

Perioperative Considerations in Restless Legs Syndrome

Lynn Marie Trotti, MD, MSc

Associate Professor of Neurology

Emory Sleep Center, Emory University School of Medicine

Disclosures

- UCB Pharma – unpaid collaborator on an investigator-initiated study
- I intend to discuss off-label use of approved medications



Thomas Willis
(1672)



Karl-Axel Ekbom
(1945)

Outline

- Diagnostic criteria, clinical features, and epidemiology
- Genetics and pathophysiology
- Treatment
- Perioperative considerations



Clinical presentation, diagnosis, and epidemiology

2012 Revised IRLSSG Diagnostic Criteria

U R G E S

Essential Diagnostic Criteria (all must be met)

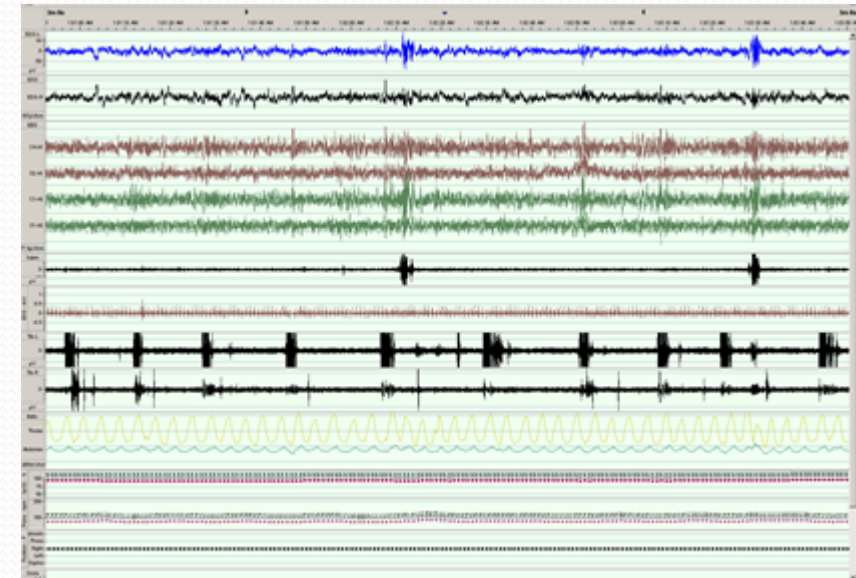
1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.^{1, 2}
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.³
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.⁴
5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).⁵

Supportive criteria (2003) can help if the diagnosis is unclear

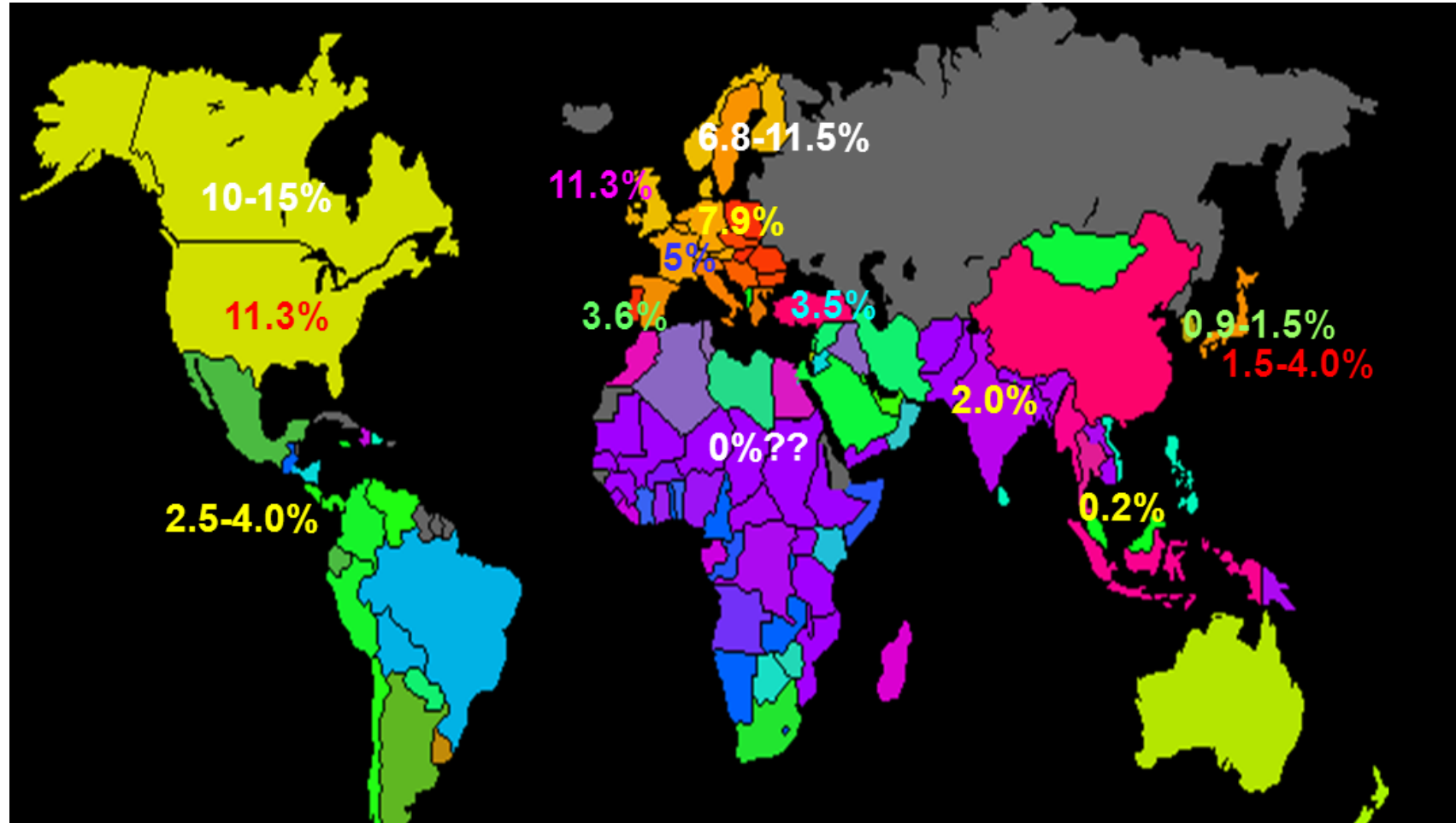
- Positive family history
- Response to treatment with dopaminergic medications
- Periodic Limb Movements (PLMs)

