Managing Restless Legs Syndrome (RLS) and its Augmentation

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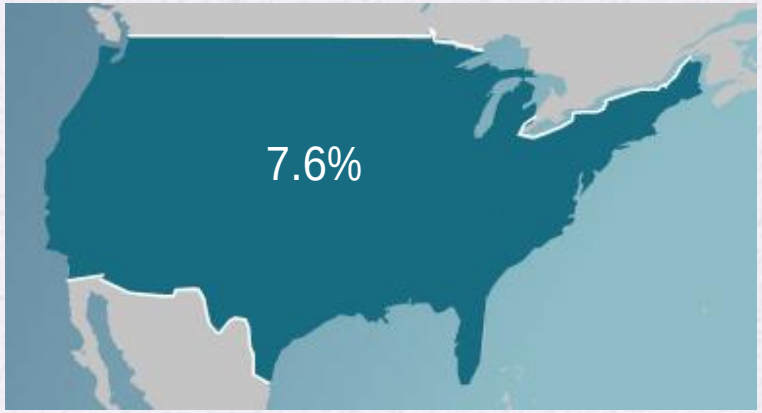
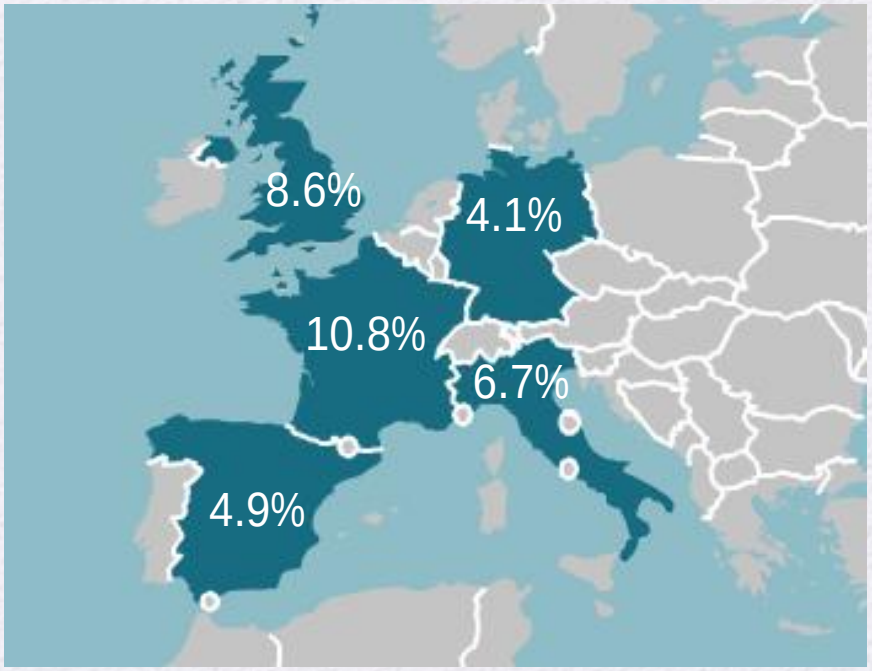
RLS symptoms are widely spread across North America and Europe



- The prevalence of RLS symptoms ranges from 4-11% in countries surveyed
- Generally, prevalence is higher in people of Northern European descent



Allen RP et al. *Arch Intern Med,* 2005.; 165: 1286

RLS Essential Criteria

Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;**4**(2)**:**101-19.

- 1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs.
- 2. The urge to move or unpleasant sensations begin or worsen during periods of rest.
- 3. The urge to move or unpleasant sensations are partially or totally relieved by movement.
- 4. The urge to move or unpleasant sensations are worse in the evening or night than during the day.

RLS Essential Criteria

Supportive clinical features of RLS

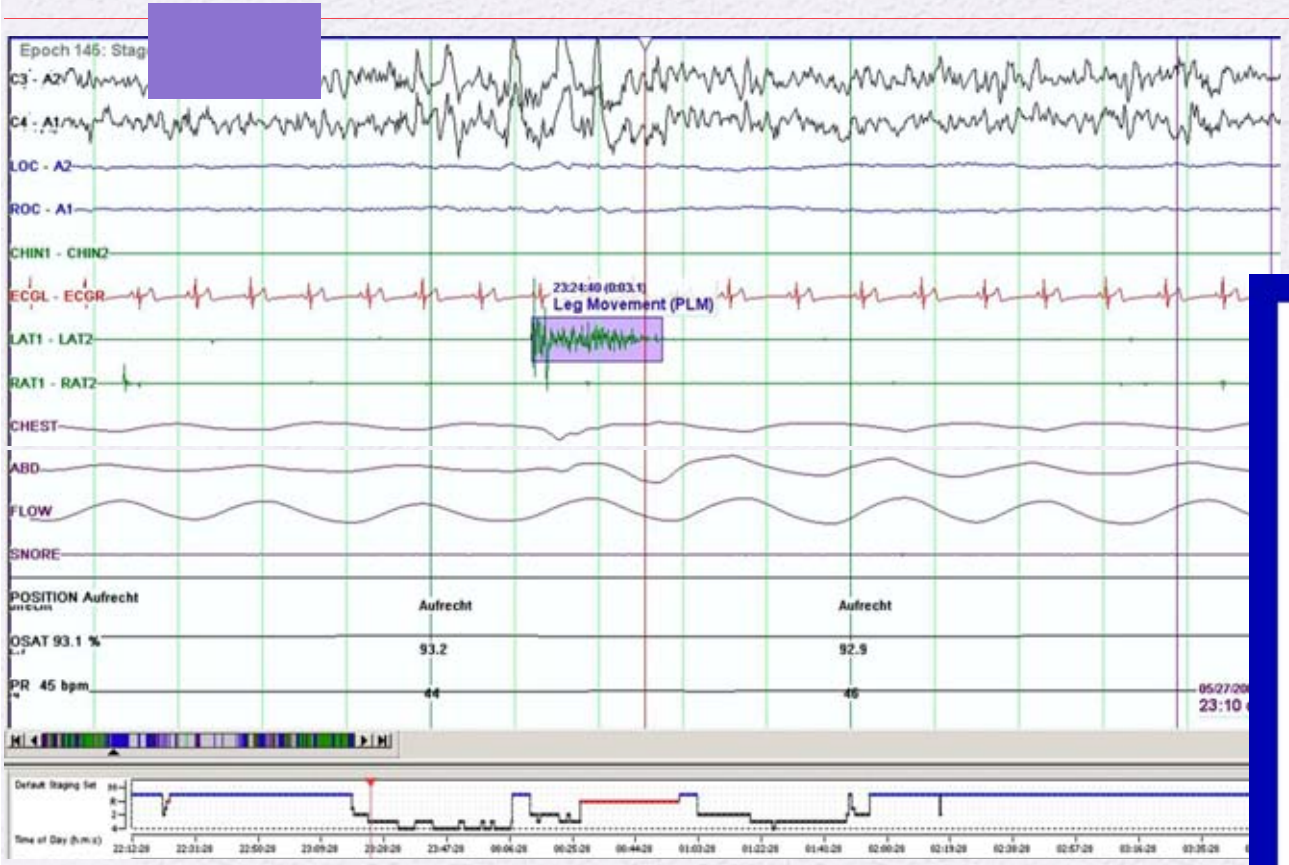
- **Family history positiv**
- **Response to dopaminergic therapy**
- **Periodic limb movements (during wakefulness or sleep)**

