

# Basics of Restless Legs Syndrome (Willis-Ekbom Disease)

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# Objectives

- Understand how RLS is diagnosed
- Understand what we know (and don't know!) about the causes of RLS
- Know which self-help approaches to RLS may be effective
- Be familiar with the drugs used to treat RLS and their side effects



# The Diagnosis





## ICSD-3 Criteria

### **Urge to move the legs,**

usually but not always, accompanied or caused by unpleasant leg sensations, which:

1. Are present during rest or inactivity
2. Are partially or completely relieved by movement such as stretching or walking, as long as activity continues
3. Only occur or are worst in the evening and night

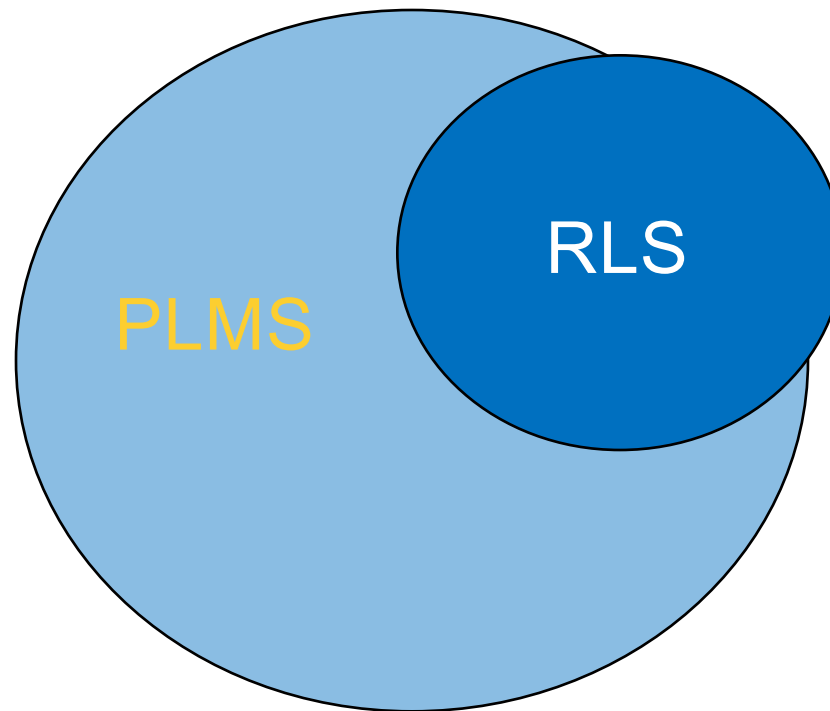


# Additional Clinical Features

- Resultant sleep onset or maintenance insomnia
- Associated with periodic limb movements



# Relationship between RLS and PLMS





# Common Questions about RLS Symptoms

## **Can RLS be painful?**

- Yes, but first consider:
  - \* arthritis
  - \* fibromyalgia
  - \* nocturnal leg cramps



# Common Questions about RLS Symptoms

Can RLS be asymmetric or only on one side?

- RLS may alternate between legs
- RLS may sometimes be consistently worse in one leg
- RLS may very occasionally only occur in one leg - other causes or an underlying condition should be considered





# Common Questions about RLS Symptoms

## **Is the urge to move essential?**

- Yes, this is the fundamental symptom of RLS
- Unconscious jiggling movements while sitting, easily discontinued with awareness, are learned habits, not RLS



# Common Questions about RLS Symptoms

**Does relief by change in position support the diagnosis?**

- Generally not
- Usually due to pressure on skin or soft tissues, especially if related to a specific leg position



# Common Questions about RLS Symptoms

## **Must the symptoms be relieved by movement?**

- Yes, but only as long as the movement continues
- In advanced RLS, relief during movement may be less evident



# What may be confused with RLS?

- Leg cramps
- Positional discomfort
- Habitual foot tapping



# How Common is RLS?

**1.5 - 2.7%**

for RLS/WED

- at least 2 days a week
- causing at least moderate distress  
(About 1 in 50 persons will have RLS)