Periodic Limb Movements (PLMS)

- Repetitive, involuntary movements
- Typically flexion of great toe & dorsiflexion of the ankle, but variable
- Remarkably periodic at 20-40 seconds (in RLS)
- Sleep or waking
- Seen in >90% of RLS patients when monitored for five nights
- Associated with increase in HR and beat-to-beat blood pressure



RLS is common in adults, with regional variation in prevalence



Epidemiology of RLS

- Onset and severity increase with age
 - affects ~2% of those aged 8-17 yrs old; in 0.5-1.0% considered clinically significant
- Twice as common in women
 - Effect of parity
 - rate in men = rate in nulliparous women

Genetics and pathophysiology

Significant associations within introns of BTBD9, Meis1, & MAP2K5/LBXCOR1

Chromosome 6p21.2: Intron 5 of the BTB (POZ) domain
containing 9 gene (BTBD9)



Chromosome 2p12: Intron 8 of the Meis1 homeobox 1 gene



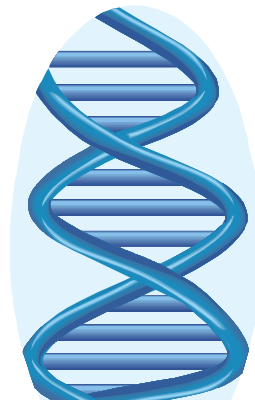
Chromosome 15q23: region of MAP2K5 & LBXCOR1



Population attributable risk of 3 SNPs = 0.70-0.80

Additional GWAS results

- PTPRD (9p22-24)
- TOX3/non-coding RNA BCo34767 (16q12.1)
- Distinct locus on 2p14 (possibly regulating Meis1)