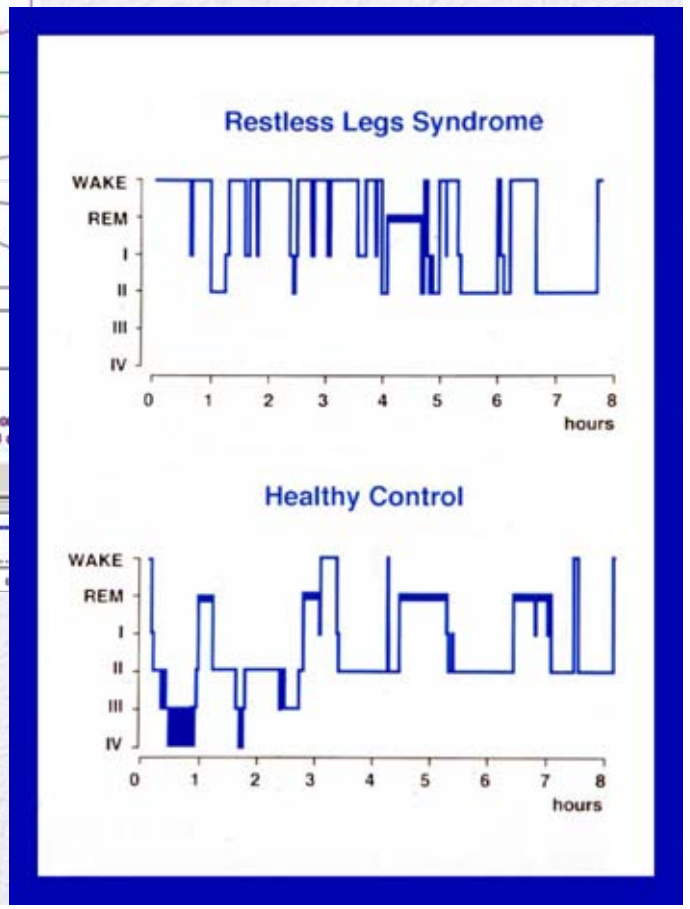
Associated features of RLS

- **Clinical course (variable)**
- **Physical examination (normal)**
- **Sleep disturbance**

Allen et al 2003

Periodic Limb Movements in Sleep (PLMS) with Arousal





Treatment of RLS: how to start

- Start with non-pharmacological therapy
  - sleep hygiene, avoiding caffeine, mild exercise, physical therapy
- Check ferritin levels and other medical conditions (uraemia, diabetes, etc)
- Indication for pharmacological treatment
  - sleep disturbance, reduced QoL, daytime symptoms

International RLS Severity Rating Scale (IRLS)

- Disease-specific, 10-item rating scale
- Measures disease severity through subjective assessment of primary sensorimotor features, associated sleep problems, and impact on patients' mood, daily life, and activities
- Patients score symptoms from 0 (none) to 4 (very severe)
- 10 items are added together to give a total IRLS score:
  - Score of 1-10: Mild RLS
  - Score of 11-20: Moderate RLS
  - Score of 21-30: Severe RLS
  - Score of 31-40: Very severe RLS

Hening W, et al. *Sleep Med,* 2003.
Allen RP, et al. *Sleep Med,* 2003.

Treatment with dopamine agonists in RLS

Ropinirole (0.25-4mg, mean: 2mg)	Pramipexole (0.54 mg of base (0.75 mg of salt)	Rotigotine patch (1mg to 3mg /24h)
Efficacious for treating RLS in patients with moderate to severe clinical symptomatology.	Efficacious for treating RLS in patients with moderate to severe clinical symptomatology.	Efficacious for moderate to severe RLS
Sleep and general RLS severity improved in all trials.	Sleep and general RLS severity improved in all trials.	Current results from clinical studies in RLS are limited but promising.
No specific concerns about hypersomnolence in RLS patients.	No specific concerns about hypersomnolence in RLS patients but driving warning for some countries	Local site reactions to the patch have been observed.

Effect of Ropinirole on Sleep Outcomes in Patients with Restless Legs Syndrome: Meta-Analysis of Pooled Individual Patient Data from Randomized Controlled Trials

Richard A. Hansen, Ph.D., Liping Song, Ph.D., Charity G. Moore, Ph.D., M.S.P.H., Alicia W. Gilsenan, Ph.D., Mimi M. Kim, Ph.D., Michael O. Calloway, Ph.D., and Michael D. Murray, Pharm.D.,

(Pharmacotherapy 2009;29(3):255–262)

Sleep Measured with MOS Sleep Scale

835 (ropinirole) and 844 (placebo) patients **: exclusion of patients with daytime symptoms (before 18.00)**

