



UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

RESTLESS LEGS SYNDROME: CURRENT UNDERSTANDING AND CLINICAL PRACTICE GUIDELINE UPDATES

CATHERINE MCCALL, MD

PULMONARY, CRITICAL CARE, AND SLEEP MEDICINE,

VA PUGET SOUND AND UNIVERSITY OF WA

PSYCHIATRY AND BEHAVIORAL SCIENCES, UNIVERSITY OF WA



SPEAKER DISCLOSURES

- ✓ I am Chair of the Sleep Medicine Sleep Medicine Initial Certification and Maintenance of Certification Exam Approval Committee. Exam content is not included in this talk.

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

Mark Duncan MD

Rick Ries MD

Kari Stephens PhD

Barb McCann PhD

Anna Ratzliff MD PhD

Betsy Payn MA PMP

Esther Solano

Cara Towle MSN RN

OBJECTIVES

1. Understand the clinical presentation and evaluation of restless legs syndrome (RLS).
2. Learn about the epidemiology and risk factors for this condition.
3. Explore the new clinical practice guidelines for management of RLS.

CASE EXAMPLE

- A 55-year-old woman presents to clinic with a complaint of being unable to get to sleep at night. Soon after getting into bed, she experiences mind racing and cannot get comfortable. In particular, she notices her legs feel very uncomfortable with a sensation she has a hard time describing. She often gets out of bed to walk around, which helps. But when she gets back in bed, the sensation returns. She is often tossing and turning for several hours before she gets to sleep.
- This problem has been going on for about 5 years now, but has gotten much worse in the last 6 months or so.
- She has a history of depression and hypertension. Her mood has been low, which she attributes to stress and inadequate sleep. She is currently taking mirtazapine for mood and sleep, and lisinopril for blood pressure.

UNDERSTANDING THE PROBLEM

ANXIETAS TIBIARUM

“We frequently see this disease in clinical practice, and yet there is no other disease on which the authors keep a more profound silence. We see everyday women, and especially men, gouty and suffering from rheumatisms, who when the evening comes, cannot keep their legs still for a single minute because of the restlessness they feel in, and that movement transitory appeases”

-Methodical nosology by Francois Boissier de Sauvages de La Croix (1706–1767)

WILLIS-EKBOM SYNDROME

- Considered by Sir Thomas Willis in the 17th century to be an “akathisiac” psychiatric disorder
- Karl-Axel Ekbom then published a detailed thesis on the condition in 1945, which established it as a neurological syndrome
- The condition then became known as Willis-Ekbom syndrome

RESTLESS LEGS SYNDROME

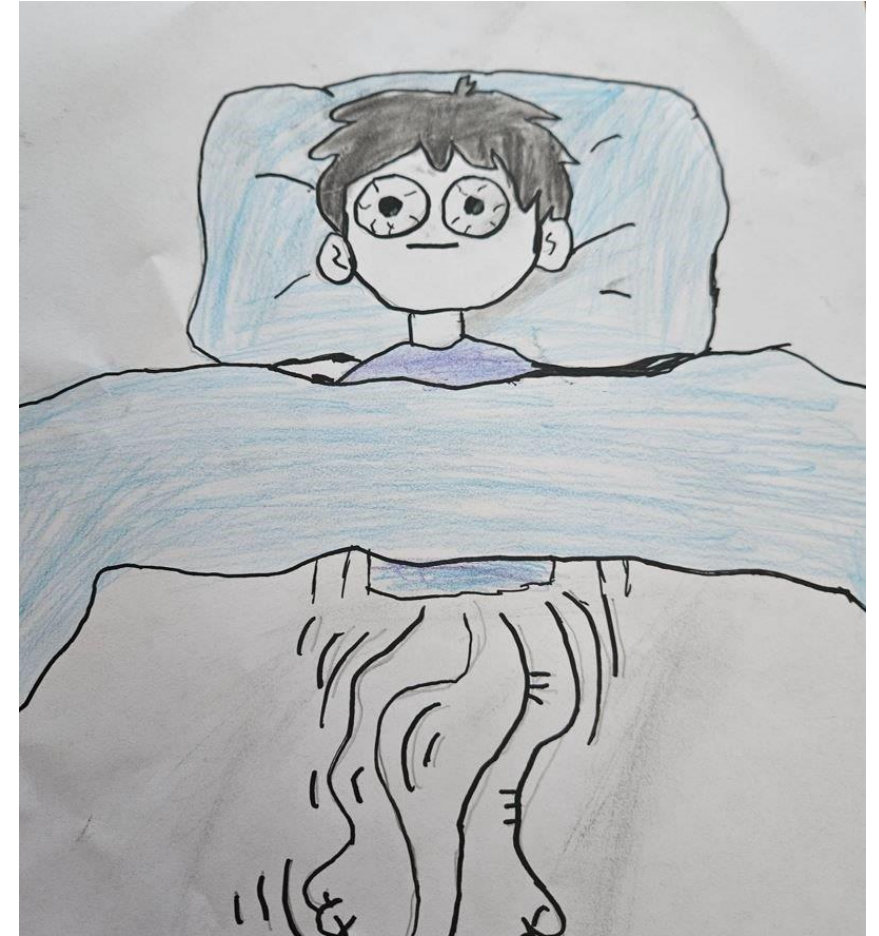
- A. Urge to move the legs, usually with uncomfortable and unpleasant sensations in the legs that:
 - 1. Worsen with rest
 - 2. Occur mostly at night
 - 3. Are relieved (temporarily) with movement
- B. The above features are not caused by an RLS mimic
- C. The symptoms of RLS cause distress, sleep disturbance, or daytime impairment