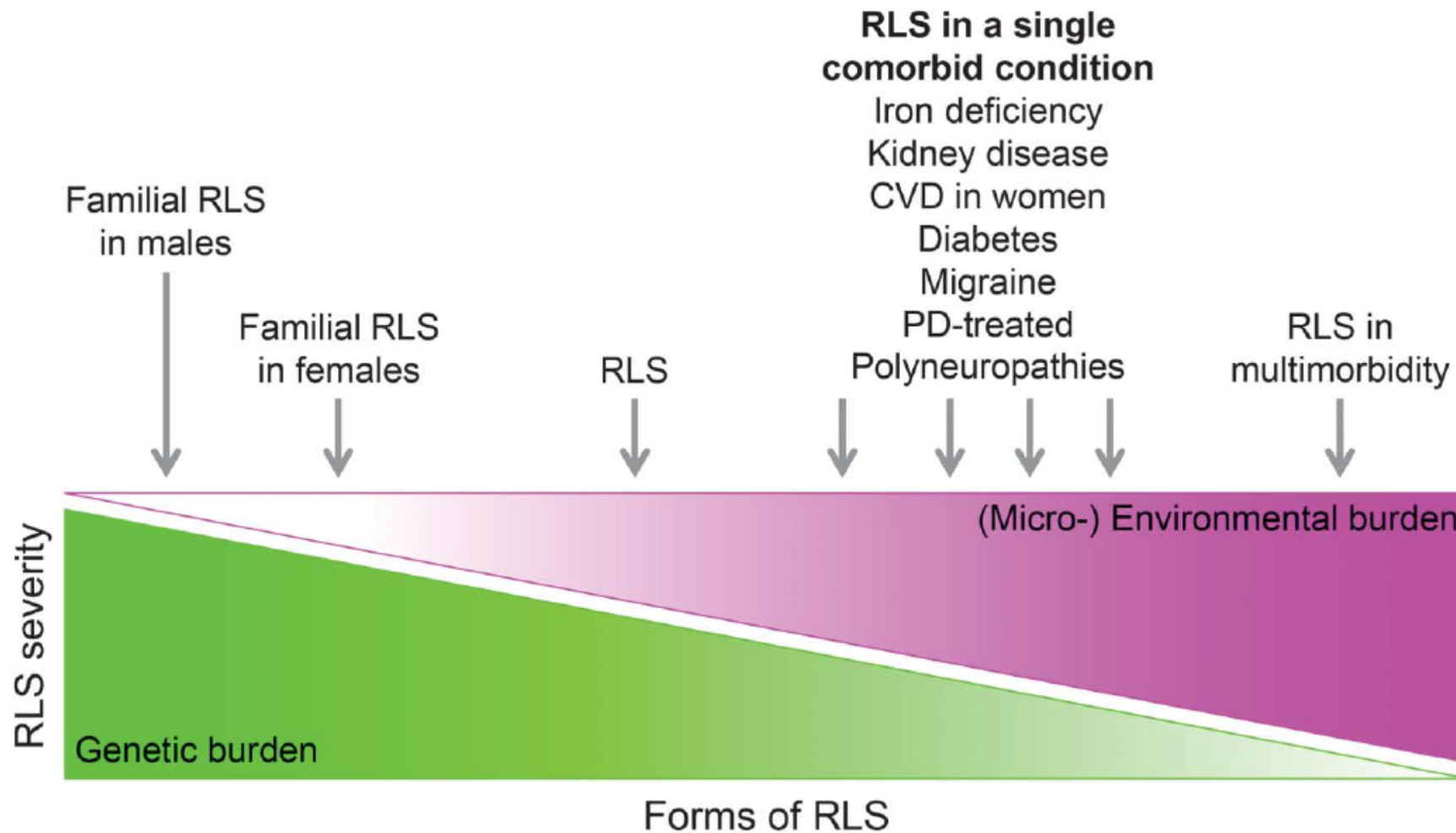


RLS susceptibility is genetically determined, environmentally provoked

- Often triggered by another condition/illness
 - Iron deficiency
 - Renal failure
 - Pregnancy
- Myelopathy, varicose veins, rheumatologic disease, pulmonary disease, GI disease ...

Figure

Model of the hypothesis that the more genetic factors contribute to the manifestation of restless legs syndrome (RLS), the less environmental trigger is needed



CVD = cardiovascular disease; PD = Parkinson disease.

Pathophysiology: Iron

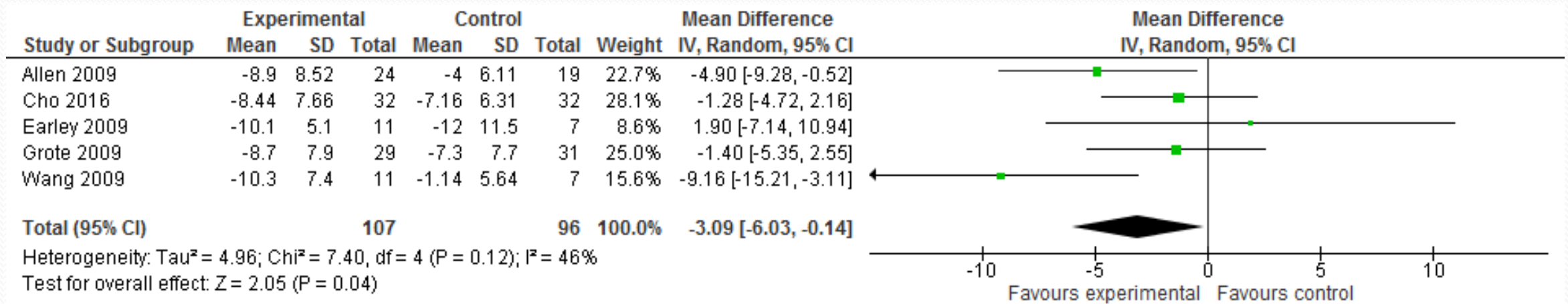
- Iron deficiency and RLS co-occur
 - Iron deficiency in 25-44% of RLS patients
 - RLS in 40% of iron deficient patients
- Pathophysiology
 - Serum iron nadirs in the evening (8 to MN)
 - Small CSF, MRI, and autopsy studies all support decreased CNS iron stores (especially in substantia nigra)
 - Iron deficient animals show abnormal function of DA system (synthesis, clearance/DAT function, receptor trafficking)