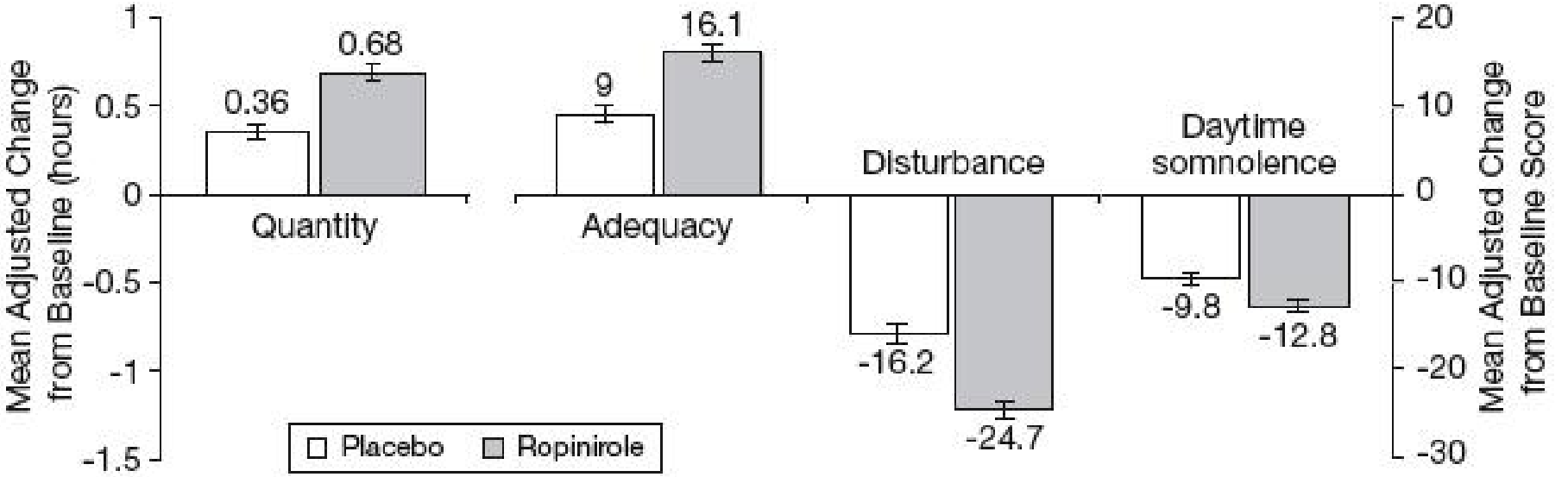
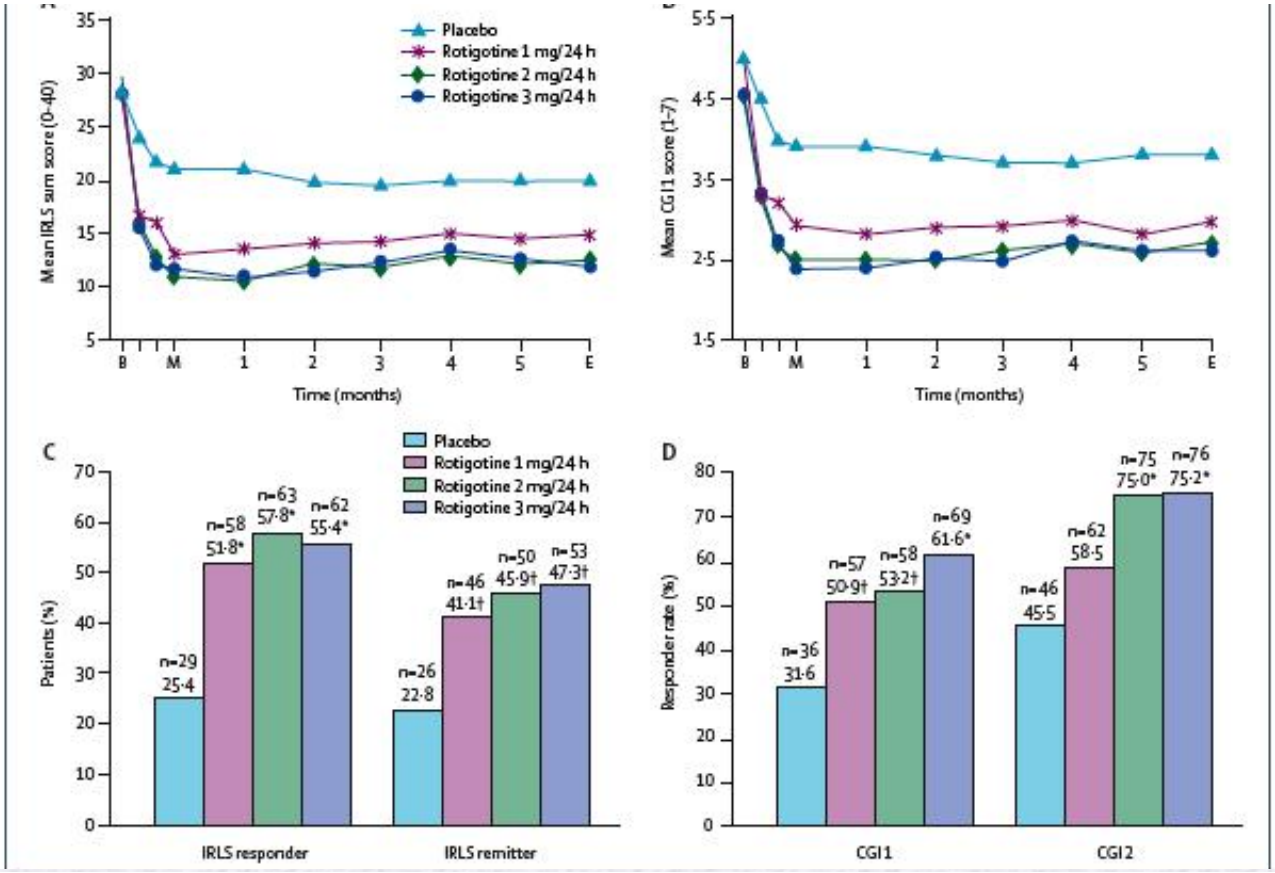


Figure 2. Change from baseline (adjusted mean ± standard error) in the four sleep domains for the intent-to-treat last observation carried forward analysis.

Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial

*Claudia Trenkwalder, Heike Benes, Werner Poewe, Wolfgang H Oertel, Diego Garcia-Borreguero, Al W de Weerd, Luigi Ferini-Strambi, Pasquale Montagna, Per Odin, Karin Stiasny-Kolster, Birgit Högl, K Ray Chaudhuri, Markku Partinen, Erwin Schollmayer, Ralf Kohnen, for the SP790 Study Group**

