Case Presentation

- 47-year-old man presents with restlessness and urge to move at night and difficulty falling sleeping since age 17 years.
- The resulting symptoms leads to significant impairment of sleep and quality of life
- The symptoms improve somewhat when hitting his legs with a baseball bat.

Case: Assessment

Which of the following is most highly specific consistent with a diagnosis of RLS?

- 1) Depression
- **2) Urge to move**
- 3) Restlessness at night
- 4) Insomnia

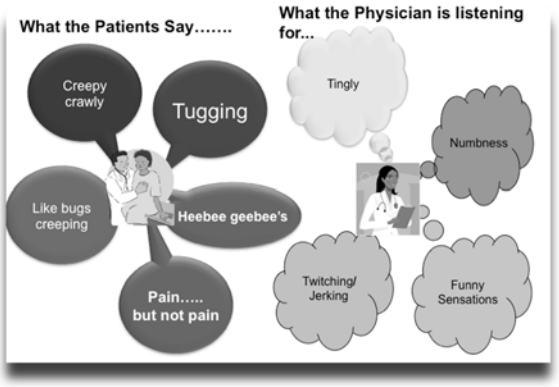
Restless Legs Syndrome (RLS)

- Neurological sensorimotor disorder characterized by an irresistible urge to move the legs accompanied by uncomfortable sensations that often occur in the evening or when at rest, which may be temporarily relieved with movement 1
- Affects approximately 10% of US adults [2,3]*
- Difficulty falling asleep is often a primary reason patients seek medical attention1
- Believed to be associated with dopaminergic dysfunction[4,5]

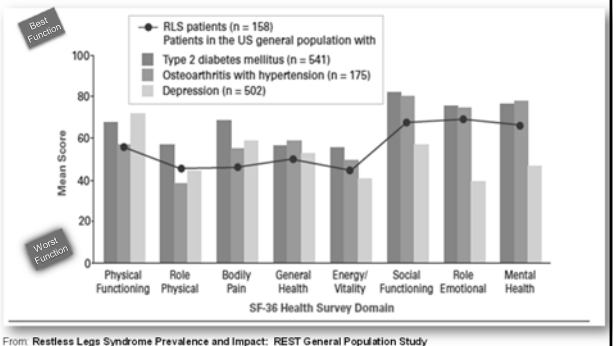
* Includes mild, moderate, and severe RLS.

1. Allen et al. *Sleep Med.* 2003;4:101-119.
2. Phillips et al. *Arch Intern Med.* 2000;160:2137-2141.
3. Hening et al. *Sleep Med.* 2004;5:237-246.
4. Allen and Earley. *J Clin Neurophysiol.* 2001;18:128-147.
5. Turjanski et al. *Neurology.* 1999;52:932-937.

RLS: The Communications Disconnect



SF36 RLS vs. Other Medical Conditions



From: **Restless Legs Syndrome Prevalence and Impact: REST General Population Study**

Comparison of mean Short Form 36 Health Survey (SF-36) scores of US patients with restless legs syndrome ("RLS sufferers") with those of US patients with common chronic medical conditions.

RLS = Willis-Ekbom Disease

Key RLS diagnostic criteria	Supportive features
Urge to move	Sleep disturbances
	PLMS
Temporary relief with movement	Positive family history for RLS
Onset at rest	Positive response to dopaminergic therapy
Circadian predilection ➡ evenings	A low serum ferritin **(50 ug/L)**

Willis-Ekbom Disease

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

* 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.

RLS

Key RLS diagnostic criteria*	Supportive features*
Urge to move the legs or arms usually accompanied or caused by uncomfortable leg sensations	Sleep disturbances
Temporary relief with movement and 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
	Positive response to dopaminergic therapy

Associated features

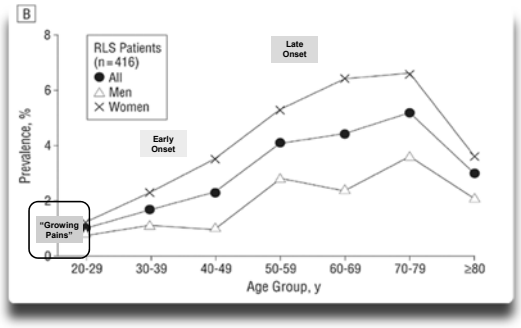
Natural clinical course of the disorder
Can begin at any age,
Most are middle-aged or older.
Most patients have a progressive clinical course, but a static clinical course is sometimes seen. Remissions of a month or more are sometimes reported

Sleep disturbance
The leg discomfort and the need to move result in insomnia

Medical investigation/neurological examination
A neurological examination is usual in idiopathic and familial forms of the syndrome.
Peripheral neuropathy or radiculopathy are sometimes carried out in the non-familial form of the syndrome.
A low serum **ferritin (50 g/L)** may be found in the syndrome.