Pathophysiology: Dopamine

- Dopamine deficiency?
 - Dopamine agonists improve symptoms
 - Dopamine antagonists worsen symptoms
 - Diurnal variation in dopamine with nadir matching peak RLS symptoms
- Excess striatal dopamine?
 - Elevated dopamine metabolites (CSF)
 - Increased synaptic DA in striatum (balance of conflicting imaging studies)
 - Increased tyrosine hydroxylase in nigra (autopsy)

Treatment of RLS

Iron for the treatment of RLS



- Two studies not included (one beneficial, the other not)

Pharmacologic treatment

- Treatments approved by the FDA:
 - Ropinirole (Requip[®], 2005)
 - Pramipexole (Mirapex[®], 2006)
 - Gabapentin enacarbil (Horizant[®], 2011)
 - Rotigotine (Neupro[®], 2012)



Dopamine agonists

- Metabolism:
 - Pramipexole: renally excreted unchanged
 - Ropinirole/Rotigotine: hepatic metabolism
- Side effects:
 - Nausea
 - Somnolence
 - Peripheral edema
 - Impulse control disorders
 - Augmentation



Gabapentin enacarbil

- Gabapentin prodrug: NOT bioequivalent to gabapentin
 - 600 mg once a day (dinnertime) dosing
- Most common side effects:
 - Dizziness
 - Somnolence
- (Gabapentin and pregabalin also effective for RLS in clinical trials but not FDA-approved for that use)

Third-line: opiates

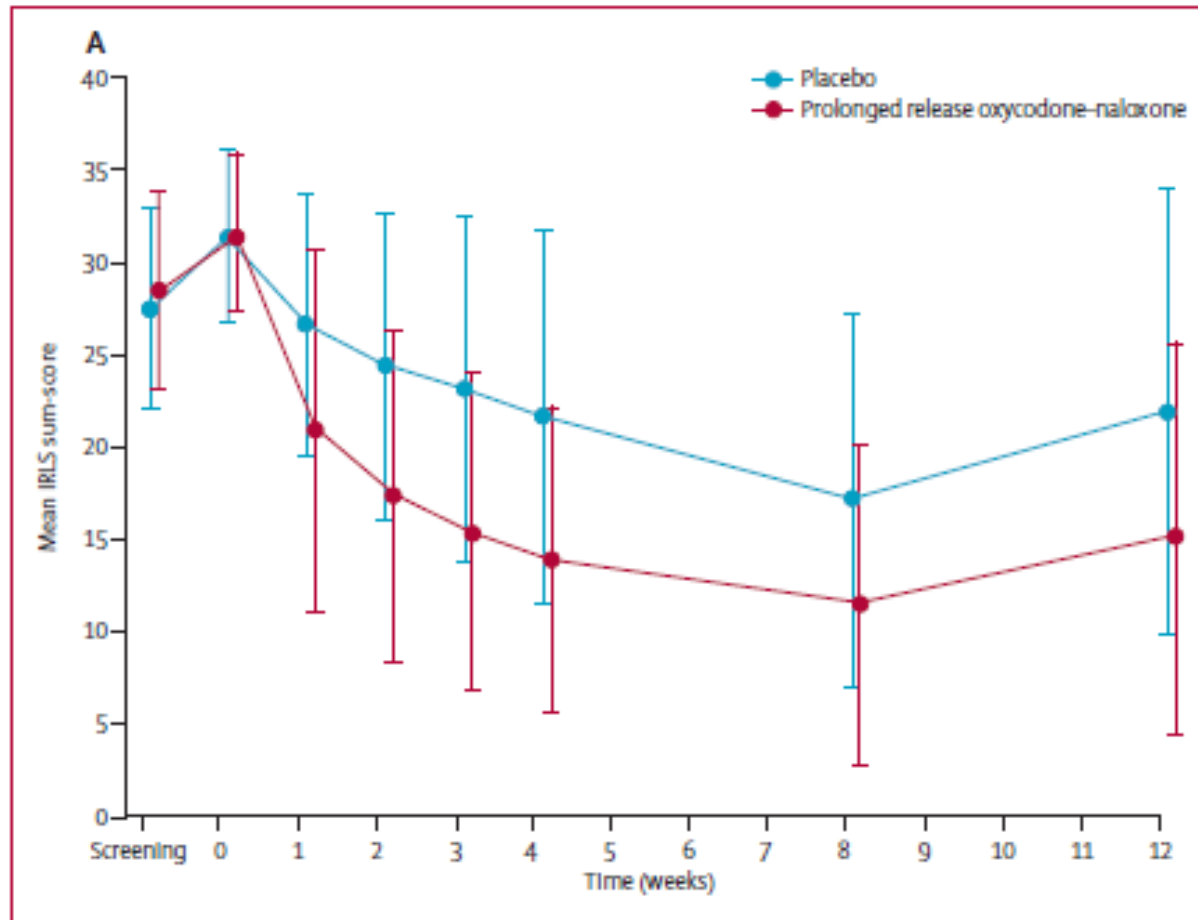
- N = 276
- IRLS > 15
- Failed other treatment
- Starting dose: oxycodone 5 mg/
Naloxone 2.5 mg bid
- Max dose: 40/20 mg bid
- Mean final dose: 11/5.5 mg bid
- CDC guidelines:
 - 50 MME = 33 mg oxycodone daily
 - 90 MME = 60 mg daily

