Restless Legs Syndrome

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Objectives

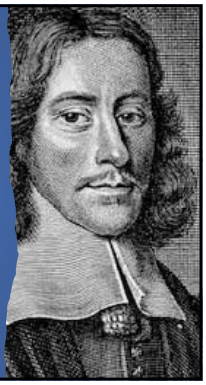
- Epidemiology of restless legs syndrome (RLS)
- Diagnostic criteria and difficulties
- Pathophysiology
- Management

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Epidemiology

- 5-15% of population
- Northern European countries have greatest prevalence
- Females have greater rates than males
  - Likely due to pregnancy
- Can occur at any age, but prevalence increases with age



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In their own words

- "need to move"
- "crawling"
- "tingling"
- "creeping"
- "pulling"
- "discomfort"



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Clinical consequences

- Sleep initiation insomnia
- Sleep maintenance insomnia
- Anxiety
- Depression
- Suicide
- Self harm
- Cardiovascular disease

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Differential Diagnosis

- Periodic limb movements of sleep
- Akathesia
- Volitional movements
- Nocturnal leg cramps
- Peripheral neuropathy
- Myelopathy
- Hypnic jerks

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Diagnostic Criteria – ICSD 3

An **urge** to move the legs, usually accompanied by or thought to be caused by uncomfortable and unpleasant sensations in the legs. These symptoms must:

- 1. Begin or worsen during periods of rest or inactivity such as lying down or sitting;
- 2. Be partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and
- 3. Occur exclusively or predominantly in the evening or night rather than during the day.

The above features are not solely accounted for as symptoms of another medical or a behavioral condition.

The symptoms of RLS cause concern, distress, sleep disturbance, or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.

- American Academy of Sleep Medicine. International classification of sleep disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014.

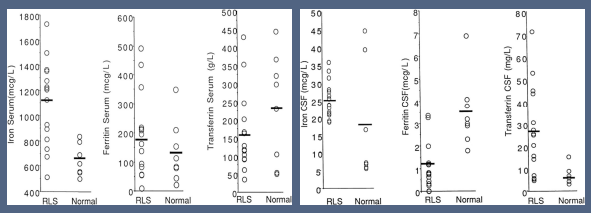
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Pathophysiology

- Iron stores
- Dopamine

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CSF Iron levels

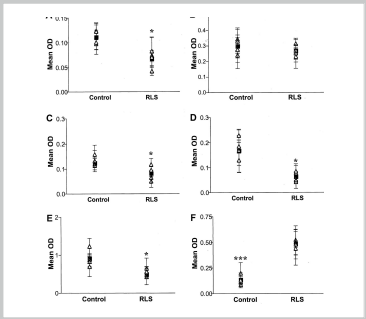


Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology*. 2000;54(8):1698-1700. doi:10.1212/wnl.54.8.1698

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Brain iron stores

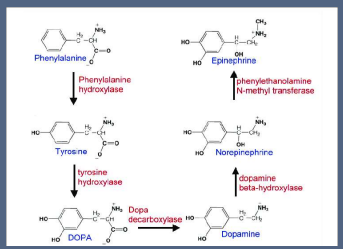
- Ferritin Heavy chain (A), divalent metal transporter 1 (C), ferroportin (D), transferrin receptor (E), all decreased.
- Ferritin light chain (B) similar
- Transferrin (F) increased



Connor JR, Wang XS, Patton SM, et al. Decreased transferrin receptor expression by neuromelanin cells in restless legs syndrome. *Neurology*. 2004;62(9):1563-1567. doi:10.1212/01.wnl.0000123251.60485.ac

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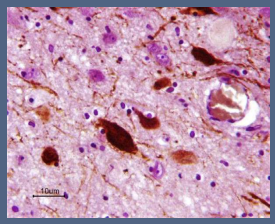
Dopamine Synthesis



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Dopamine Activity

- Multiple studies have demonstrated no significant differences in levels of dopamine levels, dopaminergic activity, and dopamine receptor levels in patients with RLS compared to controls.



Earley CJ, Allen RP, Connor JR, Ferrucci L, Troncoso J. The dopaminergic neurons of the A11 system in RLS autopsy brains appear normal. *Sleep Med*. 2009;10(10):1155-1157. doi:10.1016/j.sleep.2009.01.006

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Risk Factors

- Low iron stores
- Uremia
- Genetics
- Pregnancy
- Multiple sclerosis

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Ferritin levels in patients with RLS

Groups	Ferritin level (ng/ml)
Severe–very severe RLS (*n* = 49)	26.01 ± 15.82
Mild–moderate RLS (*n* = 54)	49.87 ± 23.24
Significance	$p < 0.001$

Çurgunlu A, Döventaş A, Karadeniz D, et al. Prevalence and characteristics of restless legs syndrome (RLS) in the elderly and the relation of serum ferritin levels with disease severity: hospital-based study from Istanbul, Turkey. *Arch Gerontol Geriatr.* 2012;55(1):73-76. doi:10.1016/j.archger.2011.06.002

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Evaluation

- History
  - When did symptoms start?
  - How many nights per week? (>2?)
  - Urge to move?
  - Pain?
  - Do symptoms improve worsen with rest?
    - Car/airplane rides
  - Are symptoms worse during at night?
  - Do symptoms improve with movement
  - Family history of RLS?
  - History of sleep disordered breathing?



