Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder: an American Academy of Sleep Medicine Clinical Practice Guideline

American Academy of Sleep Medicine (AASM)

Background

- Primary RLS: Idiopathic
  - familial link in 40-60%
  - Several genetic loci possibly associated with RLS, some involving dopamine signaling and iron metabolism
- Secondary RLS: Caused by an identifiable condition
  - Assess for and address exacerbating factors
  - Alcohol, caffeine, antihistaminergic meds, serotonergic meds, antidopaminergic meds
  - CKD
  - Sleep apnea, PLMS (PLMS vs RLS 

)

Comparison: RLS vs PLMS

Aspect	Restless Legs Syndrome (RLS)	Periodic Limb Movements in Sleep (PLMS)
Timing	Occurs during wakefulness	Occurs exclusively during sleep
Symptoms	Urge to move legs; uncomfortable sensations	Involuntary limb movements
Awareness	Patient is aware	Patient is often unaware
Diagnosis	Based on clinical history	Confirmed via polysomnography
Treatment	Dopaminergic agents, gabapentinoids, iron supplements	Focus on underlying conditions

1. American Academy of Sleep Medicine (AASM): 'Clinical Practice Guidelines for RLS and PLMS', https://jcsm.aasm.org/doi/pdf/10.5664/jcsm.11390
2. UpToDate: 'Clinical features and diagnosis of restless legs syndrome and periodic limb movement disorder in adults', https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-restless-legs-syndrome-and-periodic-limb-movement-disorder-in-adults

Key Differences: Primary vs Secondary RLS

Aspect	Primary RLS	Secondary RLS
Cause	Idiopathic; no known cause	Associated with underlying conditior
Onset	Early (often <40 years)	Later (often >40 years)
Family History	Common	Rare
Progression	Chronic, slowly progressive	May resolve with treatment of cause
Triggers	None identified	Iron deficiency, pregnancy, CKD, medications
Treatment	Symptom-focused	Treat underlying cause + symptoms

RLS Treatment Recommendations Overview

Issued by the American Academy of Sleep Medicine (AASM)

Target group: Adults with Restless Legs Syndrome (RLS)

Recommendations classified as 'strong' or 'conditional' with varying levels of evidence

Summary of the Updates

- Evaluate for and treat underlying conditions that can exacerbate RLS
  - Iron Deficiency
  - OSA, PLMS
  - CKD, ESRD
  - Alcohol, caffeine, antihistaminergic, serotonergic, antidopaminergic medications
  - Diabetes, COPD
- Check iron status and supplement iron if indicated
- Strong recommendation for alpha-2-delta ligands as first line therapies for RLS
  - Gabapentin enacarbil, Gabapentin, Pregabalin
- Move away from using dopaminergic drugs (pramipexole, ropinirole, rotigotine) as first line agents due to risk of augmentation.
- New Non-pharm treatment: high-frequency peroneal nerve stimulation

Good Practice Statement for RLS Management

#1 First Step

Address exacerbating factors

- Alcohol, caffeine, antihistaminergic, serotonergic, antidopaminergic medications
- Untreated obstructive sleep apnea
- CKD
- Pregnancy

Good Practice Statement for RLS Management

Iron Studies

- Regular testing of serum iron studies (ferritin and transferrin saturation) is essential for patients with significant RLS
- Conduct iron tests in the morning and avoid iron supplements/foods 24 hours before test

Iron Supplementation Thresholds:

- Adults:
  - Serum ferritin ≤ 75 ng/mL or transferrin saturation < 20% (oral/IV).
  - Use only IV iron for ferritin levels 75–100 ng/mL.
- Children: Serum ferritin < 50 ng/mL (oral/IV).
- Thresholds differ from general population recommendations.