European Alliance for Restless Legs Syndrome

RESTLESS “LEGS” – NARROWING IT DOWN

- 21-57% of individuals with RLS may also describe restless arms (but very rare to be ONLY arms)
- Most frequently and severely felt in the calves



European Alliance for Restless Legs Syndrome

RLS SENSATIONS CAN BE HARD TO VERBALIZE

- Sometimes adults and especially children can find it difficult to put the problematic sensation into words
 - Most commonly described as, “restless,” “uncomfortable,” “twitchy,” “need to stretch,” “urge to move”
 - Sometimes described as painful



RLS Foundation

RLS DIAGNOSTIC CONSIDERATIONS

- RLS “mimics” are NOT RLS
 - Leg cramps
 - Diabetic neuropathy
 - Positional discomfort / tossing and turning
 - Myalgia
 - Venous stasis
 - Leg edema
 - Arthritis
 - Foot tapping/fidgeting
 - Akathesia
- RLS CAN be diagnosed in the setting of triggering medical conditions

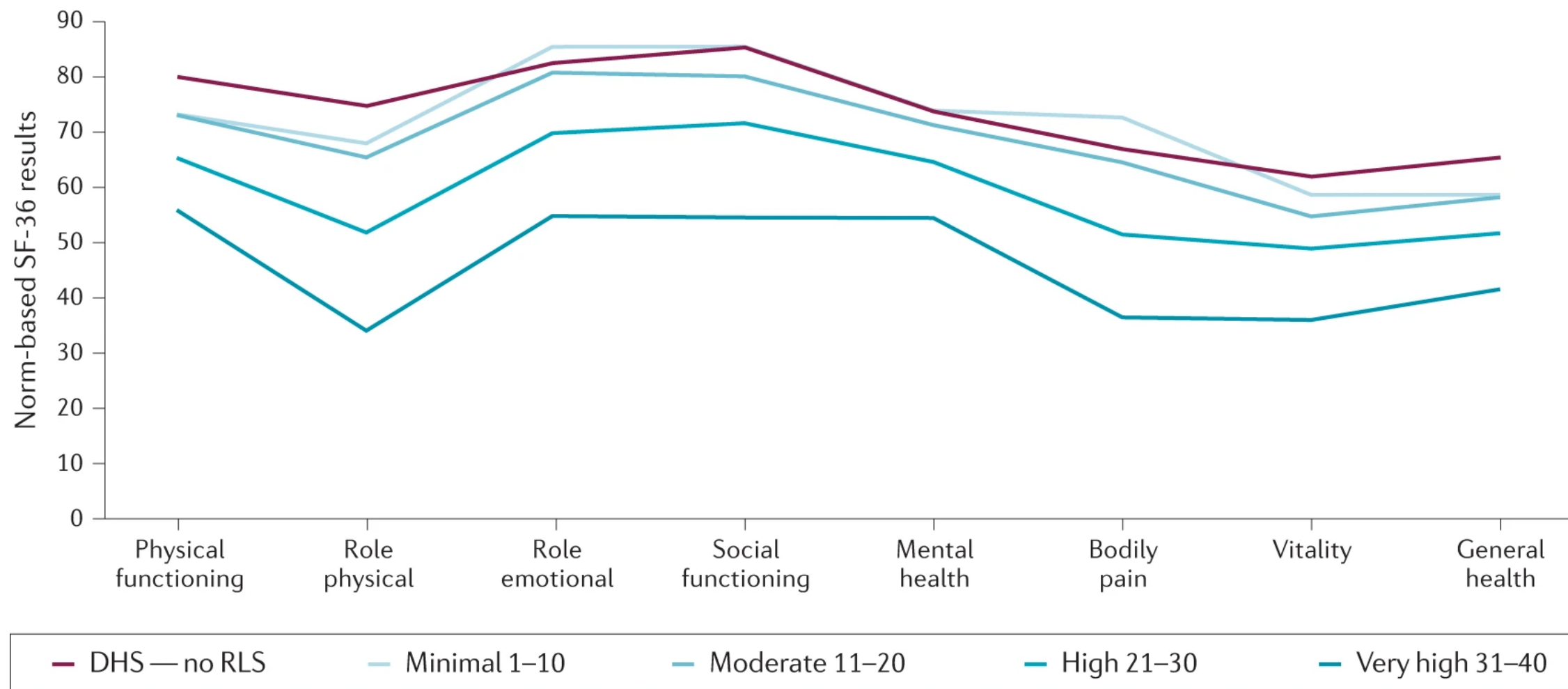
SEQUELAE OF RLS

- Disturbed sleep: 60-90%
 - 10% of patients with insomnia report RLS symptoms
- Daytime fatigue (though not as much sleepiness as with OSA)
- Periodic limb movements of sleep (PLMS) or wakefulness (PLMW)
 - NOT a diagnostic feature of RLS, but raise suspicion for RLS when observed on a laboratory polysomnogram
 - Frequently occur with brief arousals from sleep

ASSOCIATIONS WITH RLS

- Increased co-prevalence of:
 - Depression
 - Suicidality
 - Generalized anxiety disorder
 - Panic disorder
 - ADHD
 - 25% of RLS sufferers have ADHD symptoms
 - 12-35% of ADHD sufferers have RLS