458 patients
6-month duration
IRLS and CGI as
Primary endpoint



Lancet Neurol 2008

Efficacy of rotigotine versus placebo

Severity during day at rest and during activity

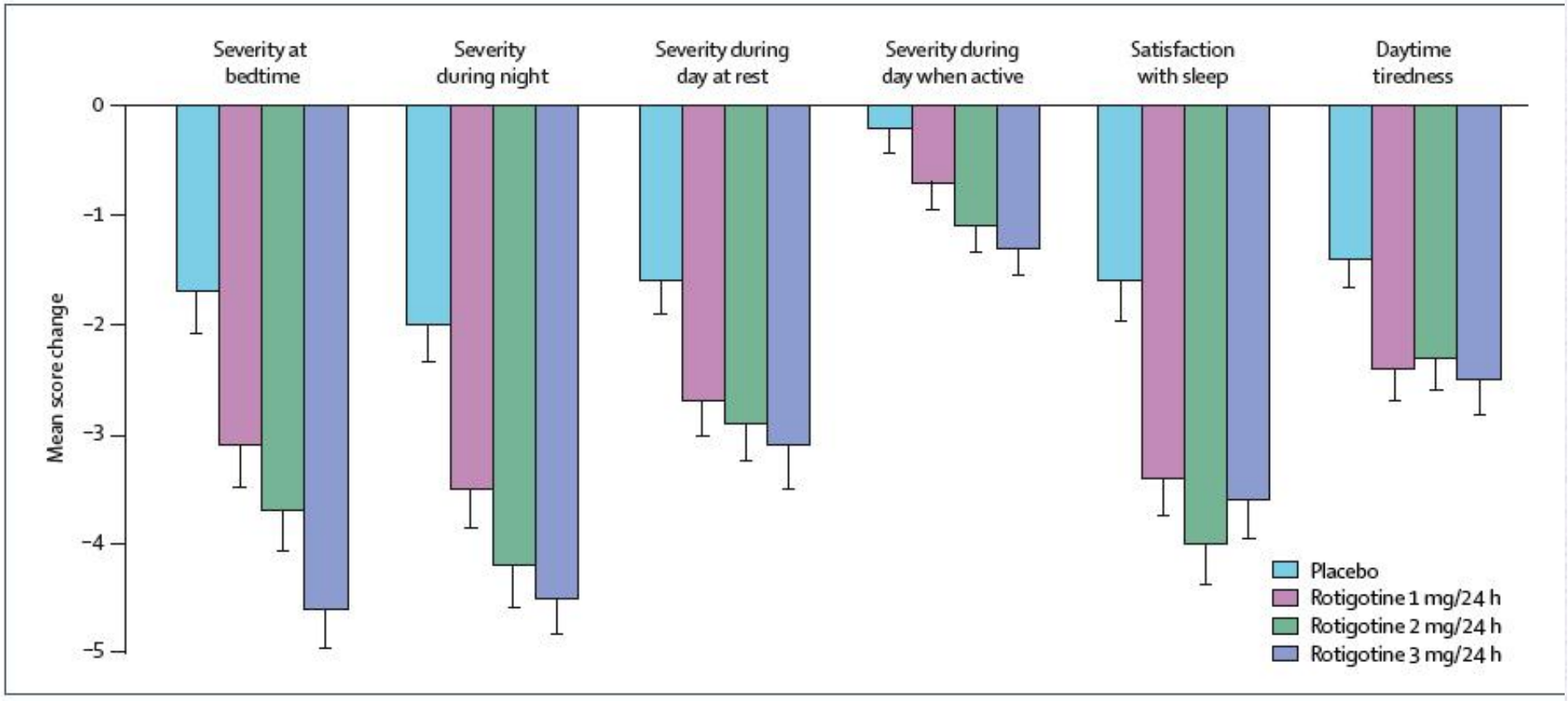


Figure 4: Mean change from baseline to end of maintenance in RLS-6 rating scales

Full analysis set; dropouts who did an early withdrawal assessment are included. Negative values indicate improvement.

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Sleep Medicine xxx (2007) xxx–xxx

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Orginal article

First night efficacy of pramipexole in restless legs syndrome and periodic leg movements

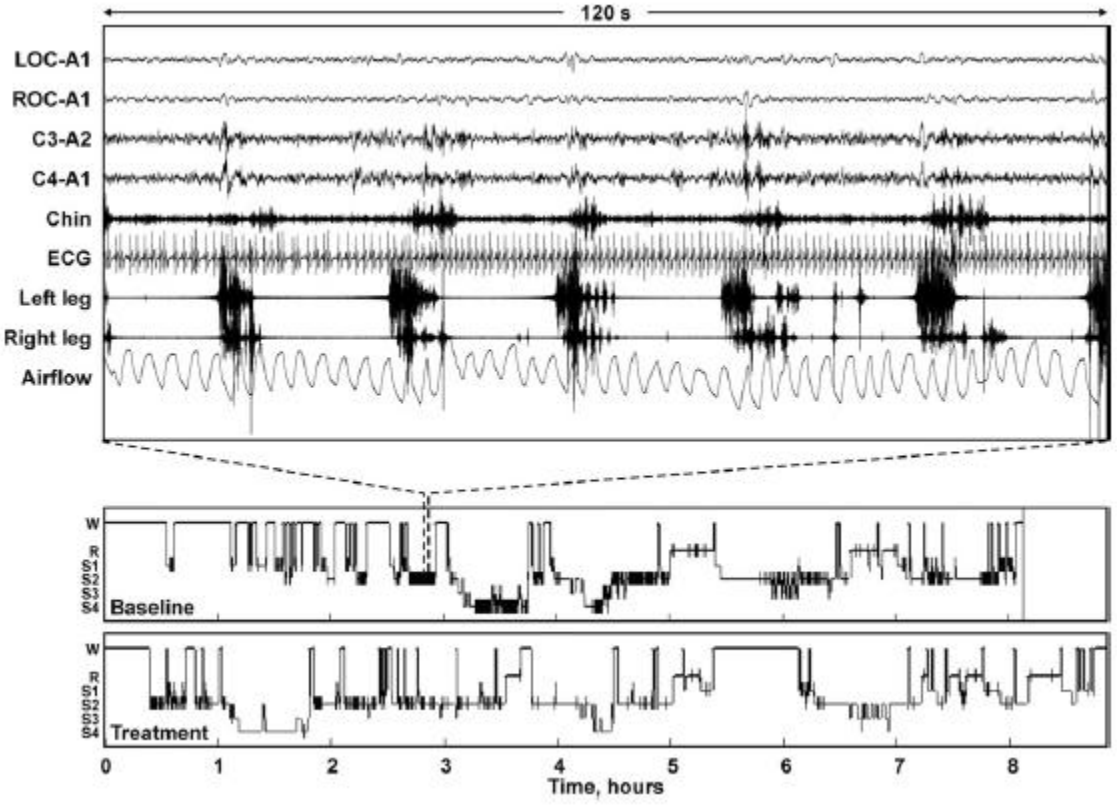
Mauro Manconi [a,*], Raffaele Ferri [b], Marco Zucconi [a], Alessandro Oldani [a], Maria Livia Fantini [a], Vincenza Castronovo [a], Luigi Ferini-Strambi [a]