Allen 2010, 2011

# What causes RLS?





# Genes

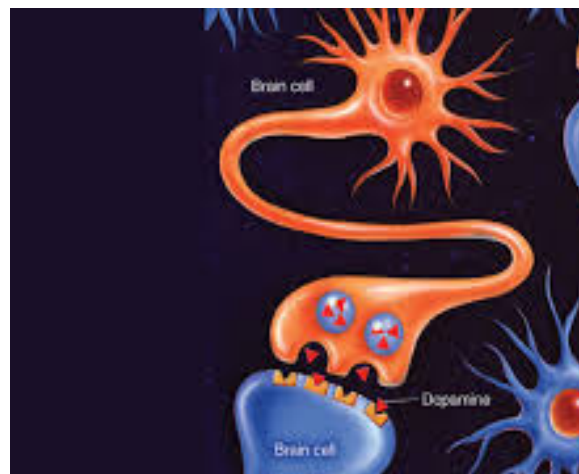
- At least 50% of RLS is genetic
- Seems to be an autosomal dominant trait
- Association with multiple chromosomes and multiple genes.
- No comprehensive model





# Dopamine

- Dopamine is a neurotransmitter in the brain associated with movement, arousal, and the reward system
- Drugs enhancing dopamine work for RLS
- The problem may be reduced dopamine receptors (the proteins which bind dopamine)







# Iron

- In some patients with RLS, iron stores are reduced in the body (blood loss, frequent blood donations)
- MRI and autopsy studies show reduced iron in areas of the brain in RLS patients
- The problem may be problems transporting iron into the brain
- Iron is needed for the dopamine receptor