QUALITY OF LIFE IMPACTS



PREVALENCE

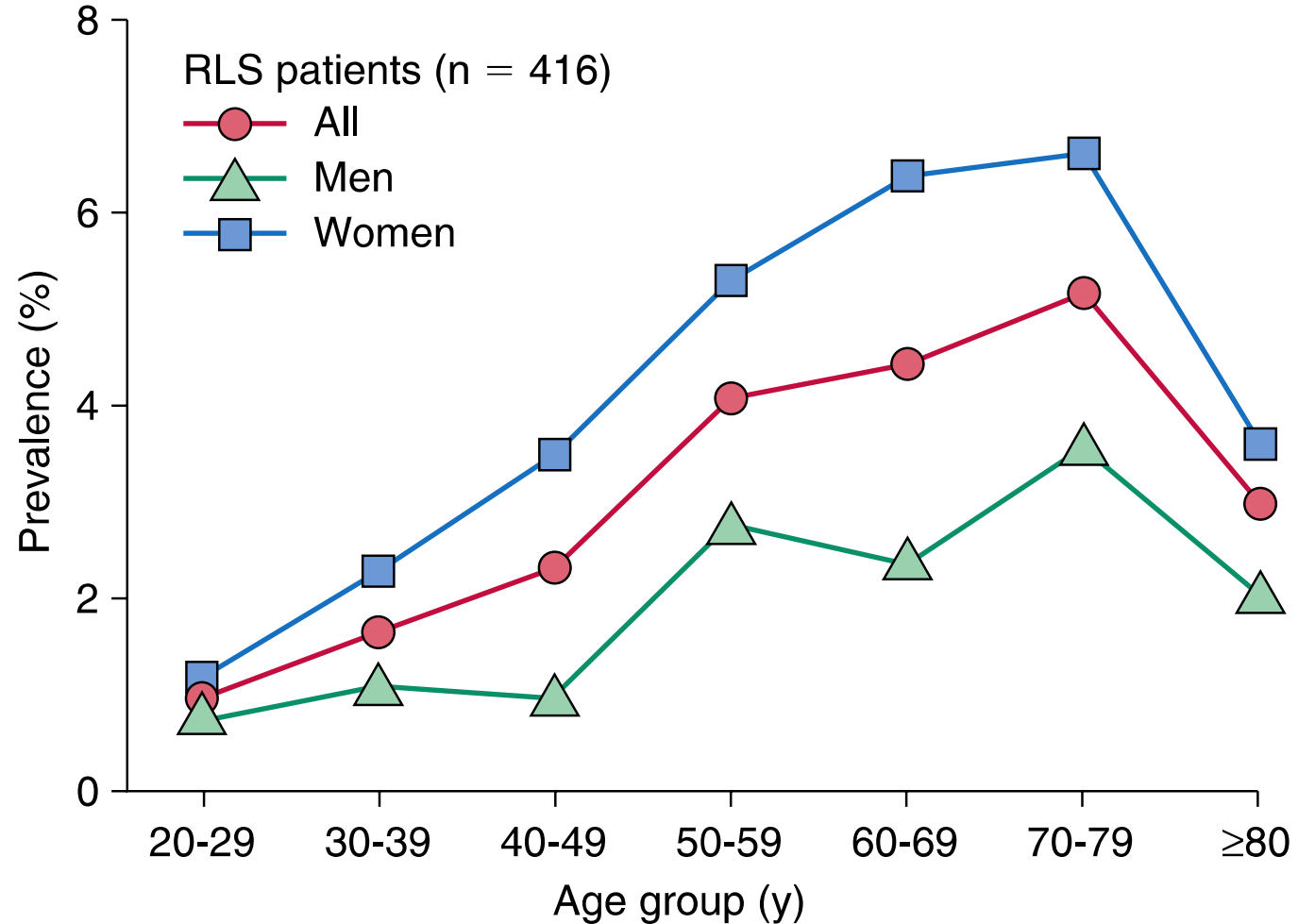
- In American and European studies: 5-10% overall
- In US/UK/Turkey children: 2-4%
 - More severe in adolescents
 - No difference between girls/boys
- Increases with age up to 60-70 years