[a] *Sleep Disorders Center, Department of Neurology, Scientific Institute and University Ospedale San Raffaele, Vita-Salute University, Milan, Italy*

[b] *Slee*

Receiv

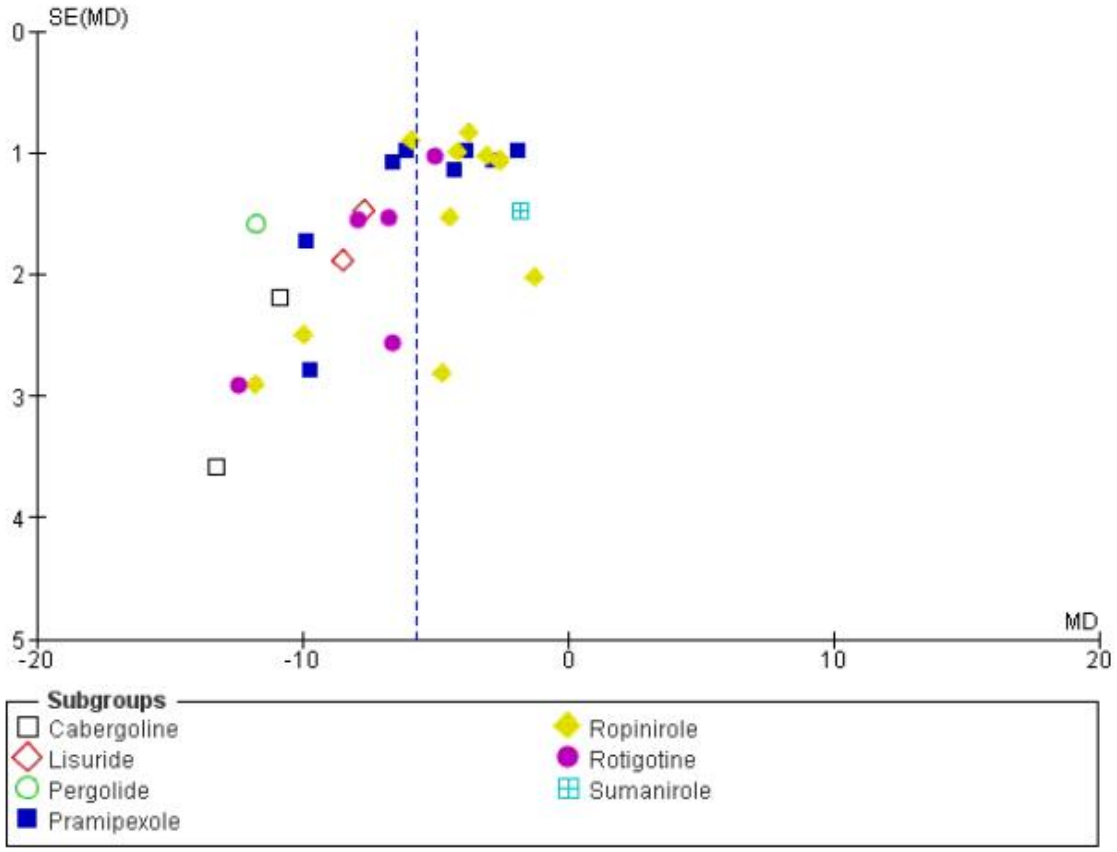
Acute treatment effect of a single dosage of 0.25mg ppx:
Significant reduction of PLMS index and improvement of sleep profile



Cochrane Database Syst Rev. 2011
Dopamine agonists for restless legs syndrome

Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M

Figure 10. Funnel plot of comparison: 1 Dopamine agonists versus placebo, outcome: 1.2 Medication subgroups: change on IRLS.



Conclusion:

The meta-analyses show the superiority of dopamine agonists over placebo in RCTs up to seven months. Cabergoline and pramipexole showed larger efficacy compared to levodopa in some but not all outcomes.

Possible Conclusion from Cochrane Analysis

- Dopamine agonists with long half life may have better efficacy
- Non-pulsatile dopaminergic stimulation may improve RLS during long-term treatment
- Any relevance of stimulating different dopamine receptors? D3 versus D2?

Non-dopaminergic drugs in RLS

- Gabapentin: evidence class II
- Gabapentin enacarbil (pro-drug): evidence class I
- Pregabalin: evidence class I
- Opioids: oxycodon, methadon, tramadolol, oxycodon/naloxon ret.; evidence class III
- Iron: oral and i.v. ; evidence class III-II

Treatment of restless legs syndrome with pregabalin: a double-blind, placebo-controlled study.

Garcia-Borreguero D et al, Neurology 2011

58 Patients were randomized to receive pregabalin or placebo for 12 weeks under a flexible-dose schedule with PSG

RESULTS: Treatment with pregabalin also resulted in a reduction of the mean (+/-SD) PLM index ($p < 0.001$). Furthermore, there was a marked improvement in sleep architecture with an increase in slow wave sleep ($p < 0.01$), and decreases in wake after sleep onset and stages 1 and 2 ($p < 0.05$). Adverse events were mild but common, and included unsteadiness, daytime sleepiness, and headache.

CLASSIFICATION OF EVIDENCEThis study provides Class II evidence that pregabalin is effective for the treatment of restless legs syndrome and improves sleep architecture and periodic limb movements in placebo-unresponsive patients.