Articles

Prolonged release oxycodone–naloxone for treatment of severe restless legs syndrome after failure of previous treatment: a double-blind, randomised, placebo-controlled trial with an open-label extension

*Claudia Trenkwalder, Heike Beneš, Ludger Grote, Diego García-Borreguero, Birgit Högl, Michael Hopp, Björn Bosse, Alexander Oksche, Karen Reimer, Juliane Winkelmann, Richard P Allen, Ralf Kohnen, for the RELOXYN Study Group**





$P < 0.0001$ for placebo vs oxycodone/naloxone at 2, 3, 4, 8, 12 week time points

Perioperative considerations

Does spinal anesthesia cause RLS?

	Hogl B et al, Neurology, 2002	Crozier TA et al, NEJM, 2008
	Prospective, n = 202 (spinal)	Prospective, n = 147 (spinal)
RLS diagnosis	Expert diagnosis vis IRLSSG questions; IRLS severity; at 48-72 hrs, 1 wk, 1 mo, 3 mo, 6 mo	Standardized questionnaire at admission, 1 wk, and 4 weeks post op; positives confirmed
Controls	--	General anesthesia
Anesthetic agent	Bupivacaine	Bupivacaine or mepivacaine
Surgical procedures	Ortho (n = 90) C-sections (n = 72) Urologic (n = 28) Gyn (n = 8) Vascular (n = 4)	Ortho (n = 85) Urologic (n = 59) Inguinal (n = 3)
Demographics	71% women, mean age 53	43% women, mean age 62
Results	-14 new cases of RLS (8.7%; of 147 without pre-existing RLS) -average onset 7.3 d after surgery -sx persisted average 33 d	0 new cases of RLS; 0 exacerbations of RLS

RLS and surgery

- Missed medication doses
- Restraints/immobilization
- Medications that exacerbate RLS
- Others: sleep deprivation, blood loss (CNS iron deficiency), peripheral injury