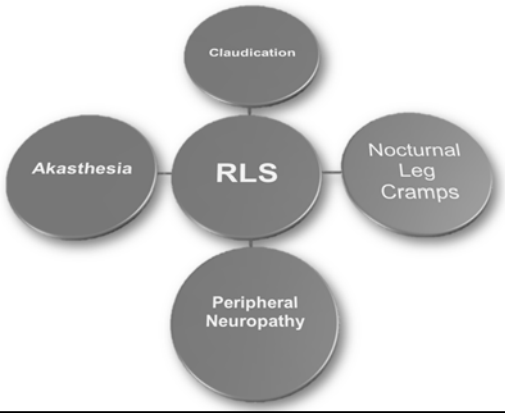
REST General Population Study

Presence, frequency, and severity of RLS in 16,202 adults throughout the U.S and 5 EU countries



Allen R, Walters A, Montplaisir J, et al. *Arch Intern Med.* 2005;165:1286-1292.

Differential Diagnosis of RLS



Restless Legs Syndrome (RLS) "URGE"

- **U**rge to move limbs
- **R**est or inactivity precipitates or worsens symptoms
- **G**etting up improves the sensation
- **E**vening or night time predominance

• Allen R, Picchietti D, Hening W, et al. *Sleep Med. 2003;4:101-119.*
• Walters AS. *Mov Disord. 1995;10:634-642.*.

Classification of RLS

- **Primary/Idiopathic**
- **Secondary**
  - Iron deficiency
  - Pregnancy
  - Renal insufficiency
  - Neuropathy
  - Hypo/hyperthyroidism
  - Drugs (AEDs, neuroleptics, antidepressants,anti-emetics)

Pregnancy

- 19% report RLS symptoms during pregnancy;
  - ⋆ 7% “severe”
- Resolution of symptoms in 96% within 1 month of delivery

Earley CJ. N Engl J Med. 2003;348:2103-2109.
Image used with patient's permission.

Early Onset RLS	Late Onset RLS
Age ≤ 45	Age> 45
Slowly progressive	Rapidly progressive
Familial	Sporadic
Primary	Secondary/Primary

Differential Diagnosis of RLS & Mimics

Diagnosis	Clinical Features	Circadian Timing
RLS	Clinical symptoms of uncomfortable sensation brought on at time of inactivity or rest with relief once movement commences.	Night
PLMD	PSG findings characterized by periodic episodes of repetitive and stereotyped limb movements that occur during sleep. Lack sensory symptoms of RLS.	Night
Nocturnal leg cramps (‘Charlie horse cramps’)	Painful and palpable muscular contractions. Relieved with stretching,	Night
Painful Peripheral Neuropathy	Sensory symptoms described as numbness, burning and pain. Typically not relieved while walking or during sustained movement.	Diurnal, Increased at night
Neuroleptic induced akathisia	Described as a “whole body sensation” rather than centered only in limbs. Do not improve with movement. Positive history of specific medication exposure.	None
Arthritis lower limb	Discomfort is centered in the joints.	None
Volitional movements, foot tapping leg rocking	Occurs in fidgety patients, during times of anxiety or boredom. Typically lack sensory symptoms, discomfort or the urge to move.	None
Positional discomfort	Associated with prolonged sitting or lying in the same position, relieved changing position.	None

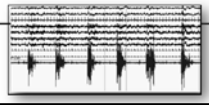
Modified after: Lesage S, Hening WA. The restless legs syndrome and periodic limb movement disorder: a review of management. Semin Neurol 2004;24-3:249-59.