Treatment with Opioids

- Opioids, especially oxycodone, tramadol, and methadone have been used in idiopathic RLS
- probably interacting with dopamine on a spinal level and acting on the medial pain system centrally for analgesia
- Reducing numbers of PLMS with oxycodone (Walters et al 1993); tramadol effective for RLS (Lauerma 1999) stable results in long-term cohorts with different opioids (Walters et al 2001, Silver et al 2011)

Oxycodon/Naloxone sustained release: a RCT in severe RLS after failure of other treatments

(Trenkwalder et al, abstr, 2013, WCN, Sept. 25th, 11-12.30)

- 304 severely affected RLS patients significantly improved measured by IRLS (difference compared to placebo: 8!) with oxycodone/naloxone sustained release (12 week controlled, up to 1 year long-term open treatment, no withdrawal effects,mean dosage: 10-15mg bid; no augmentation
- Opioids are considered a second line treatment for RLS
- Problems: withdrawal symptoms, sleep apnea?, long-term results, currently not licensed in any country for RLS

A Randomized, Double-Blind, Placebo Controlled, Multi-Center Study of Intravenous Iron Sucrose and Placebo in the Treatment of Restless Legs Syndrome

Ludger Grote, MD, PhD,[1]* Lena Leissner, MD,[2] Jan Hedner, MD, PhD,[1] and Jan Ulfberg, MD, PhD[3]

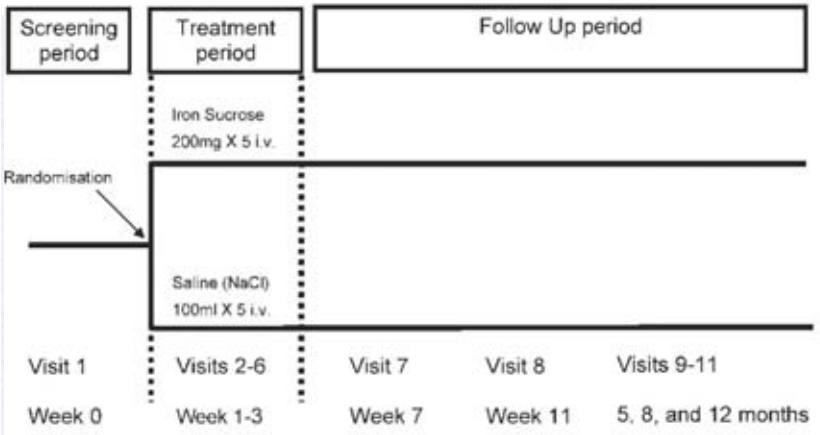


FIG. 2. Schematic overview of study related procedures.

Treatment with iron sucrose in female RLS patients with low ferritin shows sustained efficacy

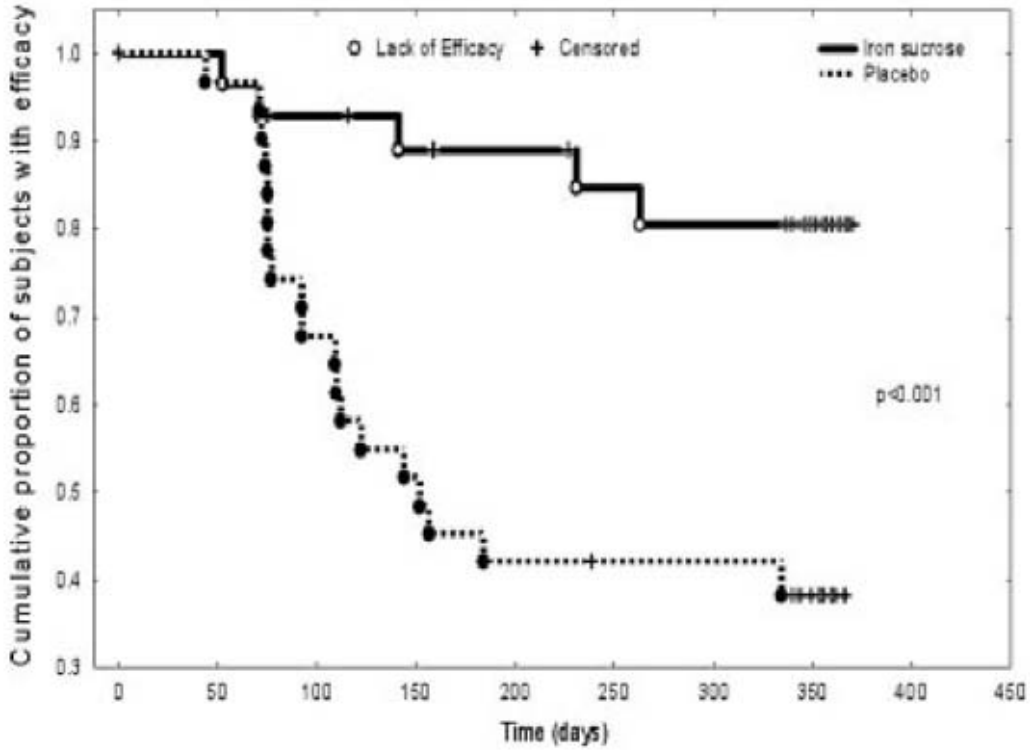


FIG. 4. Cumulative proportion of patients remaining in the study indicating drop out frequency because of lack of treatment effect (Kaplan–Meier curve, log rank test, $P < 0.001$).

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Contents lists available at SciVerse ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Clinical efficacy and safety of IV ferric carboxymaltose (FCM) treatment of RLS: A multi-centred, placebo-controlled preliminary clinical trial

Richard P. Allen [a,*], Charles H. Adler [b], Wei Du [c], Angelia Butcher [d], David B. Bregman [d,e], Christopher J. Earley [a]

[a] Department of Neurology, Johns Hopkins University, Baltimore, MD, USA
[b] Department of Neurology, Mayo Clinic Scotsdale, AZ, USA
[c] Clinical Statistics Consulting, Blue Bell, PA, USA
[d] Luitpold Pharmaceuticals, Inc. Norristown, PA, USA