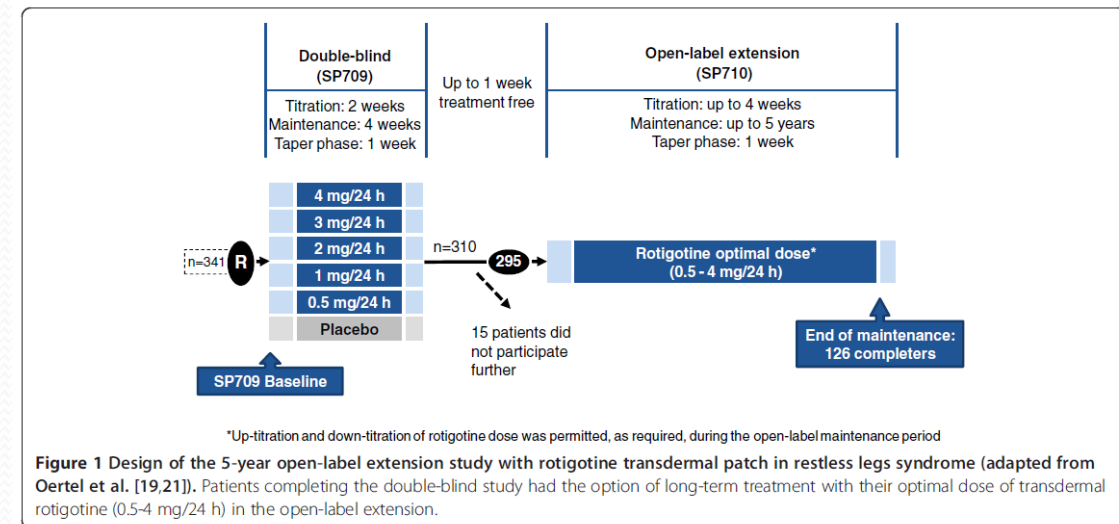


Missed medications/NPO

- 2 hours from oral dosing to relief of symptoms
 - Anticipate rather than respond to symptoms
- Dopamine discontinuation syndrome
- Strongly circadian
 - Try to schedule for am procedures
- Parenteral opiate until tolerating po
- Rotigotine patch if prolonged NPO anticipated?

Rotigotine patch and surgery in RLS

- Retrospective review of open-label extension data
- 61 surgeries in 52 patients
- Mean dose 3.1 +/- 1.1 mg
- 95% continued same dose throughout perioperative period
- Suspended in 1 (for surgery)
- Discontinued in 2 (one for pregnancy, other unclear)



Rotigotine patch and surgery in PD

- 14 PD patients converted from dopaminergics to rotigotine patch
- Last oral dose taken noon on preop day; first patch applied 7 pm on preop evening
- 5 serious AEs
 - 1 very likely related (hallucinations)
 - 1 possibly related (12 s asystole)

Table 1 Feasibility of switching to rotigotine treatment during the perioperative period rated by neurologists, anesthesiologists, and patients (full analysis set; $n = 9$)

	I completely agree 1	2	3	4	5	I do not agree at all 6
Neurologists						
Switch from previous PD medication was easily feasible	8 (88.9%)	0	0	1 (11.1%) ^a	0	0
Re-switch was easily feasible	8 (88.9%)	0	0	0	0	1 (11.1%)
No unexpected PD symptoms perioperatively	7 (77.8%)	2 (22.2%)	0	0	0	0
The patch is a feasible option	8 (88.9%)	1 (11.1%)	0	0	0	0
Anesthesiologists						
No unexpected PD symptoms perioperatively	8 (88.9%)	1 (11.1%)	0	0	0	0
Handling of the patch was simple	7 (77.8%)	2 (22.2%)	0	0	0	0
Handling was not time consuming	8 (88.9%)	1 (11.1%)	0	0	0	0
The patch is a feasible option	6 (66.7%)	2 (22.2%)	0	1 (11.1%) ^a	0	0
Patients						
Perioperative patch treatment was easily feasible	8 (88.9%)	1 (11.1%)	0	0	0	0
The symptoms of my PD were well controlled	7 (77.8%)	2 (22.2%)	0	0	0	0
In the course of surgery, I felt safe with the PD patch	6 (66.7%)	2 (22.2%)	0	1 (11.1%)	0	0

Data are number of patients (%)