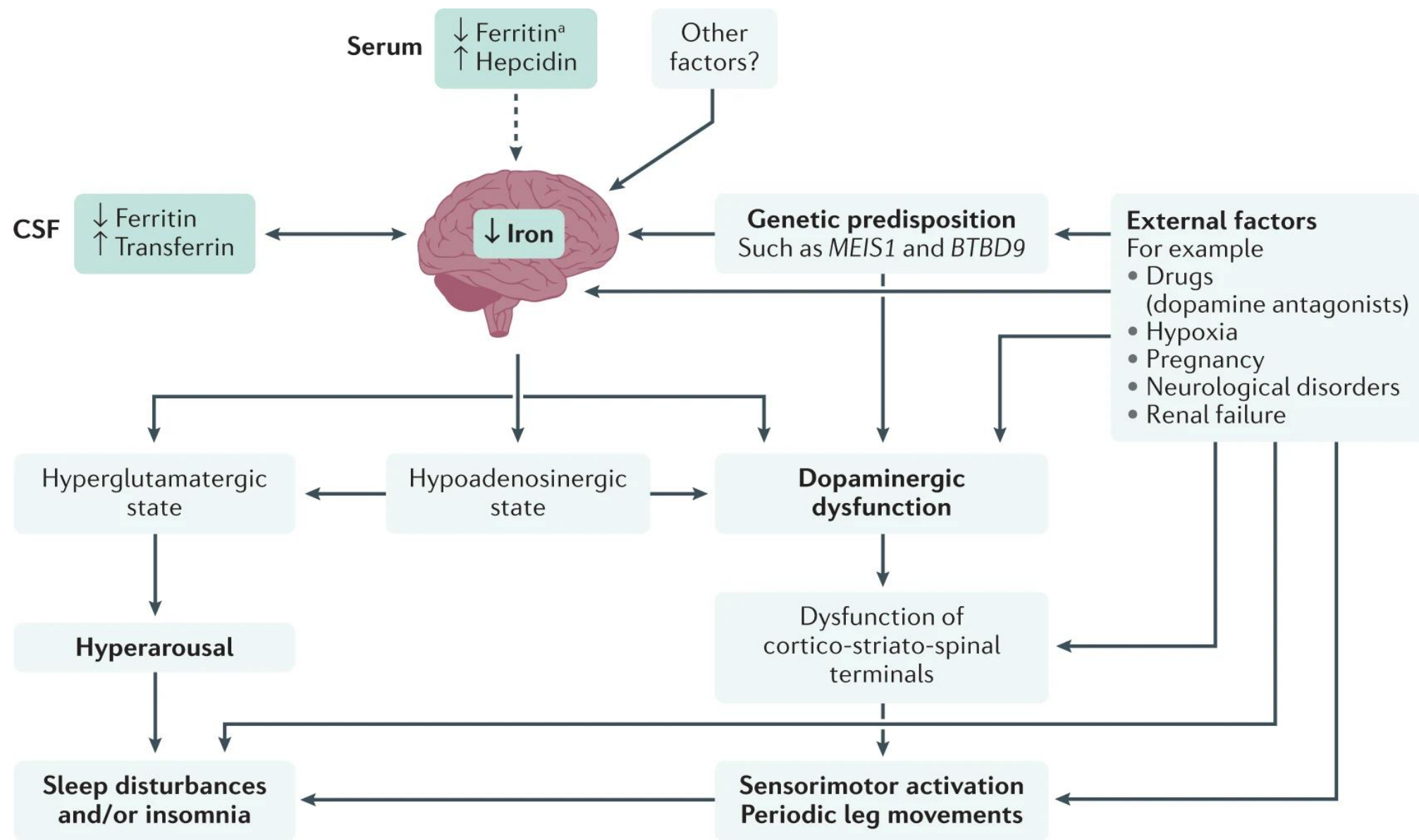


RLS Foundation

PREVALENCE

- Twice as high in women as in men
 - Increases with pregnancy to 3x the general population (peak 3rd trimester) and may resolve around childbirth
 - Individuals who had RLS during pregnancy have a 4x risk of RLS reappearing later in life