RLS

- **RLS is a symptom based Dx**
- **RLS is Dx in the physician’s office**
- **80% of people who have RLS will have PLM’s**

PLMS

- **PLMS are an EMG finding**
- **PLM’s are Dx in the sleep lab**
- **30% of individuals who have PLM’s have RLS symptoms**

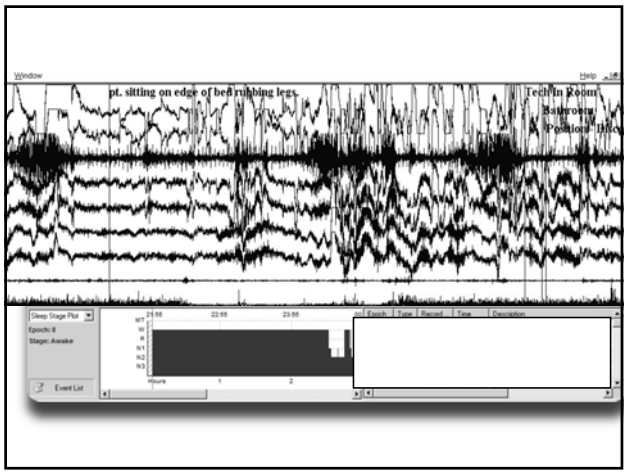


Definitions

- **RLS** = Restless Legs Syndrome: Uncontrollable urge to move the legs, while at rest, worse in the evening, gets better with movement.
- **PLM** = Periodic limb movements recurring periodically (5 to 90 sec period) in a series (4 or more) in any sleep or wake state
- **PLMW** = PLM in wake: usually seen as part of a nocturnal PSG, but not necessarily scored.
- **PLMS** = PLM in sleep: characteristic movements that occur during sleep
- **PLMD** = PLM disorder: a sleep disorder based on a finding of PLMS (usually > 15/hr of sleep) with an associated sleep dysfunction

When to Order Polysomnography in RLS ?

- If the diagnosis of RLS is uncertain
- If sleep apnea or PLMD is suspected
- If RLS symptoms are minimal but sleep disruption occurs nightly
- If frequent sleep disruption continues despite apparently adequate treatment of RLS



RLS Pathophysiology: Iron-DA Model of RLS

Intracerebral Iron Insufficiency

↓

CNS DA Abnormalities

↓

RLS

Allen RP, Earley CJ. J Clin Neurophysiol. 2001;18:128-147.

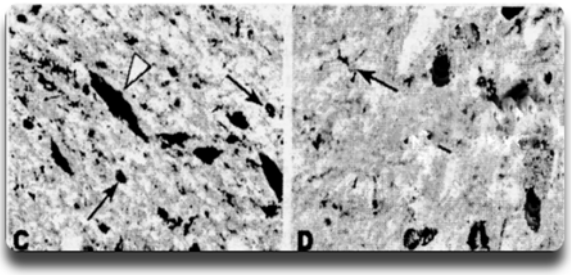
Pathophysiology of RLS

- Although the pathophysiology of RLS is largely unknown, a leading hypothesis is brain dopamine dysfunction. This could involve changes in[1-3]:
  - Dopamine receptors and their function
  - Uptake of dopamine
- May involve a circadian mechanism[4]
  - Circadian fluctuations in dopamine function?
- Deficiencies in other substances, such as iron, may play a role[1,2]

1. Allen & Earley. *J Clin Neurophysiol.* 2001;18:128-147.
2. Earley et al. *J Neurosci Res.* 2000;62:623-628.
3. Cervenka. *Brain.* 2006;129:2017-2028.
4. Garcia-Borreguero et al. *Sleep Med.* 2002;3(suppl):S17-S21.

RLS Pathophysiology: Brain Iron Insufficiency
Neuropathological Exam using Iron Stain

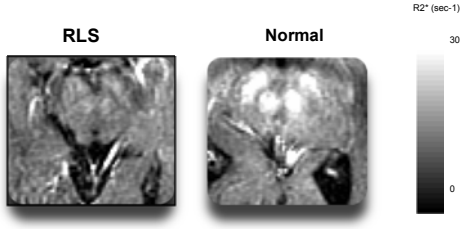
Control **RLS**



Connor JR, Boyer PJ, Menzies SL, et al. Neurology. 2003;61:304-309.

MRI studies in RLS

RLS Patients Have Low Brain Iron Tissue Concentrations on MRI



R2* images in a 70 year old RLS patient and a 71 year old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both red nucleus and substantia nigra.

