Diagnostic advances and treatment of movement disorders in sleep

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Disclosure

- RLS:

C.T. received fees for Advisory Boards from Mundipharma Research GmbH & Co. KG, UCB, Vifor. Payment for Lectures from: UCB and Mundipharma.

- other topics: nothing to disclose

Learning Objectives

- Movement disorders in sleep including restless legs syndrome, PLMS, bruxism and others will be presented by videos, treatment options will be provided.

- Identify various motor disorders in sleep and characterize restless legs syndrome including treatment options.

Motor disorders in sleep: Differential diagnosis

Always exclude seizures!

- Nocturnal seizures
  - Frontal seizures
  - Predominantly in young patients
  - be aware of post-traumatic seizures
  - Only polysomnography can reliably differentiate between parasomnias and seizures!

Bruxism: frequent in young people

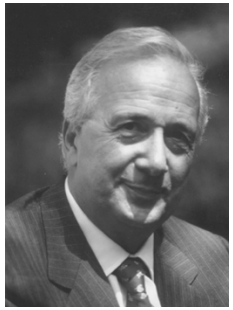
PLMS Periodic Limb Movements in Sleep

Nocturnal Myoclonus	**Symonds 1956**
Periodic Leg Movements	**Lugaresi et al 1968**
	Coleman 1982

Definition: ***Sequence of at least 4 leg movements***

0.5 - 5 sec duration, 4 - 90 sec intermovement interval

(ASDA criteria, 1990)



Lugaresi E, Cirignotta F, Coccagna G, Montagna P,
Nocturnal Myoclonus and Restless Legs Syndrome
Adv Neurol, 1986

Coleman et al Sleep 1982; 5 Suppl 2: S191-202
Zucconi et al Sleep Med 2006 Mar; 7(2): 175-83

ELSEVIER

Sleep Medicine 7 (2006) 175–183

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Special Section

The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG)

Marco Zucconi *, Raffaele Ferri, Richard Allen, Paul Christian Baier, Oliviero Bruni, Sudhansu Chokroverty, Luigi Ferini-Strambi, Stephany Fulda, Diego Garcia-Borreguero, Wayne A. Hening, Max Hirshkowitz, Birgit Högl, Magdolna Hornyak, Martin King, Pasquale Montagna, Liborio Parrino, Giuseppe Plazzi, Mario G. Terzano

Received 28 December 2005; received in revised form 3 January 2006; accepted 3 January 2006

- Criteria separately defined for clinical use and for research
- Definition of duration, onset, bilateral movements, arousals