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Restless Legs Syndrome Rating Scale

Have the patient rate his/her symptoms for the following ten questions.
The patient and not the examiner should make the ratings, but the examiner should be available to clarify any misunderstandings the patient may have about the questions.
The examiner should mark the patient's answers on the form.

In the past week...
(1) Overall, how would you rate the RLS discomfort in your legs or arms?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(2) Overall, how would you rate the need to move around because of your RLS symptoms?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?
_ (4) No relief
_ (3) Mild relief
_ (2) Moderate relief
_ (1) Either complete or almost complete relief
_ (0) No RLS symptoms to be relieved

In the past week...
(4) How severe was your sleep disturbance due to your RLS symptoms?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(5) How severe was your tiredness or sleepiness during the day due to your RLS symptoms?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(6) How severe was your RLS as a whole?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(7) How often did you get RLS symptoms?
_ (4) Very often (5 to 7 days in 1 week)
_ (3) Often (4 to 5 days in 1 week)
_ (2) Sometimes (2 to 3 days in 1 week)
_ (1) Occasionally (1 day in 1 week)
_ (0) Never

In the past week...
(8) When you had RLS symptoms, how severe were they on average?
_ (4) Very severe (8 hours or more per 24 hour)
_ (3) Severe (5 to 8 hours per 24 hour)
_ (2) Moderate (1 to 5 hours per 24 hour)
_ (1) Mild (less than 1 hour per 24 hour)
_ (0) None

In the past week...
(9) Overall, how severe was the impact of your RLS symptoms on your ability to carry out your daily affairs, for example carrying out a satisfactory family, home, social, school or work
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

In the past week...
(10) How severe was your mood disturbance due to your RLS symptoms - for example angry, depressed, sad, anxious or irritable?
_ (4) Very severe
_ (3) Severe
_ (2) Moderate
_ (1) Mild
_ (0) None

Sum of scores =

Scoring criteria are: Mild (score 1-10); Moderate (score 11-20); Severe (score 21-30); Very severe (score 31-40)

1. Answers for the RLS are scored from 4 for the first (top) answer (usually 'very severe') to 0 for the last answer (usually none). All items are scored. The sum of the item scores serves as the scale score.

The International Restless Legs Syndrome Study Group holds the copyright for this scale.

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Exacerbating medications

- Antihistamines
- Dopamine receptor antagonists
- Antidepressants

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Lab work

- Ferritin
- Iron
- TIBC
- Transferrin saturation

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When to start iron

- If ferritin ≤ 75 ug/L or transferrin saturation less than 45%
- Consider transferrin less than 20% in presence of inflammation or malignancy
- Iron can be oral or IV
- 325mg (65mg elemental) iron with 100 to 200mg of vitamin C
  - Daily or every other day
  - Empty stomach if possible
  - Take at night
  - Recheck levels every 3-6 months until ferritin greater than 100 ug/L

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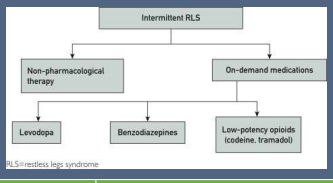
IV Iron

- Consider if
  - Oral replacement ineffective
  - Issues with absorption
  - Chronic persistent or refractory RLS
  - Ferritin between 76 to 100 ug/L

Formulation	Dose
Ferric Carboxymaltose	Single dose 1000mg or two 500mg doses (5-7 days apart)
Low molecular weight iron dextran	1000mg single dose
Ferumoxatol	1020mg single dose

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Intermittent RLS



Medication	Dose
Carbidopa/levodopa	25mg/100mg
Codeine + acetaminophen	30 to 90mg
Tramadol	50 to 100mg
Zolpidem	5 to 10mg
Temazepam	15-30mg

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Non-pharmacologic therapy

- Iron
- Mental alerting exercises
- Caffeine – alcohol avoidance
- Treat underlying sleep disorders

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Chronic persistent RLS – alpha 2 delta ligands

	Gabapentin	Pregabalin	Gabapentin enacarbil
Time to maximum blood level	2 h	1.5 h	7-9 h
Elimination half-life	5-7 h	6 h	Relatively stable plasma levels during 18-24 h (elimination half-life, 6 h)
Metabolism and excretion	Renal	Renal	Intestinal metabolism; renal excretion
Initial daily dose	300 mg[a]	75 mg[a]	600 mg[a]
Maximum daily dose	3600 mg	450 mg	600 (-1200)[b] mg

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Chronic persistent RLS – dopamine agonists