Strong Recommendations for Specific Treatments

- Gabapentin Enacarbil: Recommended over no treatment
- Gabapentin: Recommended over no treatment
- Pregabalin: Recommended over no treatment.
  - What is Gabapentin Enacarbil? 
- IV ferric carboxymaltose: Recommended for patients with appropriate iron status.
- Cabergoline: Strongly recommended against use

Comparison of Gabapentin, Gabapentin Enacarbil, and Pregabalin (with Cost)

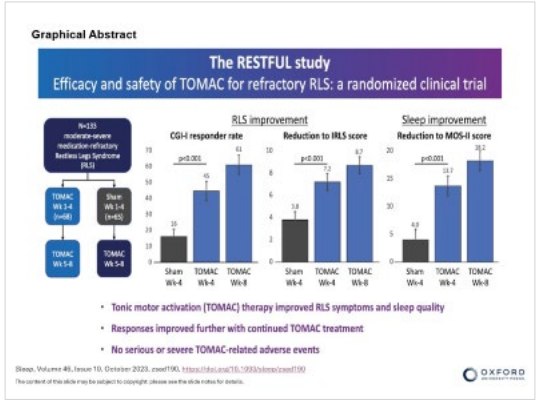
Aspect	Gabapentin	Gabapentin Enacarbil	Pregabalin
Mechanism of Action	Binds to α2δ subunit of voltage-gated calcium channels, reducing excitatory neurotransmitter release	Prodrug of gabapentin; converted to gabapentin in the intestine for extended effect	Binds to α2δ subunit of voltage-gated calcium channels, reducing excitatory neurotransmitter release
Half-Life	5-7 hours	5-7 hours (similar to gabapentin)	6-7 hours
Absorption	Variable, saturable absorption via L-amino acid transport system in the intestine	Non-saturable absorption, enabling dose-proportional pharmacokinetics	Linear absorption, not saturable
Bioavailability	Decreases with increasing doses (30-60%)	Consistently high (~68-75%) regardless of dose	High (~90%)
Clinical Indication for RLS	Off-label use for moderate to severe RLS symptoms	FDA-approved for moderate to severe RLS	Off-label use for RLS; effective for severe cases or refractory symptoms
Estimated Cost (per month)	$10-$20 (generic)	$300-$500	$100-$150 (generic)

Conditional Recommendations (Iron Treatments)

- **Ferrous Sulfate**: Suggested for appropriate iron status (moderate certainty)
- IV Low Molecular Weight Iron Dextran: Suggested for appropriate iron status (very low certainty)
- IV Ferumoxytol: Suggested for appropriate iron status (very low certainty)

Conditional Recommendations (Other Therapies)

- Dipyridamole: Suggested over no treatment (low certainty).
- Extended-release Oxycodone & Opioids: Suggested over no treatment (moderate certainty).
- **High-Frequency Peroneal Nerve Stimulation**: Suggested over no stimulation (moderate certainty).
  - Bilateral high-frequency noninvasive peroneal nerve stimulation evokes tonic leg muscle activation for sleep-compatible reduction of restless legs syndrome symptoms | Journal of Clinical Sleep Medicine
  - Results Posted | Noninvasive Peripheral Nerve Stimulation for Medication-Refractory Primary RLS (The RESTFUL Study) | ClinicalTrials.gov
  - Efficacy and safety of tonic motor activation (TOMAC) for medication-refractory restless legs syndrome: a randomized clinical trial – PMC