PLMS: onset, offset threshold; LM intervals; LM duration

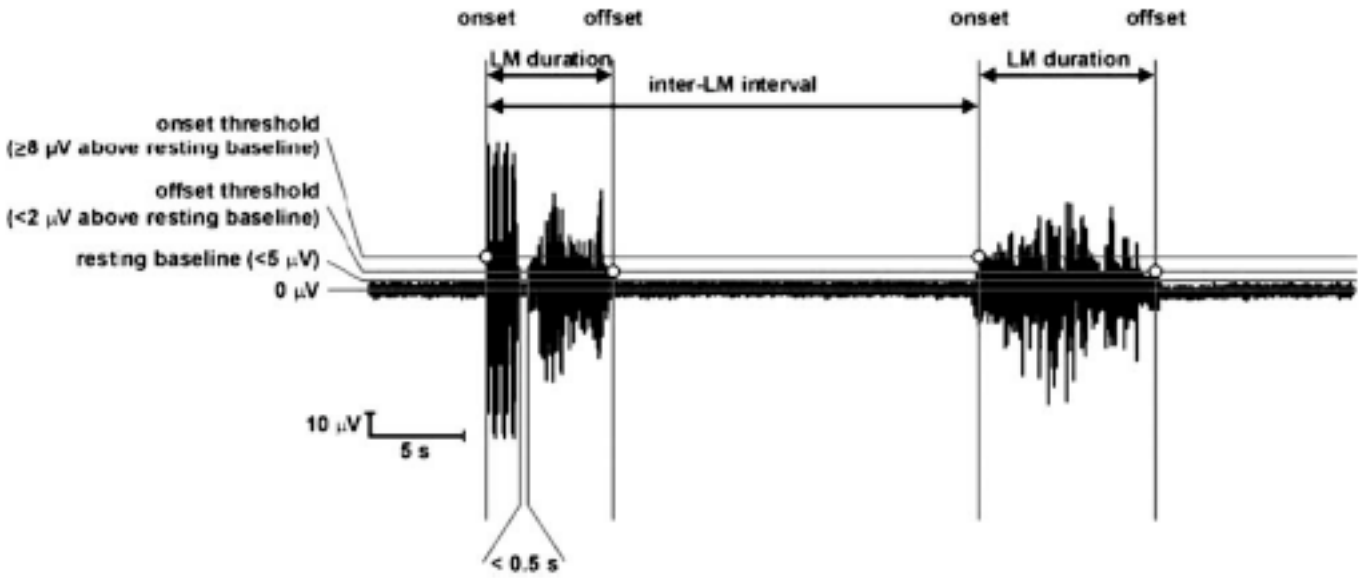
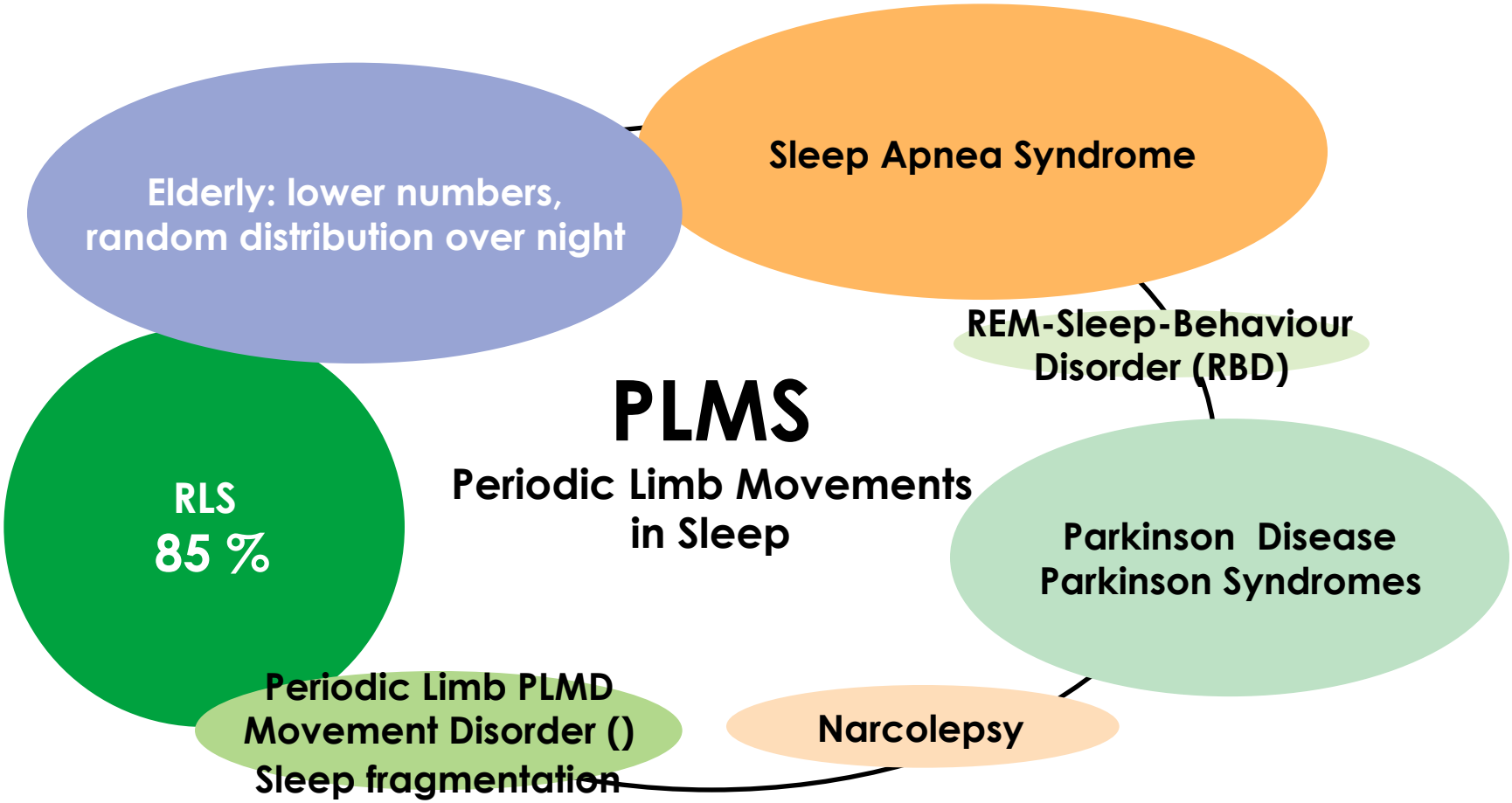


Fig. 4. Overview of the detection parameters for candidate PLM.