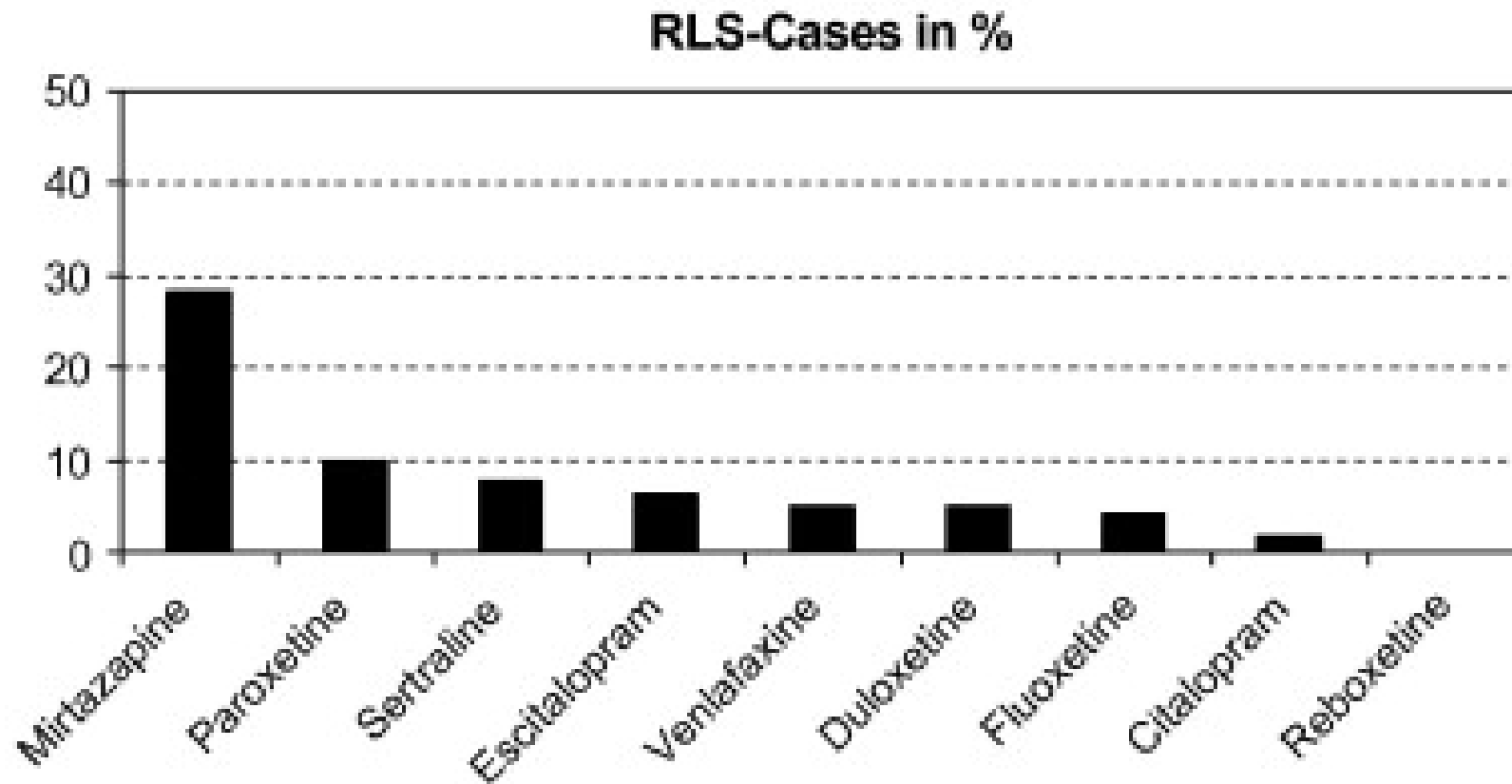


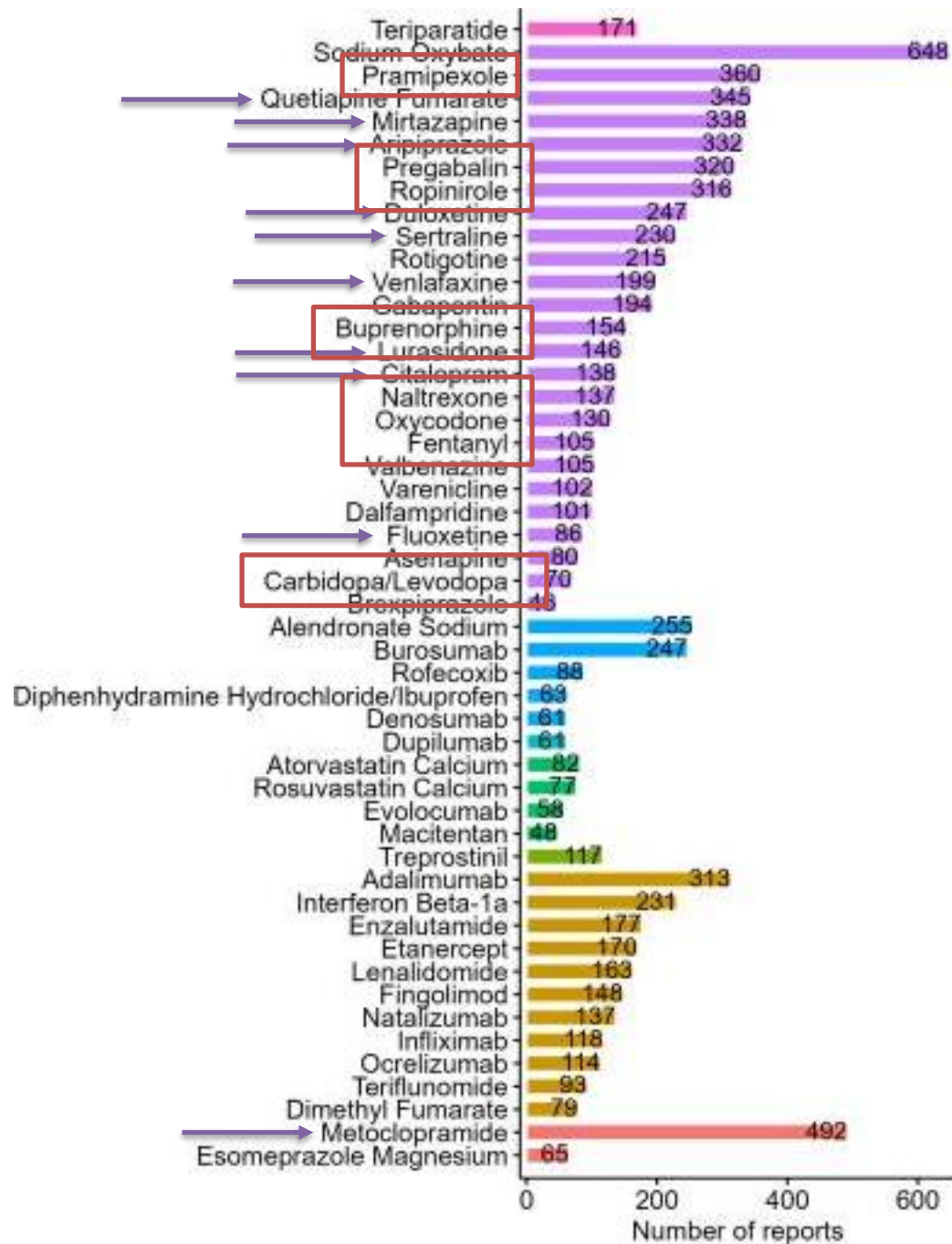


RLS TRIGGERS

- Medical conditions:
 - Iron deficiency (defined as ferritin <100 ng/ml)
 - Pregnancy
 - Chronic renal failure
 - Other sleep disorders (obstructive sleep apnea)
 - Autoimmune diseases
- MEDICATIONS/substances
 - Antihistamines
 - Serotonergic antidepressants (NOT bupropion)
 - Antipsychotics
 - Antiemetics
 - Alcohol, caffeine