# Treatment



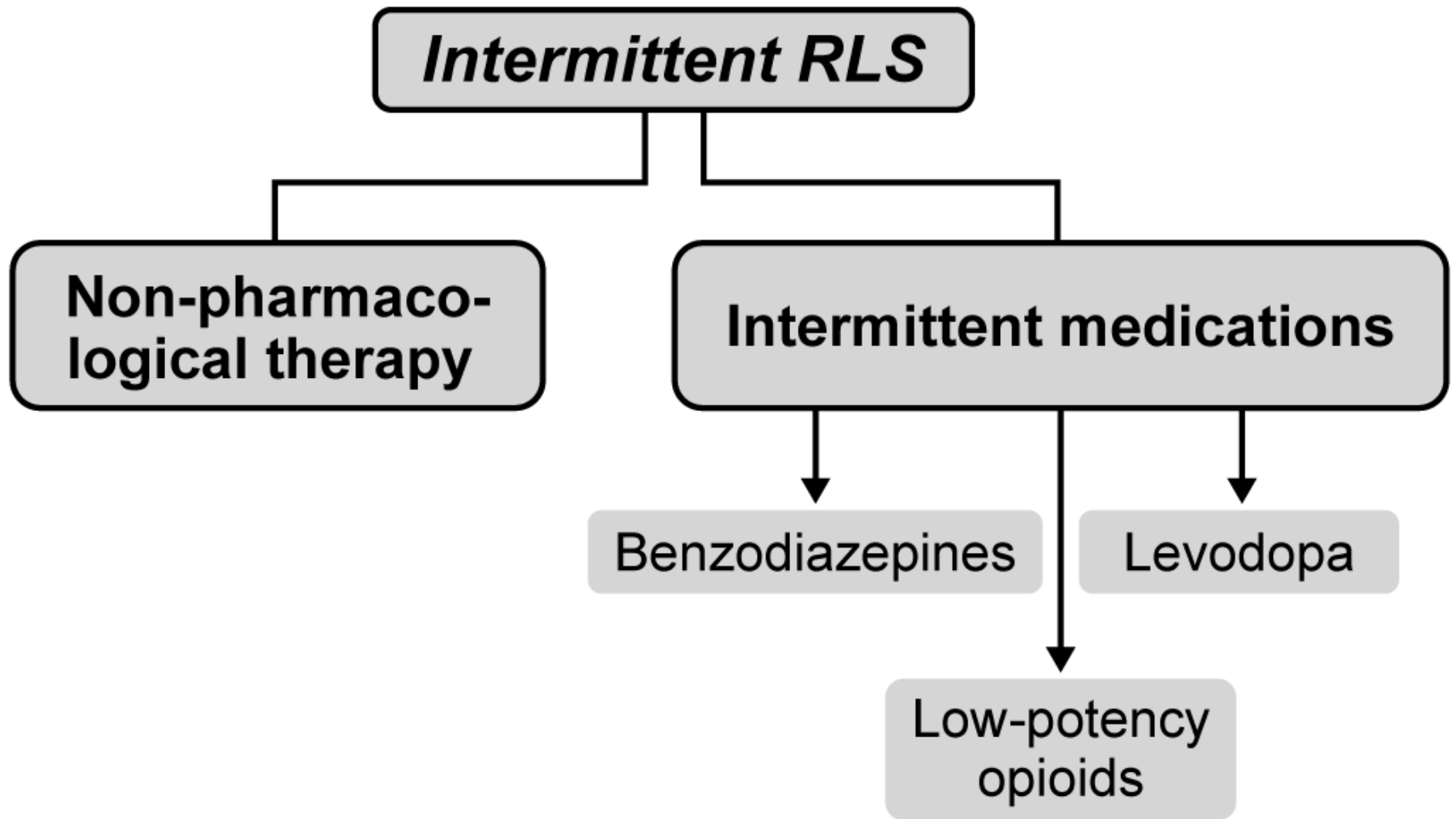


# Intermittent RLS/WED

## Definition

RLS that is troublesome enough to require treatment but occurs on an average less than twice weekly

Silber et al Mayo Clin Proc 2013





# Behavioral Therapies

- Walking, stationary bicycling, rubbing or soaking limbs
- Mental alerting techniques
- Regular moderate physical activity
- Reduction in caffeine
- Consider withdrawal of antidepressants, anti-nausea meds, antihistamines



# Iron?

- Do not take unless iron levels are low
- Consider for serum ferritin < 50-75 mcg/l
- Take under medical supervision twice a day between meals with Vitamin C
- Can cause indigestion, constipation and black stools
- Intravenous iron infusions are available if oral iron poorly absorbed or not tolerated
- Recheck ferritin every 3-6 months



# Chronic Persistent RLS/WED

## Definition

RLS which is frequent and troublesome enough to require daily therapy, usually at least twice a week causing moderate or severe distress



# Chronic Persistent RLS/WED

## Dopamine Agonist **OR** Calcium Channel Ligands

Dopamine Agonists	Calcium Channel Ligands
Very severe RLS	Comorbid pain
Comorbid depression	Comorbid anxiety
Obesity/metabolic syndrome	Comorbid insomnia
	Prior impulse control disorders or addiction





# Dopamine Agonists:

## **Pramipexole and Ropinirole**

- Bind to dopamine receptors
- Approved by the FDA for treatment of RLS
- Trials demonstrate efficacy (>1,000 patients)
- Generics available
- Limit daily dose (much less than for Parkinson disease) (pramipexole 0.5 - 1 mg; ropinirole 4 mg)



# Dopamine Agonists:

## **Rotigotine Transdermal Patch**

- Apply once a day
- Trials demonstrate efficacy (>1,000 patients)
- Approved by FDA for RLS/WED treatment
- Skin reactions common



# How successful are the dopamine agonists?

## **Much or very much improved:**

- Pramipexole: 59-75%
- Ropinirole: 53-68%
- Rotigotine: 50-75%

Oertel 2007, 2008; Winkelman 2006; Trenkwalder 2004, 2008; Walters 2004; Ferini-Strambi 2008; Giorgi 2013; Inoue 2013



# Long Term Follow Up

	<b>Pramipexole</b>	<b>Pramipexole</b>	<b>Rotigotine</b>
Patients	50	164	295
% on drug after 5 years	90	58	43
% on drug after 10 years	82	25	-
	Lipford 2012	Silver 2011	Oertel 2011



# Dopamine Agonists

## **Mild Side Effects**

- Lightheadedness
- Nausea or indigestion
- Nasal congestion
- Leg swelling
- Sleepiness



# Dopamine Agonists

## **Serious Side Effects**

- Augmentation
- Impulse control disorders



# Augmentation

## **Development of worsening RLS with increasing doses of dopaminergic medication**

- Earlier onset symptoms (2-4 hours+)
- Spread to arms or trunk
- Shorter duration of response to medication