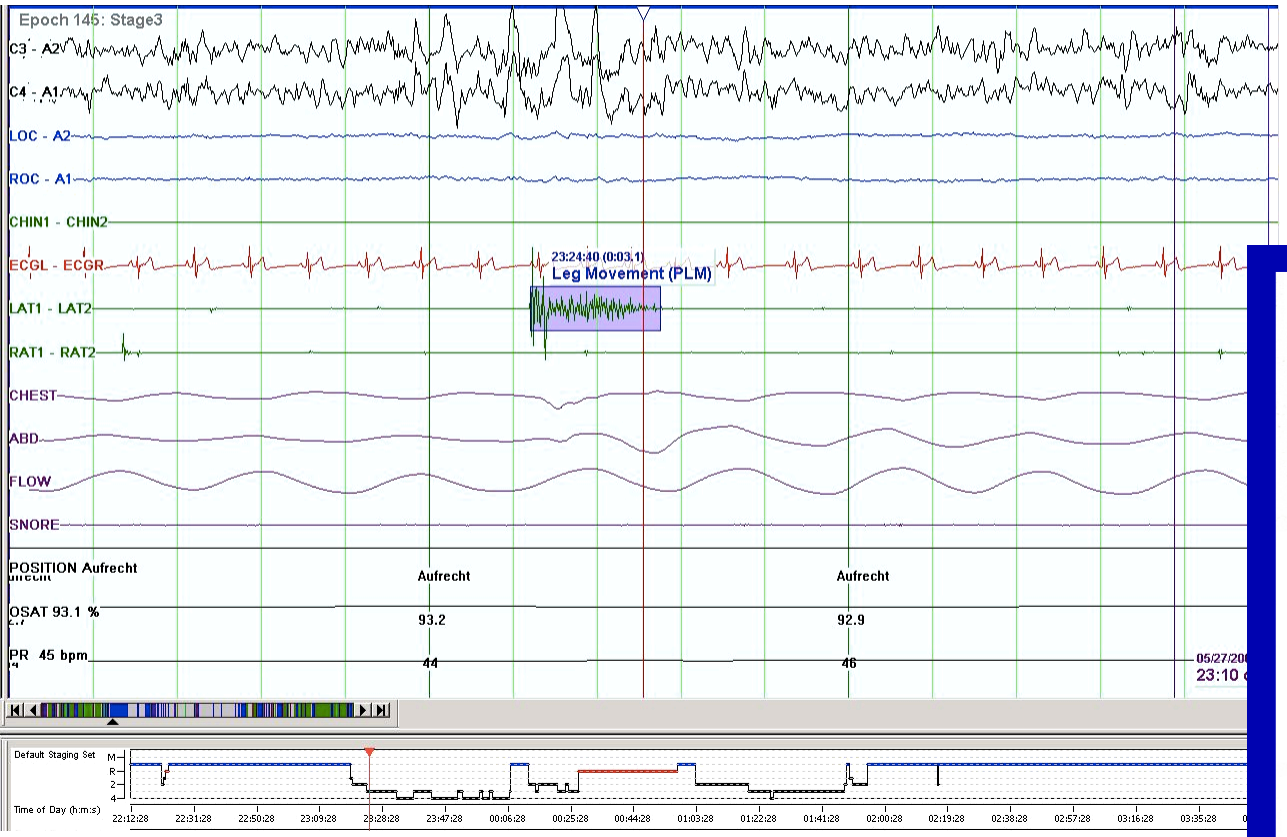
Zucconi et al 2006: WASM criteria

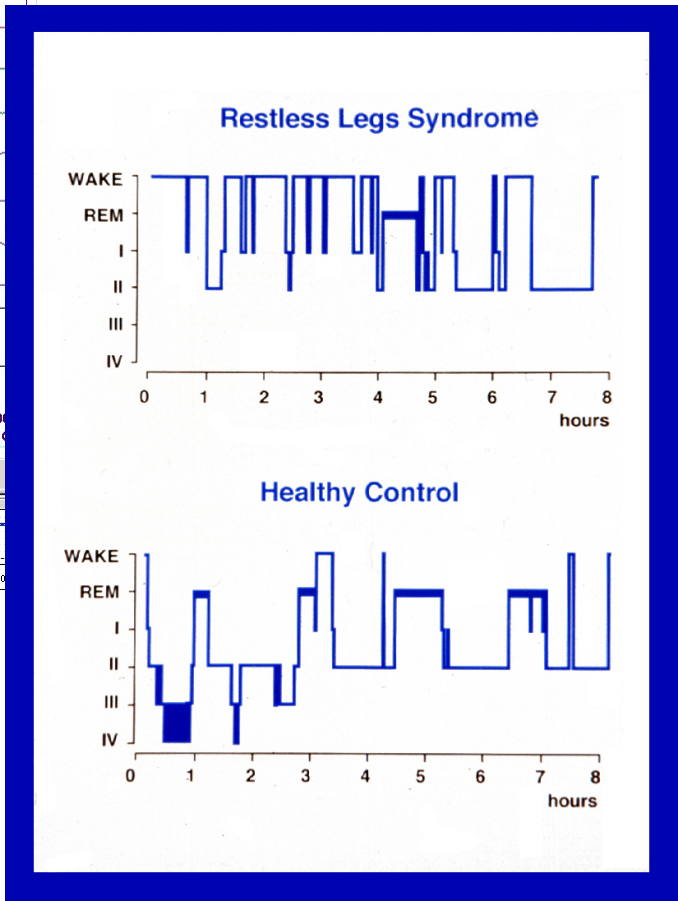
PLMS are unspecific and associated with various disorders and diseases



ICSD-2

Periodic Limb Movements in Sleep (PLMS) with Arousal





Restless Legs Syndrome

- **Diagnostic Criteria:**
- 4 Essential Criteria, now revised into 5 criteria
- Polysomnography is not necessary to diagnose RLS
- The occurrence of periodic limb movements are part of additional, non obligatory characteristics in RLS (no sleep measure included)
- Conclusion: RLS is primarily a clinical diagnosis without PSG measures

Allen et al, Sleep Med 2003; Allen, Picchietti et al, Sleep Med 2014, ICSD Criteria, ICD.

RLS Essential Criteria

Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. *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.

Sleep Medicine xxx (2014) xxx–xxx

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

Special Section in Sleep Medicine

Restless legs syndrome/Willis–Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria – history, rationale, description, and significance

Richard P. Allen [a], Daniel L. Picchietti [b,*], Diego Garcia-Borreguero [c], William G. Ondo [d], Arthur S. Walters [e], John W. Winkelman [f], Marco Zucconi [g], Raffaele Ferri [h], Claudia Trenkwalder [i,j], Hochang B. Lee [k], on behalf of the International Restless Legs Syndrome Study Group

Changes :

5. The occurrence of the above features is 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).

Specifiers for clinical course of RLS/WED:

A**. Chronic-persistent RLS/WED**: symptoms when not treated would occur on average at least twice weekly for the past year.

B. **Intermittent RLS/WED**: symptoms when not treated would occur on average <2/week for the past year, with at least five lifetime events.