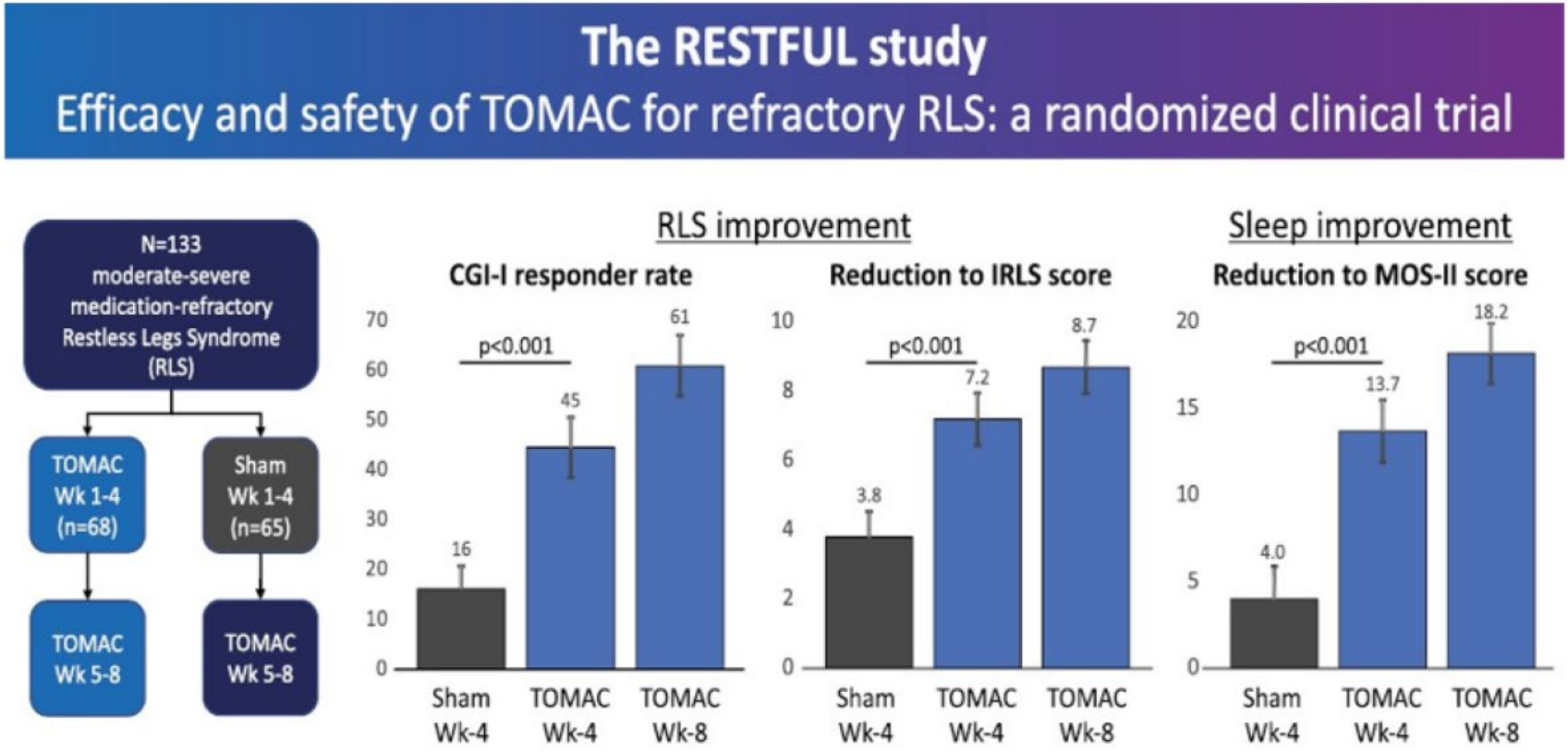
Nidra – RLS Relief

Nidra Therapy

- Non-invasive, drug-free wearable therapy
- Personalized, adjustable, and sleep compatible
- Relief from symptoms in as little as 30 minutes[1]

1. Buchfuhrer MJ, et al. J Clin Sleep Med. 2021;17(8):1685-1694.

Graphical Abstract



- Tonic motor activation (TOMAC) therapy improved RLS symptoms and sleep quality
- Responses improved further with continued TOMAC treatment
- No serious or severe TOMAC-related adverse events

Sleep, Volume 46, Issue 10, October 2023, zsad190, https://doi.org/10.1093/sleep/zsad190