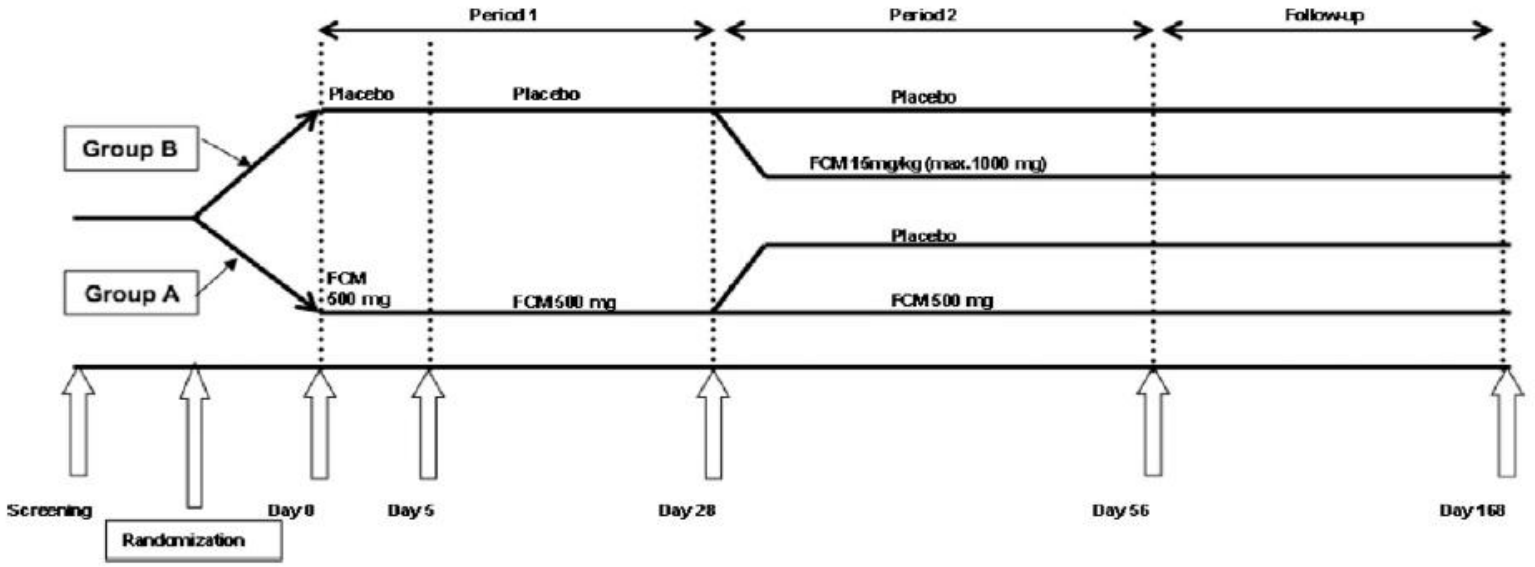

Fig. 1. Overall study design.

Low ferritin is a risk factor for developing augmentation

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Sleep Medicine 9 (2008) 572–574

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Brief Communication

Augmentation in restless legs syndrome is associated with low ferritin

Claudia Trenkwalder [a,b,*], Birgit Högl [c], Heike Benes [d], Ralf Kohnen [e]

[a] *Paracelsus-Elena Hospital, Kassel, Germany*

[b] *Department of Clinical Neurophysiology, University of Goettingen, Germany*

Original Article

severity range of restless legs syndrome (RLS) and augmentation
rospective patient cohort: Association with ferritin levels

her, Viola Gschliesser, Elisabeth Brandauer, Essam El-Demerdash, Matthias Kaneider,
*Verner Poewe, Birgit Högl **

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Available online 5 February 2009

http://dx.doi.org/10.5665/sleep.1988

The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder in Adults—An Update for 2012: Practice Parameters with an Evidence-Based Systematic Review and Meta-Analyses

An American Academy of Sleep Medicine Clinical Practice Guideline

Practice Parameter	Strength of Recommendation	Body of Evidence Level	Harm/burden Assessment	FDA status
Standards for use in RLS				
Clinicians should treat patients with RLS with pramipexole.	(STANDARD)	High	Benefits clearly outweigh harms	Approved for indication
Clinicians should treat patients with RLS with ropinirole.	(STANDARD)	High	Benefits clearly outweigh harms	Approved for indication
Standards against use in RLS				
Clinicians should not treat RLS patients with pergolide because of the risks of heart valve damage.	(STANDARD)	High	Harms clearly outweigh benefits	Discontinued
Guidelines for use in RLS				
Clinicians can treat RLS patients with levodopa with dopa decarboxylase inhibitor.	(GUIDELINE)	High	Benefits closely balanced with harms. This is particularly true for those with intermittent RLS who use this medication sporadically.	Approved, but off-label use
Clinicians can treat RLS patients with opioids.	(GUIDELINE)	Low	Benefits clearly outweigh harms	Approved, but off-label use
Clinicians can treat patients with RLS with gabapentin enacarbil.	(GUIDELINE)	High	Uncertainty in balance between benefits and harms	Approved for indication
Given the potential of side effects, including heart valve damage, clinicians can treat RLS patients with cabergoline *only if* other recommended agents have been tried first and failed, and close clinical follow-up is	(GUIDELINE)	High	Benefits closely balanced with harms	Approved, but off-label use

Options for use in RLS

Options for use in RLS				
Clinicians may treat RLS patients with gabapentin.	(OPTION)	Low	Unclear benefit/harm balance	Approved, but off-label use
Clinicians may treat patients with RLS with pregabalin.	(OPTION)	Low	Benefits closely balanced with harms	Approved, but off-label use
Clinicians may treat RLS patients with carbamazepine.	(OPTION)	Low	Benefits closely balanced with harms	Approved, but off-label use
Clinicians may treat RLS patients with clonidine.	(OPTION)	Low	Unclear benefit/harm balance	Approved, but off-label use
Clinicians may use supplemental iron to treat RLS patients with low ferritin levels.	(OPTION)	Very Low	Unclear benefit/harm balance	Approved, but off-label use

AASM, Standard of Practice, 2012

Augmentation: Definition

- Paradoxical worsening of RLS symptoms during treatment with dopaminergic drugs
- Symptoms start at earlier times of the day
- Increase of severity of symptoms
- Spreading of symptoms to other body parts (i.e. to the arms)
- Increase of dosage necessary

Allen et al 2003, Garcia-Borreguero 2007

Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome

Six-month incidence of confirmed augmentation was

9.2% for pramipexole

and 6.0% for placebo

- Conclusion:

  During a 6-month period, pramipexole was effective, and safe. .....