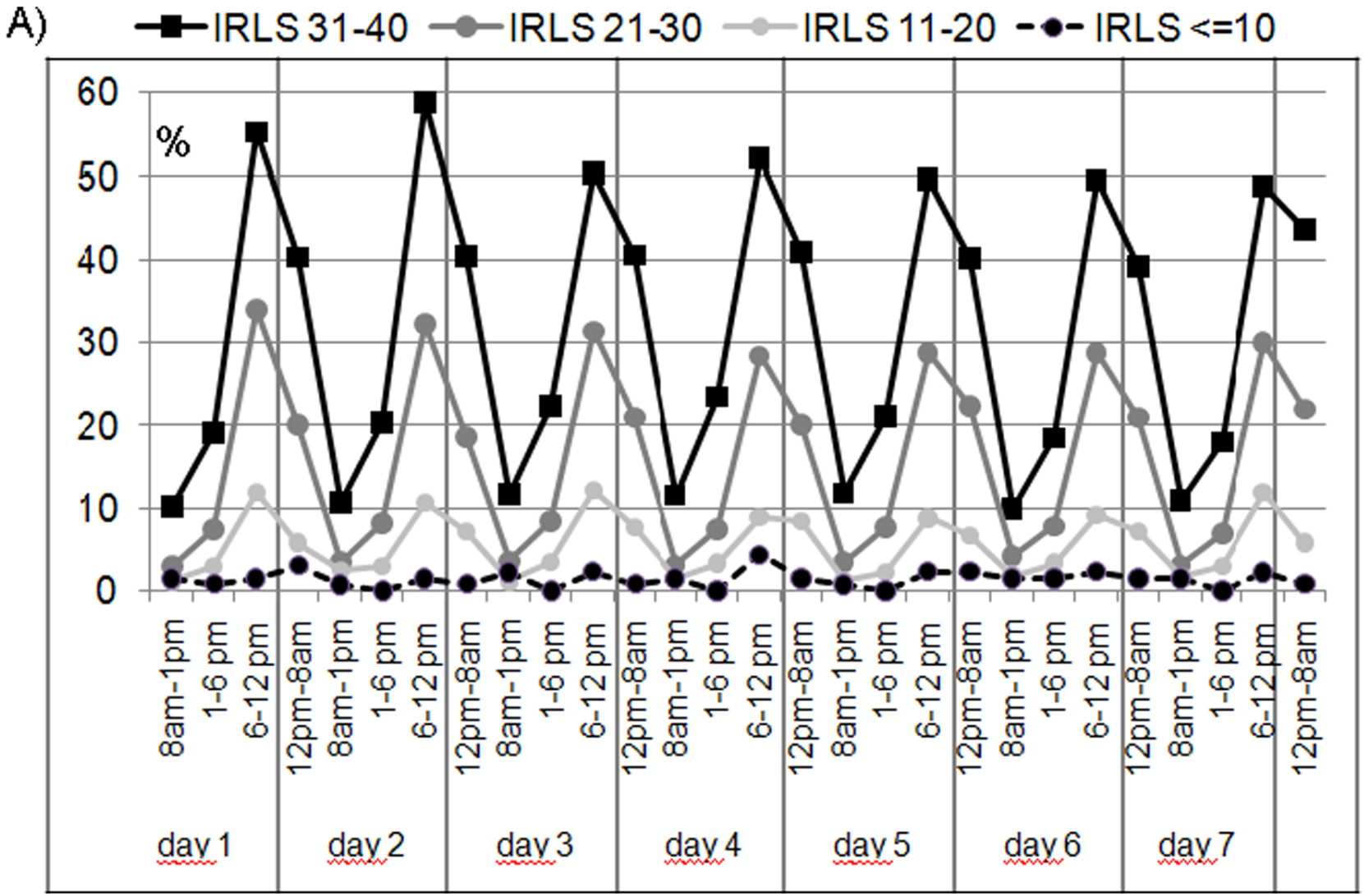
Specifier for clinical significance of RLS/WED:

"Gold Standard": 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.

Combination of a diary with the IRLS: showing circadian distribution of RLS *Fuhs et al, Plos1 2014*



Severe RLS at night:

coping strategies:

leg movements, body rocking,
arm movements, getting up and walk
stretching

Video RLS

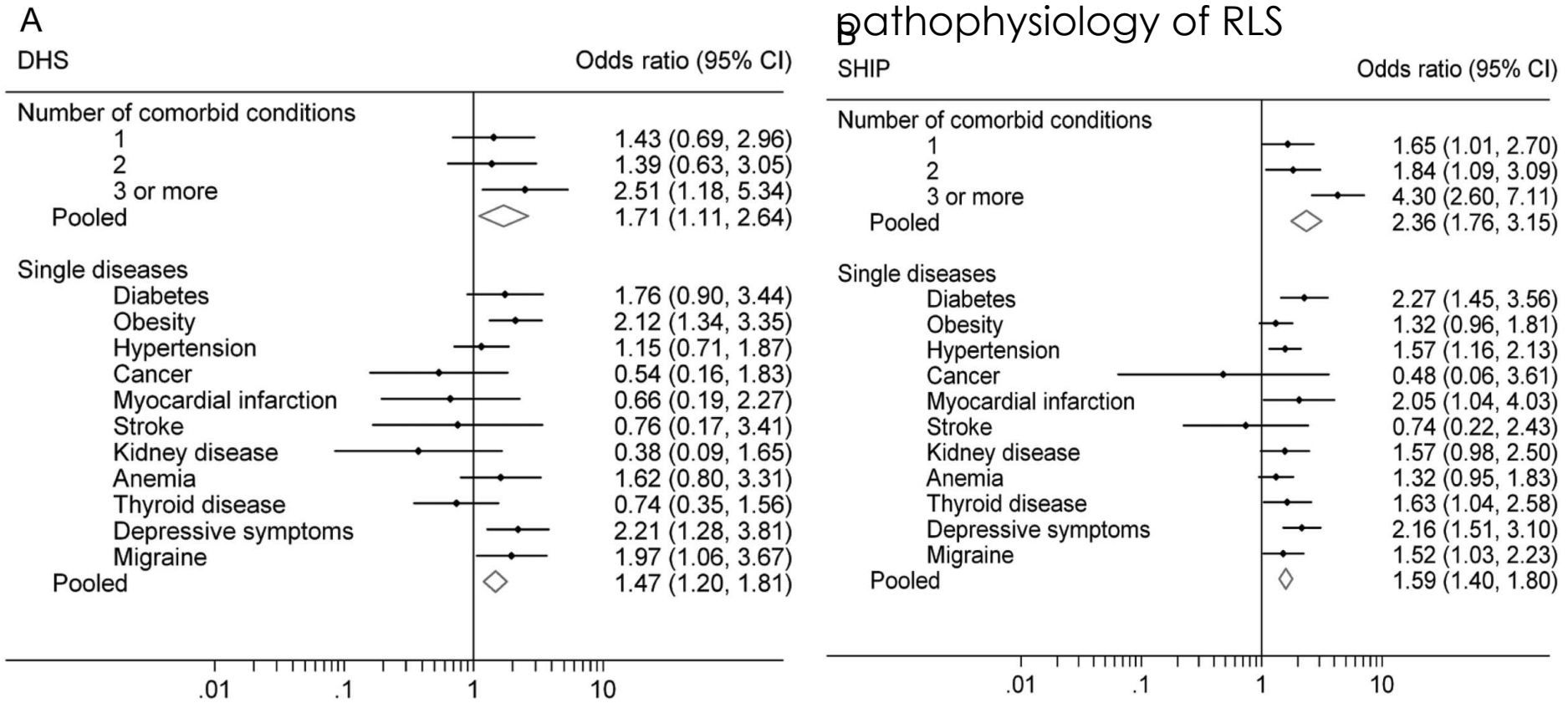
András Szentkirályi, MD, PhD
Henry Völzke, MD, Drmed
Wolfgang Hoffmann, MD, Drmed, MPH
Claudia Trenkwalder, MD, Drmed
Klaus Berger, MD, Drmed, MPH, MSc

Multimorbidity and the risk of restless legs syndrome in 2 prospective cohort studies

Neurology 82 June 3, 2014

The results support the hypothesis that cumulative disease burden is more important than the presence of a specific single disease in the pathophysiology of RLS

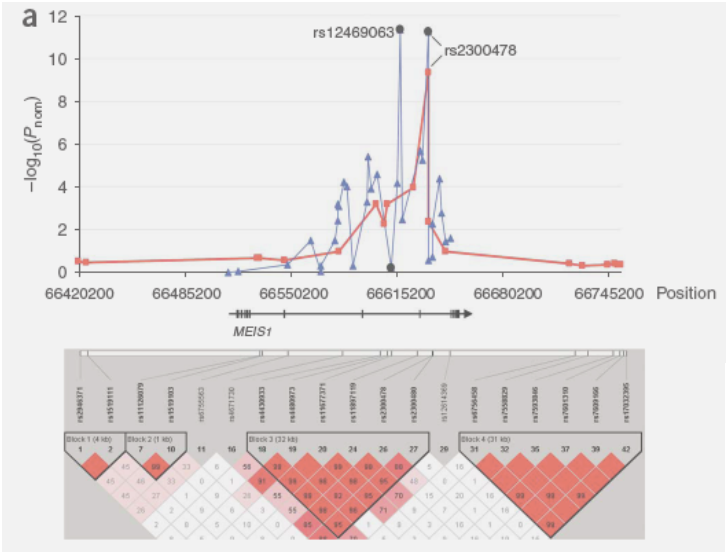
Figure 1 Odds ratios for incident restless legs syndrome associated with each comorbid category and single chronic diseases

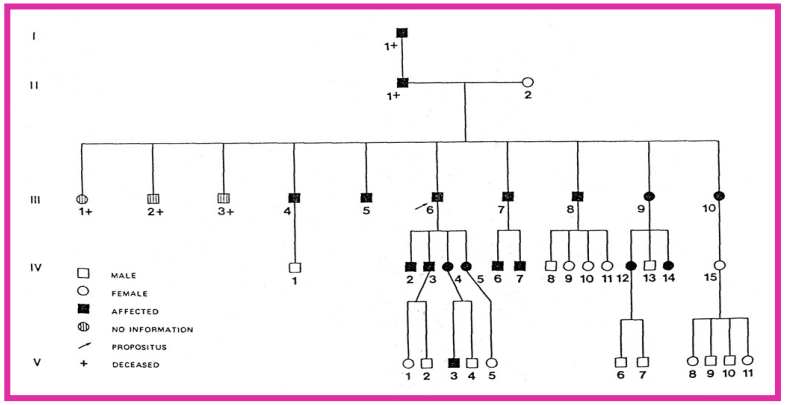


RLS Genetics

- First studies in RLS families: autosomal dominant pattern, segregation analysis shows earlier onset of familial RLS: <30 years, linkage studies identified only RLS associated loci, but no genes