RLS WITH MEDICATIONS





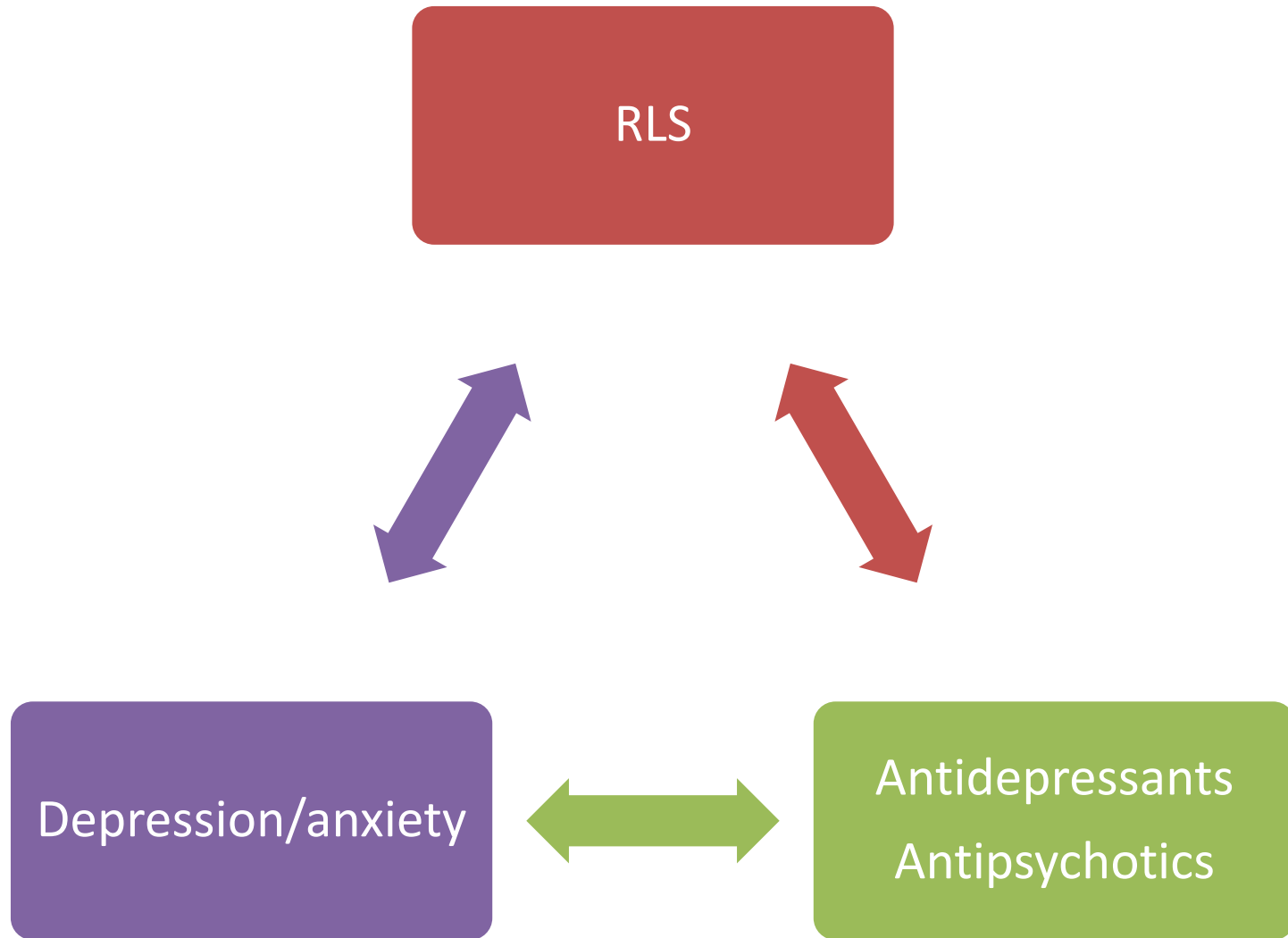
► Nat Sci Sleep. 2025 May 15;17:929–946. doi: [10.2147/NSS.S513538](https://doi.org/10.2147/NSS.S513538)

Exploring the Top 50 Drugs Associated with Restless Legs Syndrome Based on the FDA Data from 2004 to 2024

[Shiju Wei](#)¹, [Xuhua Song](#)², [Rui Chen](#)¹, [Siyu Chen](#)¹, [Baoping Lu](#)³,✉