From: C . Earley , P . B. Barker , A . Horská , R . Allen MRI-determined regional brain iron concentrations in early- and late-onset restless legs syndrome . Sleep Medicine , Volume 7 , Issue 5 , Pages 458 - 461

RLS Treatment

- RLS severity and frequency will vary from patient to patient
  - Mild, moderate, severe
  - Intermittent, frequent, daily, refractory
- Treatment is often individualized
- Need to determine the optimal medication or combination of medications, dosages, and non-pharmacological treatments

RLS Support Group

- The Restless Legs Syndrome Foundation
- Non-profit organization providing the latest information about RLS
- Goals of the Foundation are to increase awareness, improve treatments, and through research, find a cure for RLS, a condition which severely affects the lives of millions of individuals

Treatment Strategies [1-3]

Remove potential aggravators:
Sleep deprivation
Alcohol
Exercise (too much vs too little)
Caffeine
Smoking

Consider discontinuing medications that can worsen RLS:
SSRIs (eg, paroxetine, fluoxetine, sertraline)
Tricyclics (eg, amitriptyline, nortriptyline)
Dopamine antagonists (eg, clozapine, risperidone)
Antihistamines

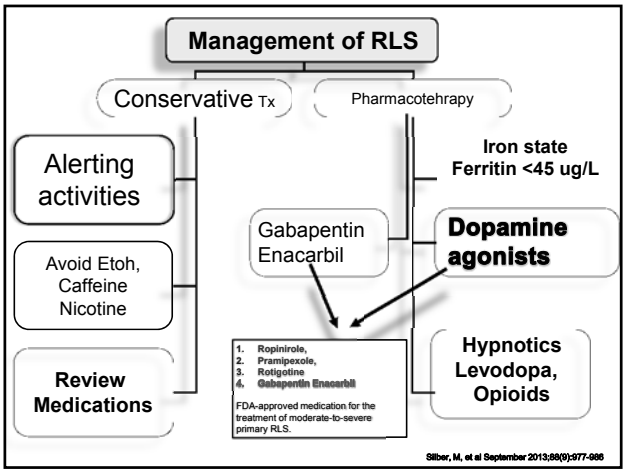
Treat secondary causes:
Iron deficiency
Renal disease

1. Stiasny K, Oertel W, Trenkwalder C. Sleep Med Rev. 2002;6:253-265.
2. Hening W, Allen R, Earley C, et al. Sleep. 1999;22:970-999.
3. Phillips B, Young T, Finn L, et al. Arch Intern Med. 2000;160:2137-2141.

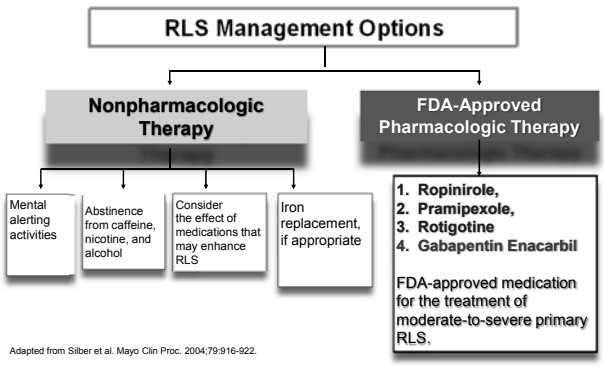
Nonpharmacological Treatment

- Improve sleep hygiene
  - Regular bedtime and wake time
  - Appropriate time in bed (no more than 8 hours)
- Moderate daytime and some evening exercise (patient dependent).
- Mental alerting techniques
- Warm baths/thermal biofeedback
- Leg massage
- Acupuncture

1. Parker KP, Rye DB. Nurs Clin North Am. 2002;37:655-673.
2. Hening W, Allen R, Earley C, et al. Sleep. 1999;22:970-999.
3. Hu J. J Tradit Chin Med. 2001;21:312-316.
4. Rajaram SS, Shanahan J, Ash C, Walters AS, Weisfogel G. Sleep Med. 2005;6:101-106.

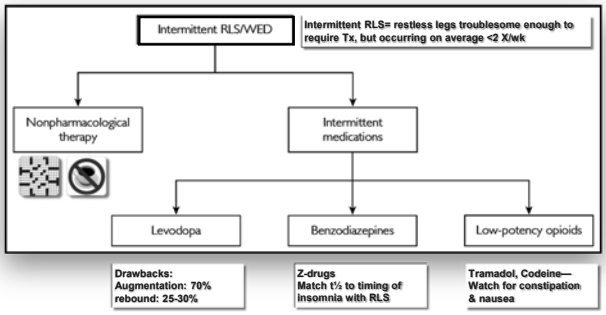


Treatment for Primary RLS



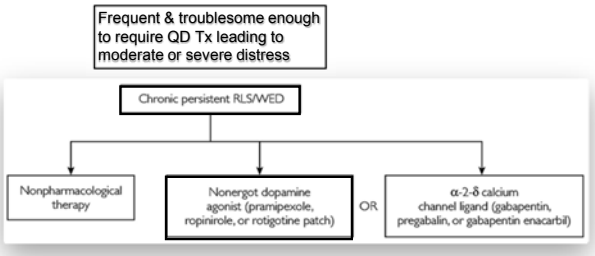
Adapted from Silber et al. Mayo Clin Proc. 2004;79:916-922.