PD Parkinson's disease

^a The same patient was rated '4' by the neurologist and the anesthesiologist

Immobilization worsens both sensory and motor components of RLS

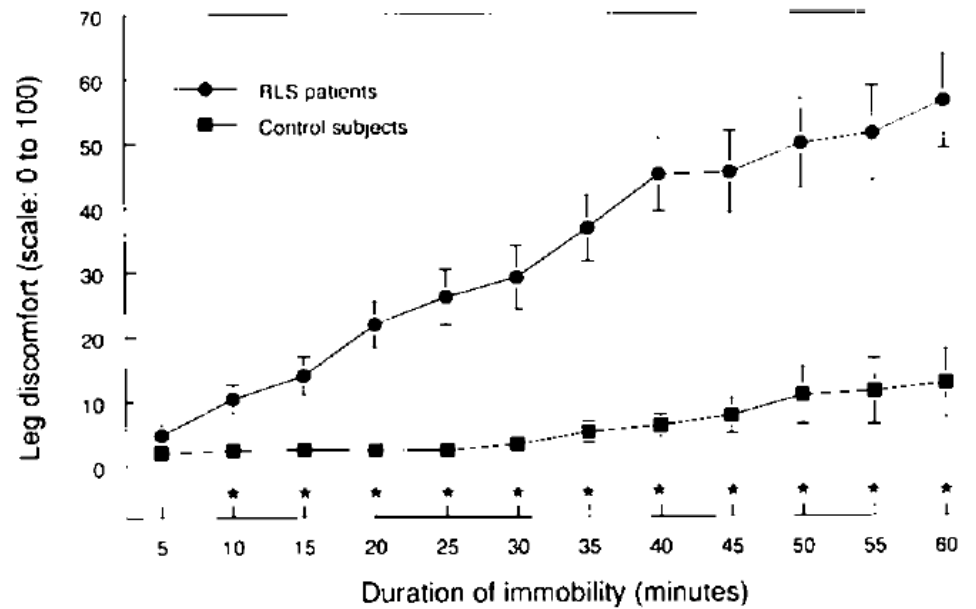


FIG. 1. Relationship between the SIT duration and mean (\pm SEM) leg discomfort scores in both RLS patients and healthy control subjects (*significant contrasts at $P < 0.05$).

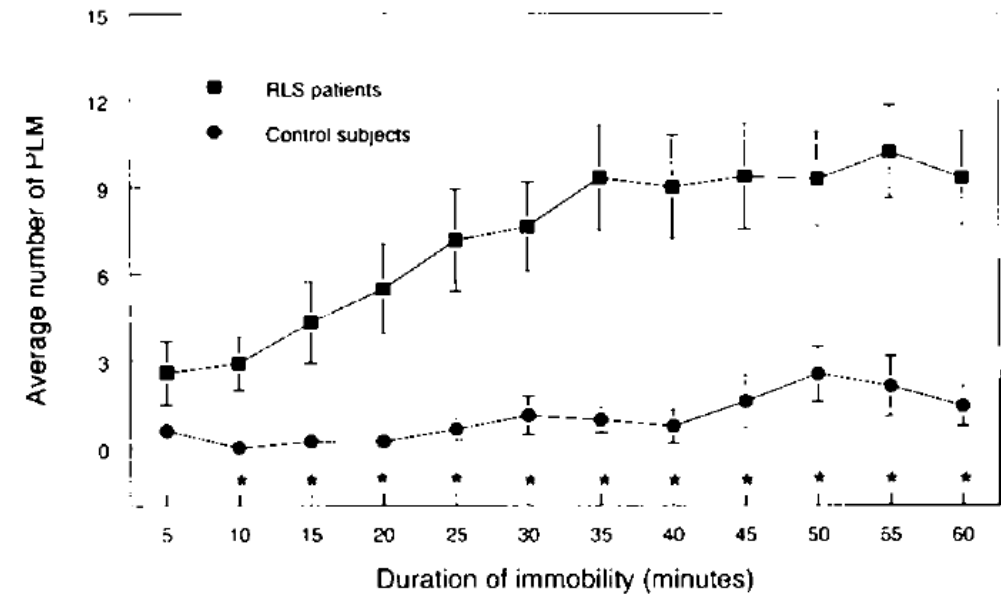


FIG. 2. Relationship between the SIT duration and average number (\pm SEM) of PLM per 5 minutes in both RLS patients and healthy control subjects (*significant contrasts at $P < 0.05$).

Medications that exacerbate RLS

Table 2

Medications reported to precipitate or worsen restless legs syndrome or periodic limb movements of sleep

Class of Medication	Medication Name
Dopamine antagonist antiemetics	Droperidol, metoclopramide, domperidone, prochlorperazine
Antipsychotics	Haloperidol, olanzapine, risperidone, quetiapine
Antihistamines	Hydroxyzine, mianserin, cimetidine
Serotonergic antidepressants	
Tricyclic	Amitriptyline, clomipramine, dibenzepine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, opipramol, trimipramine
Selective serotonin reuptake inhibitor	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline
Mixed	mirtazapine, trazodone, venlafaxine
Antiepileptics	Methsuximide, phenytoin, zonisamide
Other	Lithium, levothyroxine