- Only GWAS identified first genes: MEIS1, BTBD9





Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions

Juliane Winkelmann[1–3], Barbara Schormair[1,3], Peter Lichtner[1,3], Stephan Ripke[2], Lan Xiong[4], Shapour Jalilzadeh[1,3], Stephany Fulda[2], Benno Pütz[2], Gertrud Eckstein[1,3], Stephanie Hauk[1,3], Claudia Trenkwalder[5], Alexander Zimprich[6], Karin Stiasny-Kolster[7], Wolfgang Oertel[7], Cornelius G Bachmann[8], Walter Paulus[8], Ines Peglau[9], Ilonka Eisensehr[10], Jacques Montplaisir[11,12], Gustavo Turecki[13], Guy Rouleau[4], Christian Gieger[14], Thomas Illig[14], H-Erich Wichmann[14,15], Florian Holsboer[2], Bertram Müller-Myhsok[2,16] & Thomas Meitinger[1,3,16]

Trenkwalder et al, Mov Disord 1996, Winkelmann et al, Ann Neurol 2002, Liebetanz K/Winkelmann J et al, Neurology 2006, Kemlink et al, Mov Disord 2007; Winkelmann et al Nat Genet 2007; Johannson/Rye et al New Engl J Med 2007;

Treatment of RLS

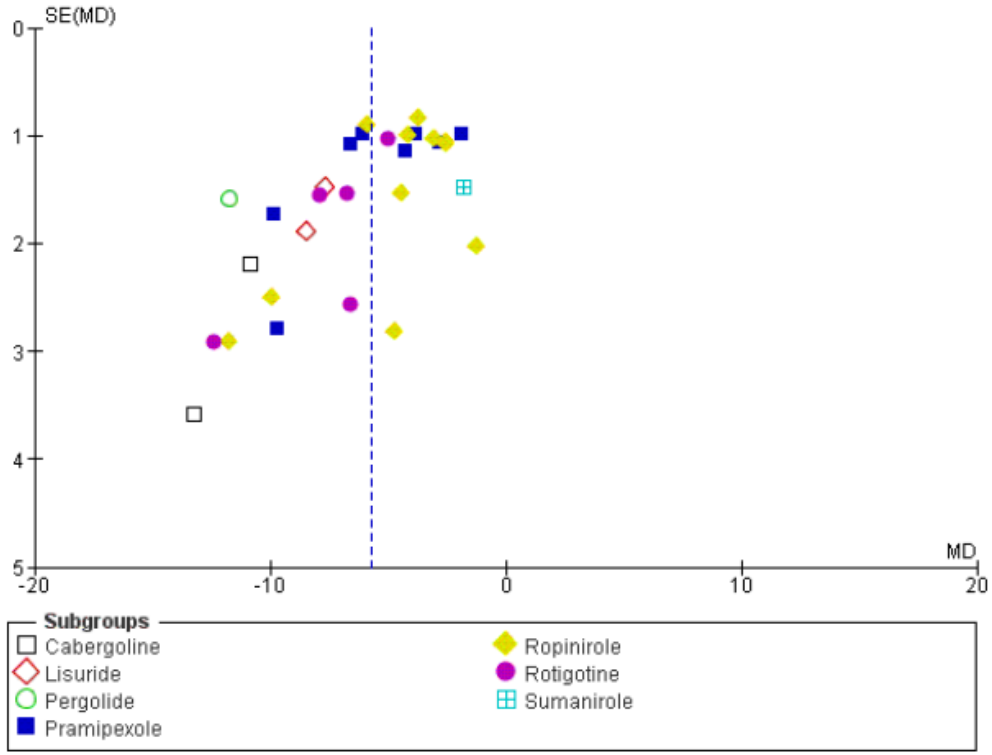
- Dopamine agonists: pramipexole, ropinirole, rotigotine transdermal patch (licensed in many countries)
- Alpha-2-delta ligands: gabapentin enacarbil (licensed in USA; Japan), gabapentine, pregabaline (off-label)
- Opioids: oxycodone/naloxone (licensed in Europe), other opioids: tramadol, methadon, tilidine, morphine (off-label)
- Iron preparations (currently all off-label): ferrocarboxymaltose (i.v.), iron succrose (i.v.)