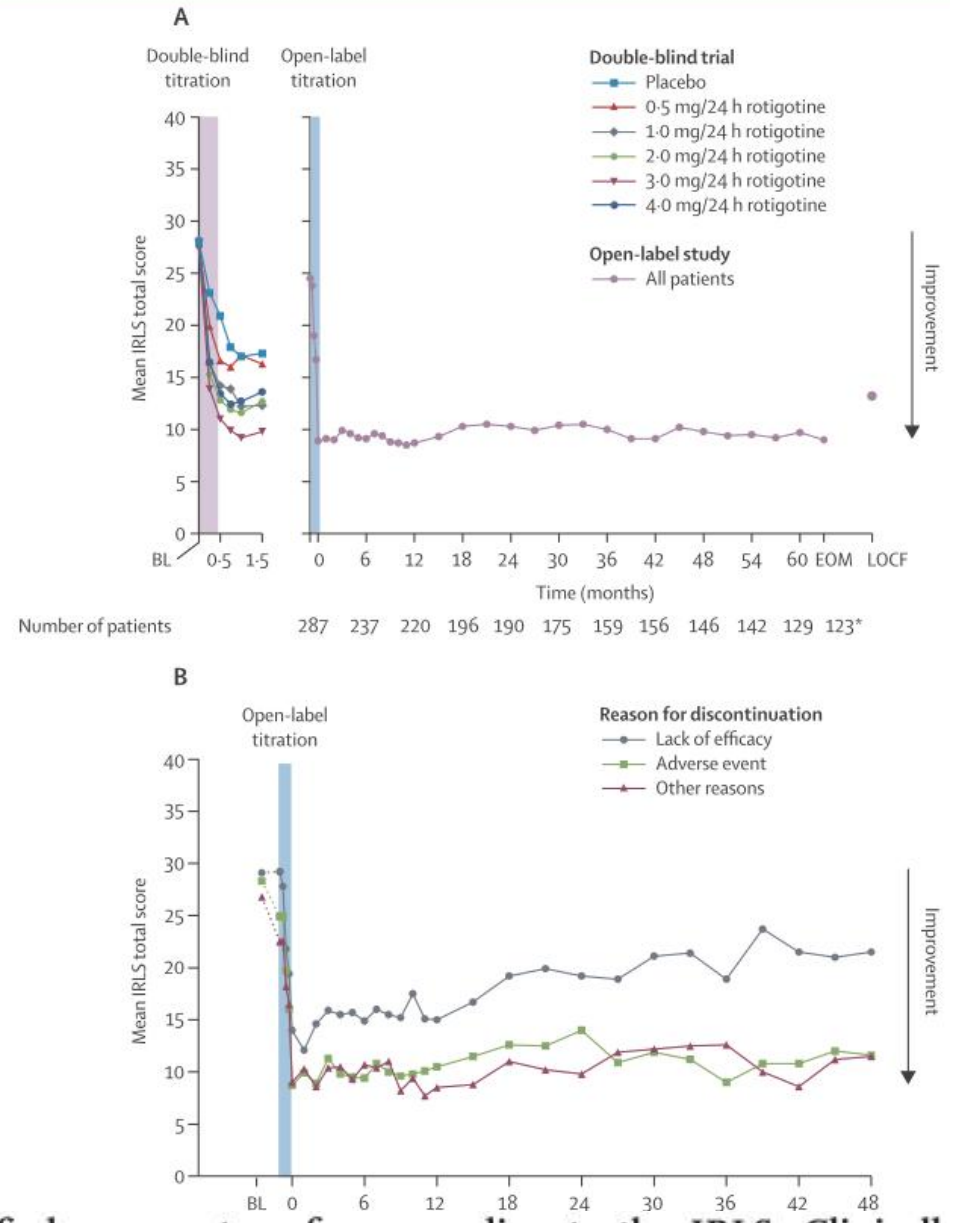
Because risk of augmentation may have increased over 6 months, it should be studied in longer trials. Beginning or mild augmentation is difficult to distinguish from natural RLS fluctuation, at least in a non-iron-deficient population.

Högl B et al, Sleep Med 2011

Long-term safety and efficacy of rotigotine transderma patch for moderate-to-severe idiopathic restless legs syndrome: a 5-year open-label extension study

Wolfgang Oertel, Claudia Trenkwalder, Heike Benes, Luigi Ferini-Strambi, Birgit Högl, Werner Poewe, Karin Stiasny-Kolster, Andreas F
Erwin Schollmayer, Ralf Kohnen, Diego Garcia-Borreguero, on behalf of the SP710 study group*

- First Long-term study for 5-year duration
- Augmentation rate for 3mg rotigotine: 5%



48/123) of patients who completed the trial were classified as symptom free according to the IRLS. Clinically significant augmentation was recorded in 39 patients (13%), of whom 15 (5%) were receiving a dose of rotigotine within the range approved by the European Medicines Agency (EMA; 1–3 mg/24 h) and 24 (8%) were receiving mg/24 h rotigotine.

What do we know about the dosage of dopaminergics in RLS?

Substance	trial design	dosage	(max.)
Levodopa/DDCI	flexible	100-200	(?)
Pramipexole	flexible/fixed	0.25-o.50mg	3.0mg
Ropinirole	flexible	mean: 2.2mg	24mg
Rotigotine	fixed	2mg	16mg
Pergolide	*flexible*	*0.5mg*	*4mg*
Cabergoline	*flexible/fixed*	*1mg (2mg)*	*6mg*

What do we know about the dosage of dopaminergics in RLS?

- Dosages of dopamine agonists are efficient only in low dosages, higher dosages are not efficient in the beginning
- Dosages are in the range of autoreceptor stimulation known from exp. Studies and PD patients
- Do dopamine agonists act on the autoreceptor level in RLS?

Management of clinically relevant augmentation (1)

- If levodopa/DDCI leads to augmentation:
  - Stop levodopa! Don‘t use levodopa as rescue medication for management of augmentation!
  - Give iron i.v. if ferritin is below 50
  - Try a long-acting dopamine agonist
  - If augmentation is severe: use an opioid both during daytime and at night
  - Try to re –introduce a dopamine agonist or pregabalin after 1-2 weeks of dopaminergic wash-out

Management of clinically relevant augmentation (2)

- If a dopamine agonist leads to augmentation:
  - Stop levodopa, reduce the dopamine agonist to the lowest level possible (only licensed dosages)
  - Give iron i.v. if ferritin is below 50
  - If augmentation is severe: use an opioid both during daytime and at night
  - Switch to an opioid for long-term treatment or try to combine a dopamine agonist and pregabaline or opioid and pregabaline
  - Avoid three substance groups when possible

Management of clinically relevant augmentation (3)

For very severely augmented patients:

- Try to admitt them on a ward specialized for Sleep or RLS as symptoms may become more severe
- Give iron i.v. if ferritin is below 50
- Try opioids, pregabline, low dose dopamine agonist, especially rotigotine patch, when available
- Use a benzodiazepine intermittently, if sleep is and anxiety is a problem, avoid antidepressants
- Management of augmentation has not been studied in clinical trials yet!!

Summary

- RLS is a clinical diagnosis, PLMS and sleep disorders are major accompanying features, but it is a 24h condition with a circadian rhythm
- Pathophysiology points to a dopaminergic dys-(hypo?)function: or even a primary hyperdopaminergic condition, that will be modulated by low-dose dopamine agonists
- Brain iron storage interact with the dopaminergic system - Measure ferritin and supply iron when low (<50)!
- Only low dosages of dopaminergic drugs seem to be effective without developing augmentation over time!
- Alternative treatments are pregabaline (gabapentine) and opioids, that can be used for managing augmentation