Approach to the management of intermittent restless legs syndrome (RLS)/Willis-Ekbom disease (WED)



Silber, M, et al September 2013;88(9):977-986

Approach to the management of chronic persistent restless legs syndrome (RLS)/Willis-Ekbom disease (WED)



Silber, M, et al September 2013;88(9):977-986

Clinical Features Guiding Choice of Initial Agent for Chronic Persistent RLS/WED

Dopamine Agonist OR α-2-δ Ligand

Dopamine agonists	α-2-δ Ligands
Very severe RLS/WED	Comorbid pain
Comorbid depression or dysthymia	Comorbid anxiety
Obesity/metabolic syndrome	Comorbid insomnia
	Previous impulse control disorder or addiction

RLS = restless legs syndrome; WED = Willis-Ekbom disease.

Because α-2-δ ligands can cause depression & wt gain

Silber, M, et al September 2013;88(9):977-986

Clinical Features Guiding Choice of Initial Agent for Chronic Persistent RLS/WED

	Pramipexole	Ropinirole
Category	**Non-ergot**	**Non-ergot**
Time to maximum blood level	**2 hours**	**1-1.5 hours**
Elimination ½	**8-12 hours**	**6 hours**
Metabolism & excretion	**Renal excretion**	**Hepatic metabolism; renal excretion**

Silber, M, et al September 2013;88(9):977-986

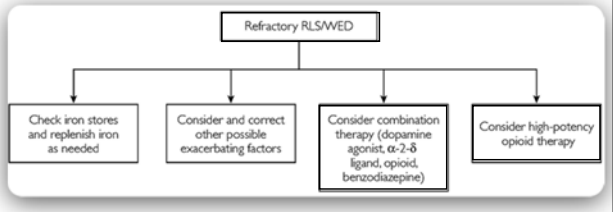
Comparison of Dopamine Agonists Used to Treat RLS/WED

Variable	Pramipexole	Ropinirole	Rotigotine patch
Time to maximum blood level (h)	2	1-1.5	Stable plasma levels over 24 h
Elimination half-life (h)	8-12 (increases with decreasing glomerular filtration rate and age)	6	Stable plasma levels over 24 h (elimination half-life biphasic: 3 and 6)
Metabolism and excretion	Renal	Hepatic metabolism and renal excretion	Hepatic metabolism and renal excretion
Initial daily dose (mg)	0.125	0.25 (−0.5)[b]	1
Maximum daily dose (mg)	0.5 (−1.0)[b]	4	3

[a]RLS = restless legs syndrome; WED = Willis-Ekbom disease.
[b]Values in parentheses differ from Food and Drug Administration–approved values.

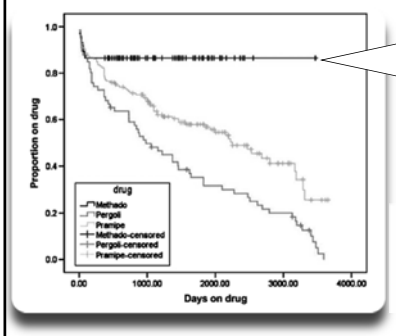
Silber, M, et al September 2013;88(9):977-986

Approach to the management of refractory restless legs syndrome (RLS)/Willis-Ekbom disease (WED)



Silber, M, et al September 2013;88(9):977-986

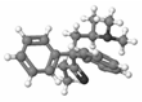
A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome



High Potency Opioids:

15% discontinued in first year

Mean increase in dose after 9 years was 10 mg



Silver, N et al Sleep Medicine, Volume 12, Issue 5, 2011, 440 - 444

(GENERIC/BRAND)	DOSE	RISKS
Iron: **Ferrous Sulfate**	325 mg BID/TID Recommended for Ferritin<50mcg	GI side effects: Constipation. Role in treatment under current investigation.
Dopamine Agonists: **Pramipexole** **(Mirapex®)** **Ropinirole** **(Requip®)** **Rotigotine** **(Neupro®)**	0.125-0.5mg, 1hr before bedtime. Start low and increase slowly (+). 0.25-2 mg 1 hr before bedime (+) 1-3 mg QD	Severe sleepiness, nausea reported in some cases. Nausea, vomiting, sleep attacks, rare compulsive gambling.
Dopaminergic Agents: Levodopa/Cardidopa (Sinemet®	25/200 mg: ½ tab-3 tabs 30 minutes before bedtime.	Nausea, sleepiness, augmentation of daytime symptoms, insomnia, sleepiness, gastrointestinal disturbances
Alpha 2 Delta Ligands: Gabapentin (Neurontin®) **Gabapentin Enacarbil** **(Horizant®)**	300-2,700 mg/day divided TID, 300-600mg Q5PM	Daytime sleepiness, nausea,
Benzodiazepines: Clonazepam (Klonopin®)	0.125-0.5 mg ½ hour before bedtime.	Nausea, sedation, dizziness
Clonidine: Catapres	0.1 mg BID May be helpful in patients with hypertension	Dry mouth, drowsiness, constipation, sedation, weakness, depression (1%), hypotension
Opiods: Darvocet (Darvoset-N®) **Darvon (Propoxyphene®)** Codeine	300mg/day 65-135 mg at bedtime 30mg	Nausea, vomiting, restlessness, constipation.. Addiction, tolerance may be possible

(+) Only FDA approved drug for RLS as of May, 2014
Modified after Avidan And Zee, handbook of Sleep Medicine

Iron-deficiency RLS Treatment

- Consider if serum ferritin <50 µg/L & Workup why
- Ferrous sulfate
  - 325 mg + 100 mg vitamin C 1 to 3 times daily on an empty stomach
  - Vitamin C improves absorption
- Iron dextran (IV) is also an option for patients with a proven iron deficiency
  - Single 1 gram iron infusion

1. Earley CJ, et al. Sleep Med. 2004;5:231-235.
2. Earley CJ. N Engl J Med. 2003;348:2103-2109.
3. Davis BJ, et al. Eur Neurol. 2000;43:70-75.

Dopamine Agonists Side Effects

- Augmentation & Rebound
- Impulse Control Behavior
- Insomnia
- Hypersomnia
- Nausea/vomiting
- Hallucinations

Augmentation

Begins in legs —> Arms
Legs + Arms as an RLS subtype

Augmentation:
Sx occurring earlier in the day

Augmentation

Begins in legs —> Arms
Legs + Arms as an RLS subtype

Augmentation:
Sx occurring earlier in the day

Augmentation

- An overall increase in symptom severity as a result of long-term dopaminergic treatment
- Primary feature
  - Earlier onset of RLS symptoms (at least 2 hours)
  - Increase of symptom severity
  - Geographic spread to other limbs, trunk, or abdomen
- Observed in up to 82% of RLS patients treated with levodopa (25-40% with DA)

Allen RP, Earley CJ. Sleep. 1996;19:205-213.

Augmentation

Screening questions to identify augmentation in patients on dopaminergic therapy for RLS/WED

Do RLS/WED symptoms appear earlier than when the drug was first started?
Are higher doses of the drug now needed, or do you need to take the drug earlier in the day to control symptoms?
Has the intensity of symptoms worsened since starting the drug?
Have symptoms spread to other body parts (eg, arms) since starting the drug?

Data from: Garcia-Borreguero D, Silber MH, Winkelman JW, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: A combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med 2016; 21:1.

Rebound

- Rebound
  - Wearing off of drug effect, typically in the AM
    - Mainly related to half-life
  - Seen in up to 25% of RLS patients treated with levodopa

1. Guilleminault C, Cetel M, Philip P. Neurology. 1993;43:445.
2. Allen RP, Earley CJ. Sleep. 1996;19:205-213.

SPECIAL POPULATIONS

Pregnancy and lactation:

- Education
- Reassurance,
- Iron supplementation

Pharmacologic therapies for severe symptoms :
- Clonazepam or
- carbidopa-levodopa

End-stage renal disease

- Dopamine agonists
- Alpha-2-delta ligands

Careful attention to iron status is especially important in this cohort

RLS Summary

- RLS is a clinical diagnosis with four essential criteria
- Therapy should be individualized based on nature and severity of symptoms
- Evaluation should always include serum ferritin and iron replacement treatment should be considered if ferritin is less than 50 µg/l