Treatments to Use with Caution

Levodopa, Pramipexole, Rotigotine, Ropinirole

- Not recommended for standard use
- May be considered for short-term relief where benefits outweigh long-term risks (e.g., augmentation)
  - Augmentation: DA medications may be effective initially but over time there is a worsening of symptoms with prolonged use.
  - Recommendations for the Prevention and Treatment of RLS Augmentation: https://www.rls.org/file/publication-loader/Recommendations-for-Augmentation-Final.pdf

- Increased risk of psychiatric side effects
  - Increased Risk for New-Onset Psychiatric Adverse Events in Patients With Newly Diagnosed Primary Restless Legs Syndrome Who Initiate Treatment With Dopamine Agonists: A Large-Scale Retrospective Claims Matched-Cohort Analysis | Journal of Clinical Sleep Medicine

Treatments Not Recommended

- Bupropion
- Carbamazepine
- Clonazepam
- Valerian
- Valproic Acid
- Cabergoline

Dopamine Agonist Withdrawal Syndrome (DAWS)

- Characterized by anxiety, panic attacks, depression agitation, irritability, dysphoria, insomnia, fatigue, generalized pain, and drug cravings.

Distinction Between RLS and PLMS

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Gabapentin vs. Gabapentin Enacarbil

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Risk of Psychiatric Adverse Events in RLS Patients Treated with Dopamine Agonists

A Retrospective Claims Analysis

Increased Risk for New-Onset Psychiatric Adverse Events in Patients With Newly Diagnosed Primary Restless Legs Syndrome Who Initiate Treatment With Dopamine Agonists: A Large-Scale Retrospective Claims Matched-Cohort Analysis | Journal of Clinical Sleep Medicine

Objective

- - Investigate psychiatric risks of dopamine agonists (DAs) in patients newly diagnosed with RLS.
- - Compare DA-treated and untreated patients.

Methods

- - Retrospective cohort study (2008-2014).
- - Patients: Newly diagnosed RLS with no prior psychiatric disorders or DA use.
- - Matching criteria: Age, sex, region, employment status, comorbidities.

Findings

- - DA-treated patients had:
- - 1.71x higher risk of any psychiatric adverse event.
- - Increased risk for:
- - Severe P-AEs: OR 1.68.
- - Moderate P-AEs: OR 1.63.
- - Mild P-AEs: OR 1.72.

Psychiatric Adverse Events

- - Types of P-AEs observed:
- - Psychosis, mania, impulse control disorders.
- - Dopamine Agonist Withdrawal Syndrome (DAWS).
- - Symptoms resolved in some cases after stopping DAs.

- Pramipexole, ropinirole, and rotigotine have a high D3 receptor affinity.
- “The D3 receptor plays an important role in modulating the physiologic and emotional experience of novelty, reward, and risk assessment, and its activation likely explains the relatively higher rates of psychopathology among patients taking DAs.”
- In comparison, L-dopa is a precursor to dopamine and increases the availability of dopamine without specificity for a dopamine receptor.
- Among patients with PD, the link between DA treatment and the development of psychiatric adverse events (P-AEs) is well documented. Such P-AEs include psychoses and hallucinations; mania and hypomania; wandering; dopamine dysregulation syndrome, in which compulsive drug consumption is accompanied by psychomotor agitation and euphoria, drug-related dyskinesias, resistance to DA dose reduction, and withdrawal symptoms which may include depression, anxiety and/or im paired occupational and social functioning; punding, which manifests as repetitive and complex, albeit pointless, behaviors; and dopamine agonist withdrawal syndrome (DAWS), which is characterized by anxiety, panic attacks, depression, agitation, irritability, dysphoria, insomnia, fatigue, generalized pain, and drug cravings.