ATC

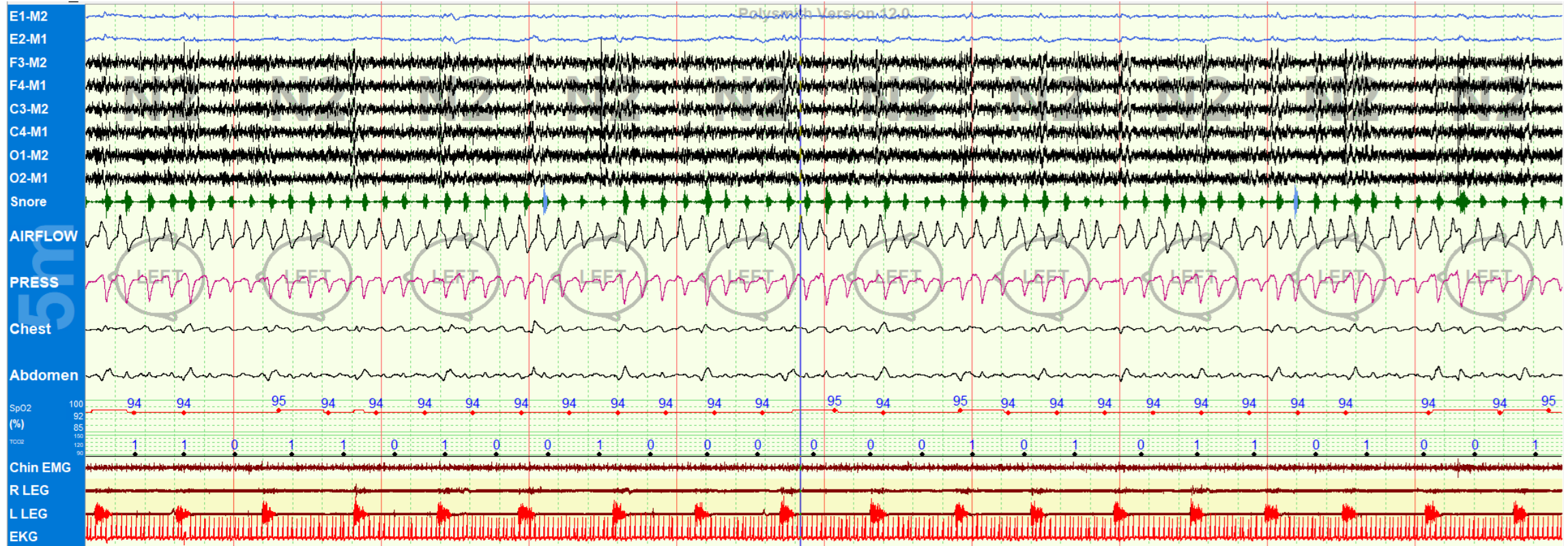
- ALIMENTARY TRACT AND METABOLISM
- ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
- BLOOD AND BLOOD FORMING ORGANS
- CARDIOVASCULAR SYSTEM
- DERMATOLOGICALS
- MUSCULO-SKELETAL SYSTEM
- NERVOUS SYSTEM
- SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS



TESTING

- RLS is a clinical diagnosis, so does not require further testing, however...
- Undiagnosed sleep disorders can worsen RLS and are worth investigating if symptoms are present
- Periodic limb movements observed on laboratory testing are NOT RLS, but occur in 80% of patients with RLS

PERIODIC LIMB MOVEMENTS AND RLS



OTHER MEASURES

- International Restless Legs Scale (IRLS)
 - 10-item rating scale developed by the International RLS Study Group
 - Can be used to evaluate baseline and post-treatment RLS severity
- Suggested Immobilization Test (SIT)
 - Patients sit in a bed with legs outstretched and are asked not to move voluntarily for 60 minutes; EMGs on anterior tibialis muscles quantify leg movements and patients are asked to score their discomfort.



Atlas of Clinical Sleep Medicine, 2024

CLINICAL PRACTICE GUIDELINES FOR MANAGING RLS

 Free Access • SPECIAL ARTICLES

Treatment of restless legs syndrome and periodic limb movement disorder: an American Academy of Sleep Medicine clinical practice guideline

John W. Winkelman, MD, PhD, FAASM, J. Andrew Berkowski, MD, Lourdes M. DelRosso, MD, PhD, FAASM, Brian B. Koo, MD, Matthew T. Scharf, MD, PhD, Denise Sharon, MD, PhD, FAASM, Rochelle S. Zak, MD, FAASM, Uzma Kazmi, MPH, Yngve Falck-Ytter, MD, Anita V. Shelgikar, MD, MHPE, FAASM, Lynn Marie Trotti, MD, Arthur S. Walters, MD, FAASM [SEE FEWER AUTHORS](#) ^

Published Online: January 1, 2025 • <https://doi.org/10.5664/jcsm.11390> • Cited by: 52

FIRST STEPS IN RLS MANAGEMENT

- Address exacerbating factors:
 - Alcohol
 - Caffeine
 - Antihistamine medications
 - Serotonergic medications
 - Antidopaminergic medications
 - Untreated OSA

IRON, IRON, IRON

- In ALL PATIENTS with significant RLS, test serum iron studies including ferritin and transferrin saturation
 - Testing should occur in the morning
 - Patients should avoid iron-containing supplements and foods ≥ 24 hours before the blood draw
- Iron supplementation is recommended if:
 - Serum ferritin ≤ 75 ng/mL or transferrin saturation $< 20\%$ $\rightarrow$ oral iron
 - Serum ferritin 75-100 ng/mL $\rightarrow$ IV iron
 - Children: serum ferritin < 50 ng/mL $\rightarrow$ oral or IV iron

IRON FORMULATIONS

- Recommended IV iron formulations:
 - Ferric carboxymaltose (strong recommendation)
 - Low molecular weight iron dextran (conditional recommendation)
 - Ferumoxytol (conditional recommendation)
- Recommended oral iron formulations:
 - Ferrous sulfate (conditional recommendation)

RECOMMENDED MEDICATION OPTIONS

- Alpha-2-delta ligands
 - Gabapentin enacarbil (strong recommendation)
 - Gabapentin (strong recommendation)
 - Pregabalin (strong recommendation)
- Dipyridamole (conditional recommendation, 1 RCT)
- Extended-release oxycodone (conditional recommendation)

MEDICATIONS NO LONGER RECOMMENDED...