Medications that exacerbate RLS

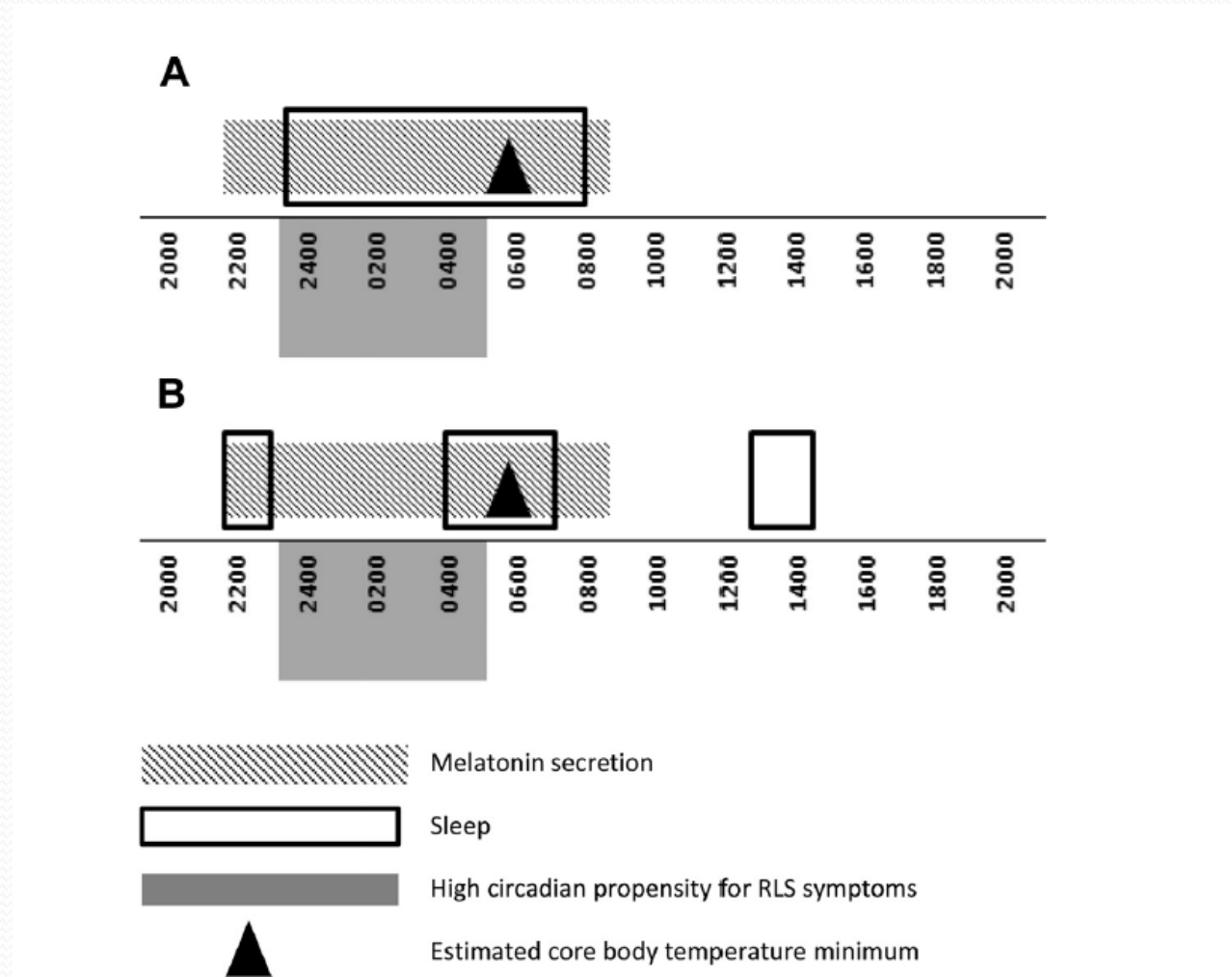
- Instead, consider:
- Antiemetics:
 - Zofran/ondansetron (selective 5HT₃ antagonist)
- Antihistamines
 - 2nd generation (loratadine, fexofenadine, cetirizine)
- Antipsychotics
 - Diagnosis?

Table 2

Medications reported to precipitate or worsen restless legs syndrome or periodic limb movements of sleep

Class of Medication	Medication Name
Dopamine antagonist antiemetics	Droperidol, metoclopramide, domperidone, prochlorperazine
Antipsychotics	Haloperidol, olanzapine, risperidone, quetiapine
Antihistamines	Hydroxyzine, mianserin, cimetidine
Serotonergic antidepressants	
Tricyclic	Amitriptyline, clomipramine, dibenzepine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, opipramol, trimipramine
Selective serotonin reuptake inhibitor	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline
Mixed	mirtazapine, trazodone, venlafaxine
Antiepileptics	Methsuximide, phenytoin, zonisamide
Other	Lithium, levothyroxine

Sleep deprivation/sleep disruption





Thank you!