# Augmentation (10 year studies)

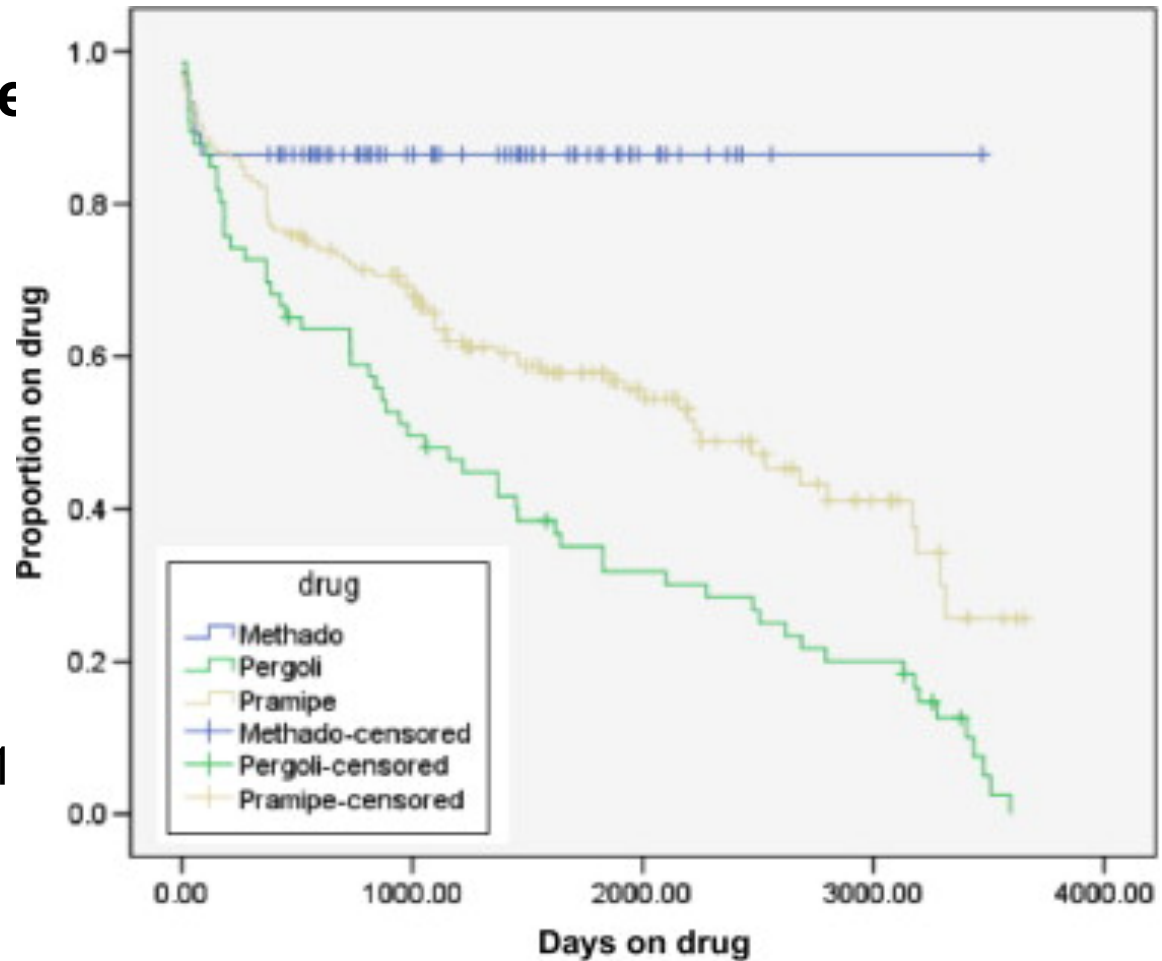
**164 patients on pramipexole**

10 years follow-up

Discontinuation rate due to  
augmentation:

7% per year

Silver 2011







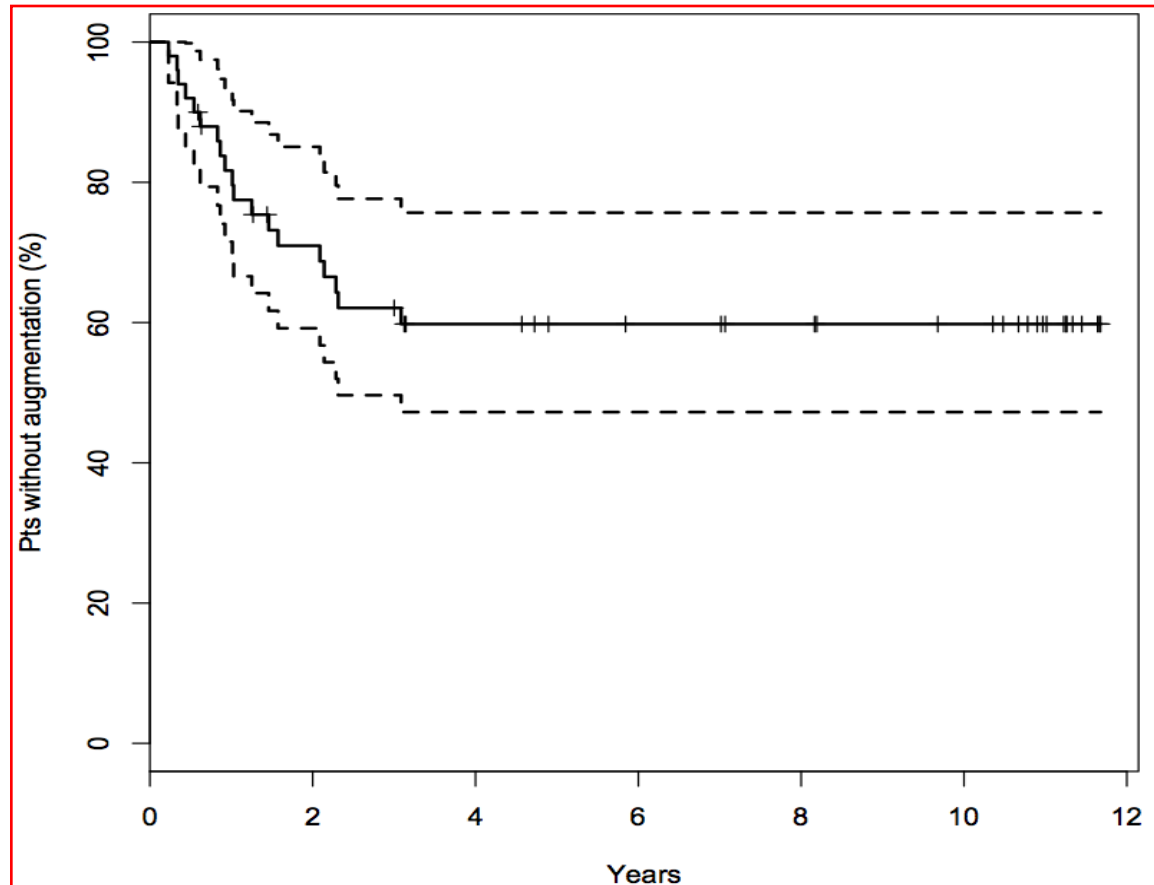
# Augmentation (10 year studies)

**50 patients on pramipexole**

Median follow-up 9.7 yrs

Augmentation rate 42%

Lipford 2012





# Augmentation (5 year study)

**295 patients on Rotigotine**

Augmentation rate 36%

Discontinuation rate due to augmentation 4%

Oertel 2011



# Impulse Control Disorders

- Any ICD 17% (control 6%)
- Pathologic gambling 9% (control 0.4%)
- Compulsive shopping 5% (control 0.7%)
- Hypersexuality 3% (control 0.4%)

Mean time of onset after starting therapy: 9 months

Cornelius Sleep 2010



# Calcium Channel Ligands

- Gabapentin
- Gabapentin Enacarbil (slow release; once a day)
- Pregabalin

Side-Effects: sleepiness, dizziness, unsteadiness, weight gain, depression



# Calcium Channel Ligands

- Only gabapentin enacarbil FDA approved for RLS
- Study showed pregabalin as effective as pramipexole, but more side effects
- No augmentation



# Augmentation

- Check ferritin
- Split agonist dose, cautiously increase total dose watching for progressive augmentation and not exceeding recommended total daily dose
- Change to rotigotine
- Change to a calcium channel ligand



# Refractory RLS/WED

## Definition

RLS unresponsive to monotherapy with tolerable doses of 1<sup>st</sup> line agents due to reduced efficacy, augmentation or side effects



# Refractory RLS/WED

- Reassess iron stores
- Use combination therapy: Reduce the dose of the first line agent and add one or more alternative agents (e.g. calcium channel ligand to agonist)
- Substitute a medium or high potency opioid





# Opioids

- Very effective for refractory RLS
- 2% serious side-effects (vomiting, constipation, ileus)
- Persistent benefit up to 10 years
- Prescribed drugs include oxycodone, methadone and others



# Opioid Side Effects

- Itch
- Constipation
- Nausea and vomiting
- Cognitive effects
- Gait unsteadiness and falls
- Sleep apnea
- Overdose
- Addiction



# Opioid Rules

- No early refills
- No replacements for lost prescriptions or drugs
- No changes in regime without discussion with provider
- Opioids from only one provider
- Random urine drug screens
- Use of state prescription monitoring programs
- Frequent reassessment of response and side effects