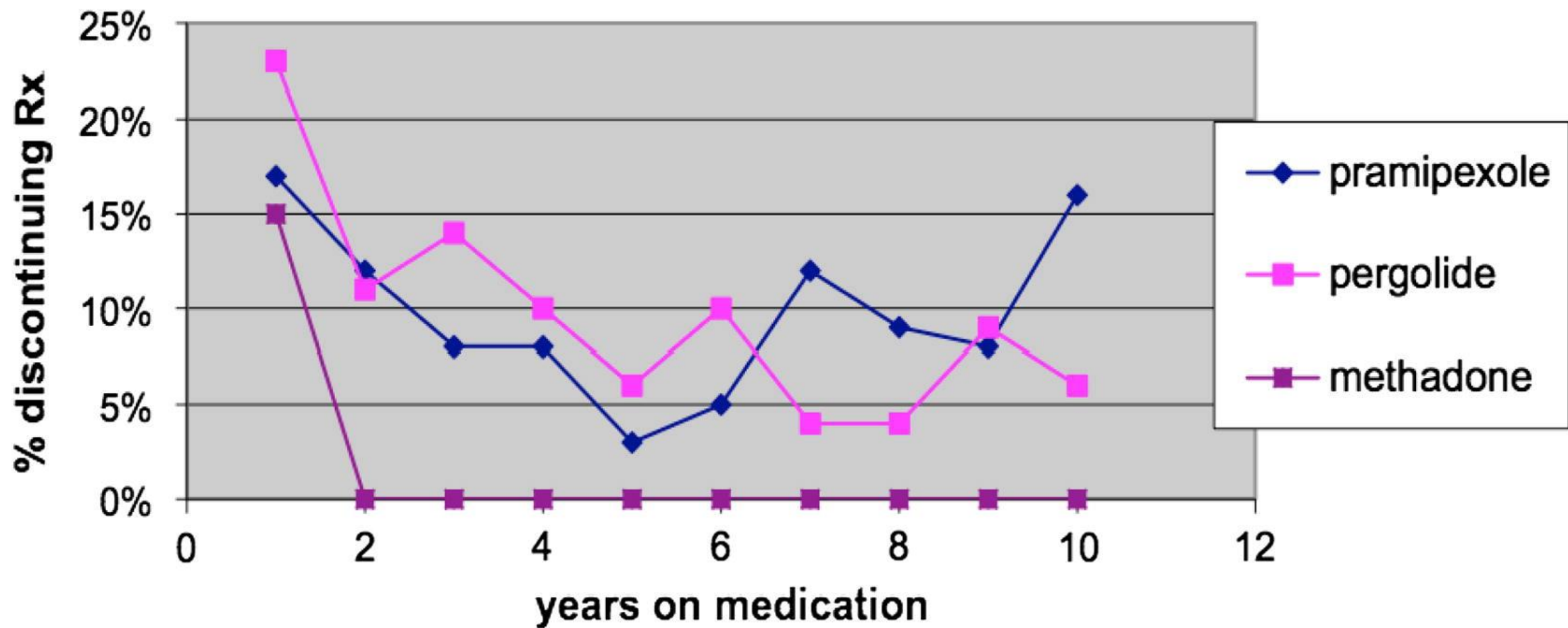
- Dopamine agonists: the previous mainstays of treatment are no longer recommended
 - Levodopa
 - Pramipexole
 - Rotigotine
 - Ropinirole
- The task force recommended that patients who are already on these medications switch to another agent when possible

AUGMENTATION

- Worsening of symptoms may occur with dopamine agonist medications. Symptoms may:
 - Increase in severity
 - Start earlier in the day
 - Start more quickly when at rest
 - Spread to other body parts (such as arms)
 - Last longer
 - Require higher doses of medication to manage
 - Paradoxically increase with higher doses of medication

AUGMENTATION

- Augmentation may gradually worsen over months to years of dopaminergic medication exposure
 - Occurs in up to 9% of patients per year on these medications
 - 45-75% of long-term users have reported symptoms of augmentation
 - Lower doses may reduce the risk of augmentation



Median methadone dose at 6 months: 10mg

PERONEAL NERVE STIMULATION

- Bilateral high-frequency peroneal nerve stimulation (conditional recommendation)
 - Uses tonic motor activation to stimulate the peroneal nerve (outer leg from knee to ankle)
 - May be of particular benefit with refractory RLS



RETURNING TO THE CASE.....

- After reviewing the clinical practice guidelines, you realize your patient's antidepressant, mirtazapine, might be exacerbating her RLS
- You work with her prescriber to safely transition her to another medication, bupropion, which is helpful for her mood.
- Switching medications helps her RLS, but she still has trouble sleeping due to sensations in her legs. You test her iron labs and find she has a ferritin level of 37 ng/mL. You prescribe an oral iron supplement with a vitamin C supplement to improve absorption, recommend to avoid calcium 2 hours before/after taking iron, and counsel about possible side effects (nausea, constipation, black stools).
- You also refer her for a sleep study because her post-menopausal status and disturbed sleep place her at elevated risk for OSA.

CASE, CONTINUED

- Her laboratory sleep study did not show OSA.
- Three months later, your patient presents to clinic and lets you know she is feeling much better after starting iron supplementation.
- She is no longer experiencing bothersome sensations in her legs that prevent sleep. Her follow-up ferritin level is 94 ng/mL.

SUMMARY

- RLS is a very distressing condition that can lead to significant sleep loss, mood/anxiety disorders, suicide risk, and global lower quality of life
- This condition can be diagnosed based on clinical interview alone
- The foundations of RLS management are to eliminate exacerbating factors and correct iron deficiency when possible
- Medications such as alpha-2-delta ligands and opioids can be helpful at relatively low, stable doses