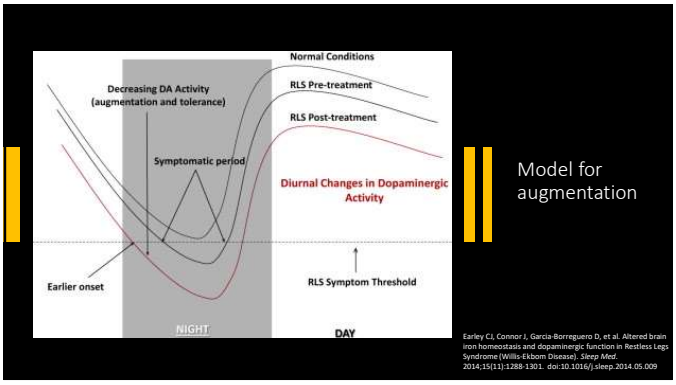
	Pramipexole	Ropinirole	Rotigotine patch
Time to maximum blood level	2 h	1-1.5 h	Stable plasma levels during 24 h
Elimination half-life	8-12 h (increases with decreasing glomerular filtration rate and age)	6 h	Stable plasma levels during 24 h (elimination half-life biphasic, 3 h and 6 h)
Metabolism and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

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Augmentation

- Symptoms occur earlier
- Intensity is worse since starting medication
- Increasing dosage of medication
- Symptoms have spread to other body parts

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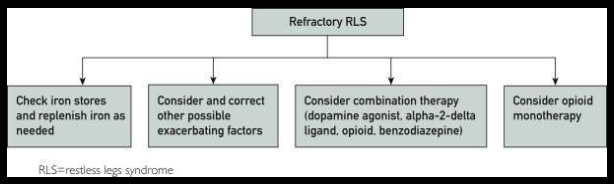
Managing augmentation

- Mild augmentation (symptoms occur up to two hours earlier)
  - Split dose
  - Consider controlled release medication
  - Can increase dose, but if augmentation recurs after 2nd dose increase
    - Titrate to alternative agent
    - Consider rotigotine patch
- Severe augmentation
  - Cross titrate to alpha – 2 delta ligand or opiate
  - Discontinue dopamine agonist and give drug holiday
  - Do not taper more than .25 mg (pramipexole) or .5mg (ropinirole) weekly

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Refractory RLS

- Symptoms do not resolve with monotherapy at appropriate doses
  - If symptoms do not respond to dopamine agonists then diagnosis should be questioned.



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Opioids

Drug	Starting total daily dose	Usual effective total daily dose
Tramadol (immediate release or ER)	50 mg (100 mg ER)	100-200 mg
Codeine	30 mg	60-180 mg
Morphine CR	10-15 mg	15-45 mg
Oxycodone (immediate release or ER)	5-10 mg	10-30 mg
Hydrocodone (immediate release or ER)	10-15 mg	20-45 mg
Methadone	2.5-5 mg	5-20 mg
Buprenorphine hydrochloride/naloxone (sublingual film or tablet)	0.5-1 mg	0.5-6 mg

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Special populations

- Pregnancy
  - Consider clonazepam .25-.5 mg (2nd and 3rd trimester)
  - Consider carbidopa/levodopa
  - Consider oxycodone 5-10 mg for severe or refractory RLS
- Lactation
  - Clonazepam .25-.5 mg
  - Gabapentin 300-900 mg
  - Tramadol 50-100 mg
  - Avoid dopamine agonists

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Pediatric RLS

- Difficult to diagnose as symptoms need to be described in childs own words
  - Family history and presence of PLMS are supportive
- Check iron stores first
  - Supplement iron if ferritin ≤ 50 ug/L
  - Ferrous sulfate 3 to 5 mg/kg daily before breakfast
  - IV iron can be used
    - Iron sucrose 5mg/kg – max 200mg over 2 hours
    - Ferric carboxymaltose 10mg/kg – max 1000mg over 1 hour
  - Non-pharmacologic therapy first

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Pediatric medications

- Alpha – 2 delta ligands are first line
  - Gabapentin 5-15 mg/kg
  - Pregabalin 2-3 mg/ kg
- Clonazepam
  - 0.1-1mg
- Dopamine agonists should be avoided if possible

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Conclusions

RLS is a complex disorder which is often under or misdiagnosed

The pathophysiology of the disorder is not completely understood, but likely is associated with iron deficiency.

Initial work management should always start with supplementing iron if low, and treating co-morbid sleep disorders
- Consider IV iron if appropriate

Dopamine agonists were long thought of as 1st line agents, but due to inevitability of augmentation they are no longer

Opioids can be very effective

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Questions



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WHITE NOISE
A SLEEP MEDICINE
PODCAST

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References

- Earley CJ, Connor JR, Beard JL, Malecki EA, Epstein DK, Allen RP. Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome. *Neurology*. 2000;54(8):1698-1700. doi:10.1212/wnl.54.8.1698
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