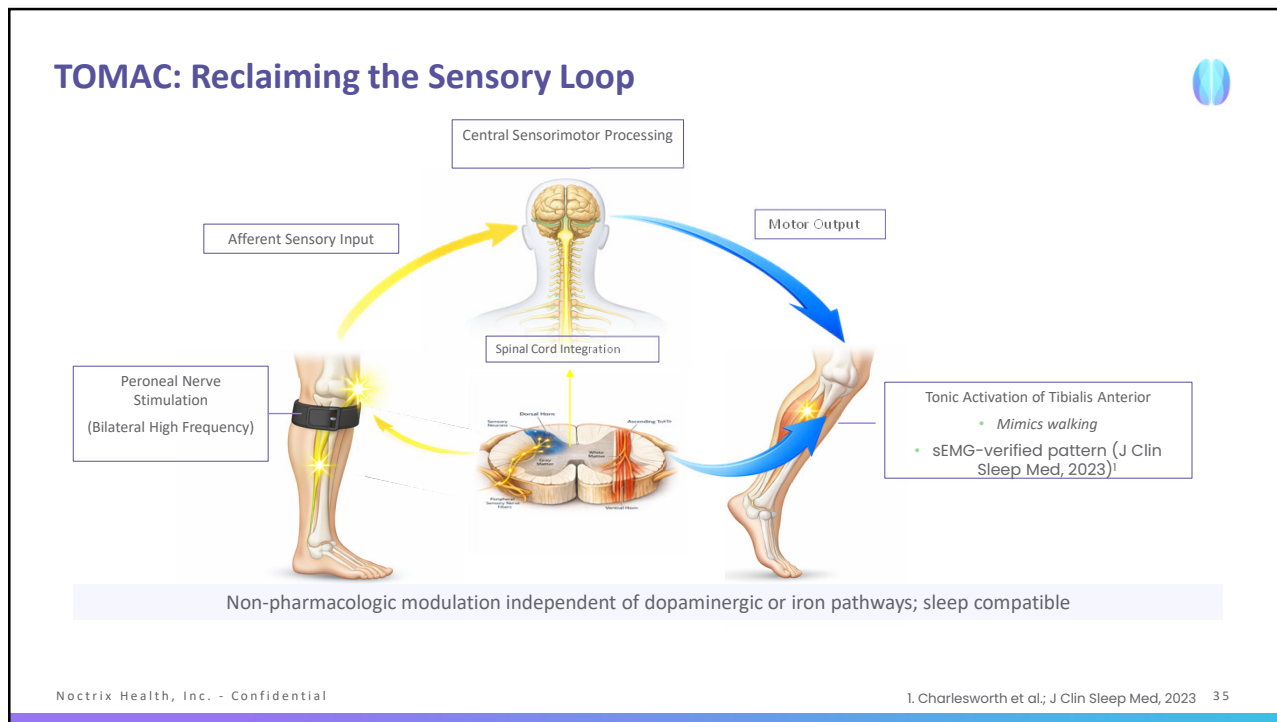
High-Frequency TOMAC Drives Tonic Motor Activation

Parameter	TENS (40 Hz)	TOMAC (4000 Hz) ¹
Primary Target	Superficial nerve endings ³	Deep peroneal nerve fibers ¹
Clinical Goal	Mask pain (paresthesia) ³	Mimic walking (Tonic Activation) ¹
FDA Indication	Temporary relief of pain ³	Mod-to-Severe Primary RLS²
Clinical Impact	Temporary sensory distraction ³	Reduced RLS severity and improved sleep²



Noctrix Health, Inc. - Confidential ¹ Charlesworth JD, Et al. J Clin Sleep Med. 2023 ² Bogan RK. Sleep. 2023 ³ Sluka KA. J Pain 2003 3 4

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Clinical Relevance of TOMAC Therapy

- Peroneal Nerve Stimulation**
 - Reduces RLS symptoms
- High-Frequency Stimulation**
 - Does not interfere with sleep
- Non-pharmacologic therapy**
 - Expands options in medication-refractory RLS

TOMAC may help reduce symptom burden while supporting sleep and daily functioning

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Clinical Evidence

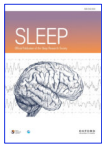
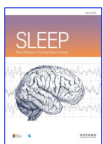
CL-01022 Rev 01

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Clinical Evidence Supporting TOMAC Therapy



RESTFUL Clinical Program

 <p>Bogan 2023 Randomized sham-controlled trial</p>	 <p>Roy 2023 24-week open label extension</p>
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Additional Peer-reviews

 <p>Buchfuerer 2021 J Clin Sleep Medicine</p>	 <p>Singh 2024 Sleep Medicine</p>
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<h3>Supportive analyses</h3> <ul style="list-style-type: none">Charlesworth 2023 J Clin Sleep MedicineRyschon 2023/24 Neurology and Therapy/J Med EconKarroum 2026 J Clin Sleep Medicine	<h3>Emerging real-world evidence</h3> <ul style="list-style-type: none">THRIVE Post-market observational study; interim outcomes reported at SLEEP 202520+ abstracts and conference presentations
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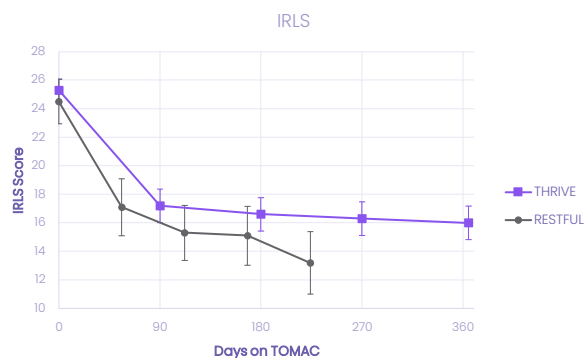
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IRLS change (International RLS rating scale)



Change from baseline to 1-year (n=171)

IRLS change	Days on TOMAC	Mean (95% CI)
THRIVE (n=171)	365	-9.3
RESTFUL (n=44)	224	-11.3



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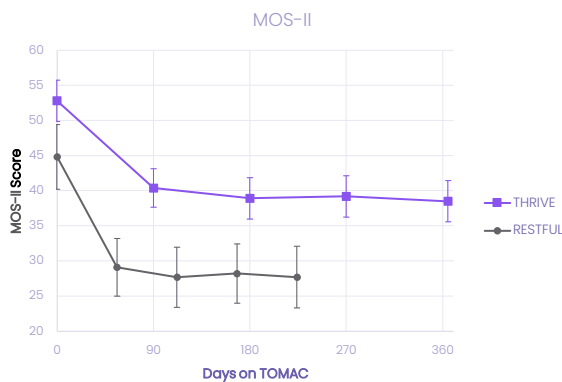
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MOS-II change (Medical Outcomes Study - Sleep Problem Index II)



Change from baseline to 1-year (n=171)

IRLS change	Days on TOMAC	Mean (95% CI)
THRIVE (n=171)	365	-14.3
RESTFUL (n=44)	224	-17.1



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Current Clinical Experience with TOMAC / Nidra

- Currently only approved for patients refractory or intolerant to medication management
- Every patient placed thus far has demonstrated improvement
- Most cases have resulted in reduction of other medications, including opiates
- All patients have expressed satisfaction with the therapy

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REFLECT NOW

<https://champions.learner.plus/sec/>

Restless Legs Syndrome

What inspired you to reflect?
Pick the context and a clinically relevant concept or phrase that inspired you to reflect.

Reflective Learning Moment

Step 1 of 4 **Next**

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