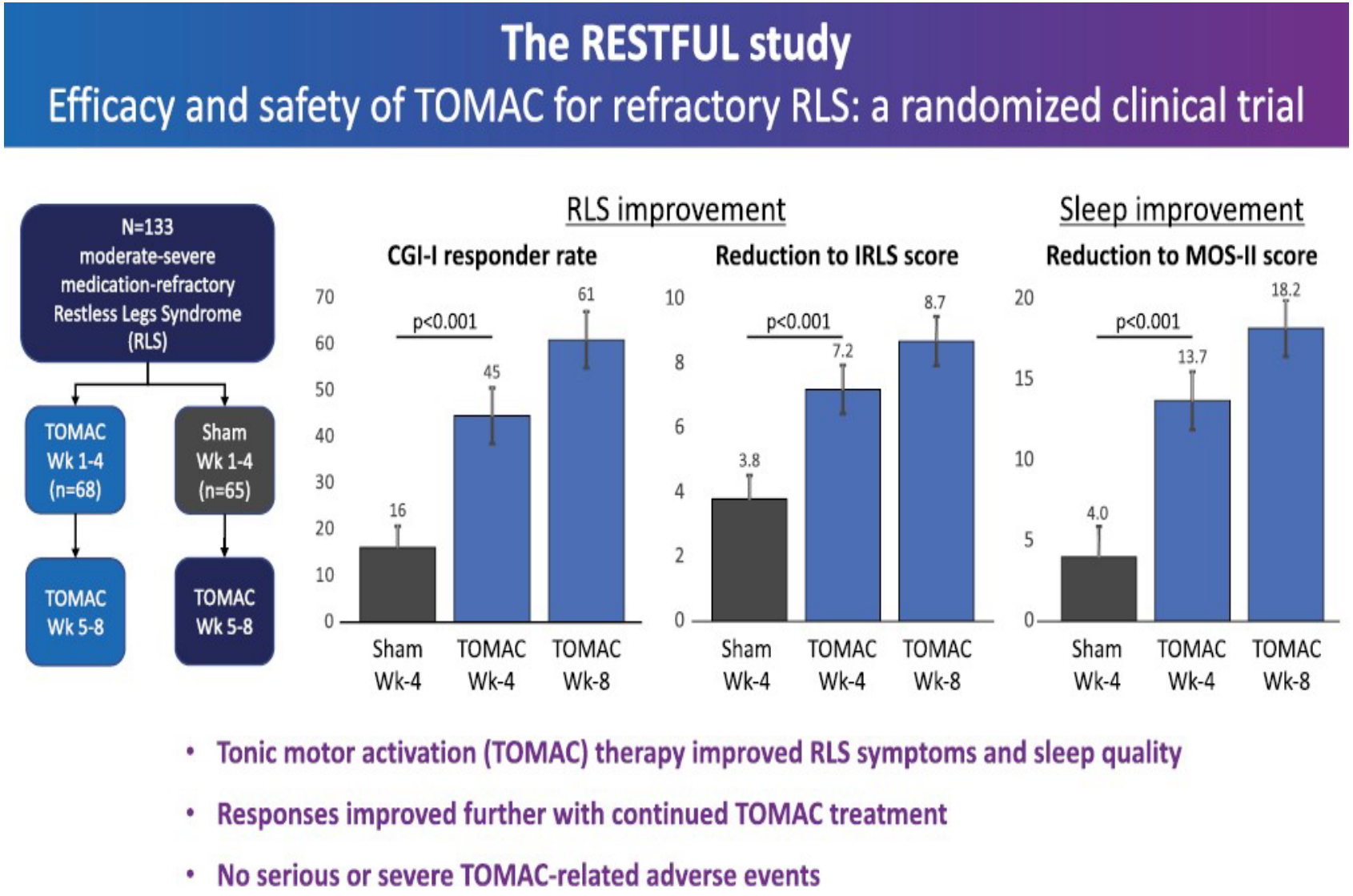
Limitations

- - Data limitations:
- - Retrospective design.
- - Psychiatric diagnoses based on clinical impression.
- - Limited generalizability.

Conclusion

- - Dopamine agonists increase the risk of psychiatric adverse events in RLS patients.
- - Clinical implication: Monitor closely for psychiatric symptoms in DA-treated patients.

Graphical Abstract



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