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.



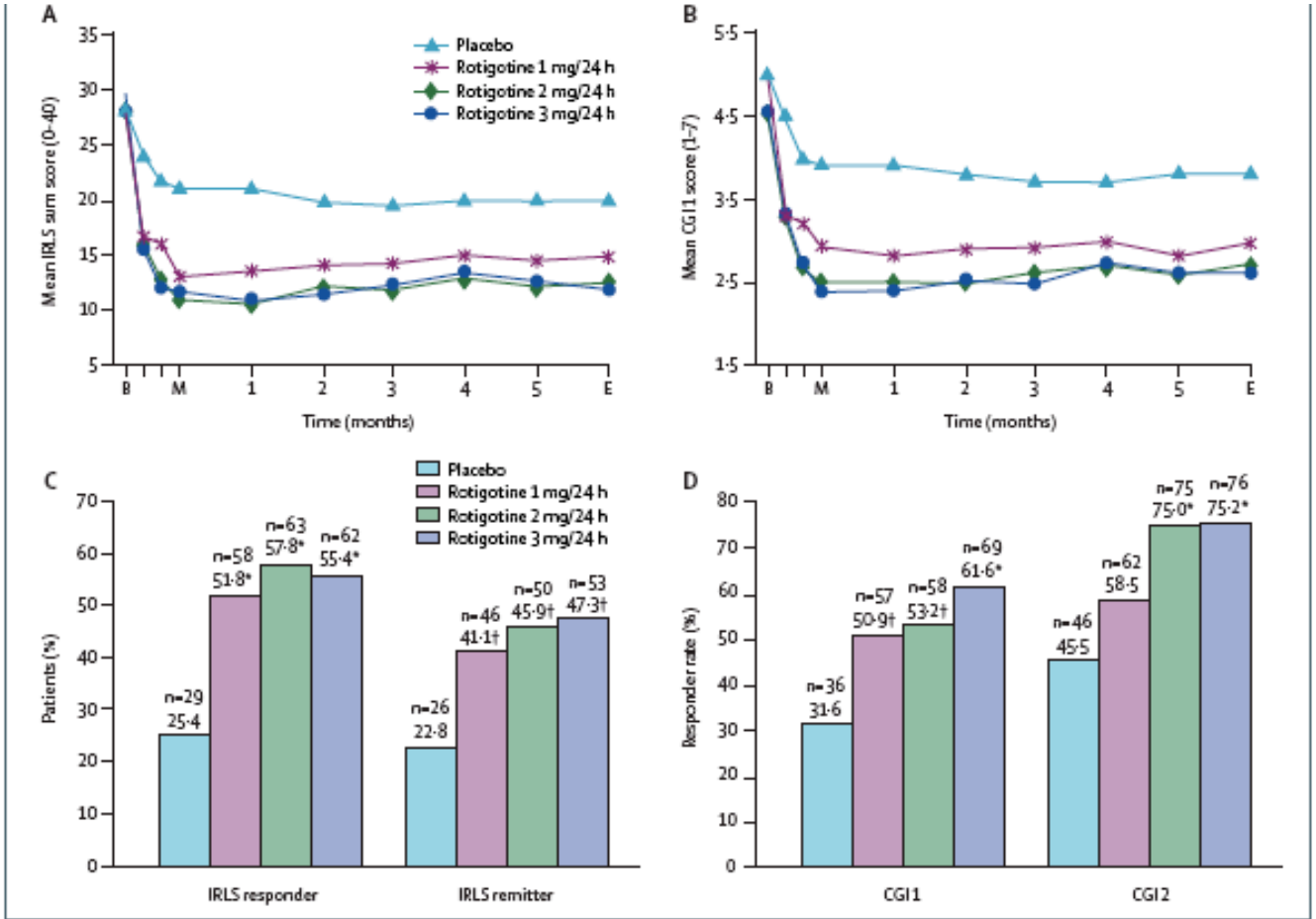
- Conclusion:
- The meta-analyses show the superiority of dopamine agonists over placebo in RCTs up to seven months. Cabergoline and pramipexole showed larger efficacy compared to levodopa in some but not all outcomes.

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

*Claudia Trenkwalder, Heike Beneš, 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**

Rotigotine
Transdermal
patch
458 patients
6-month
duration
IRLS and CGI
significant
for 1,2,3 mg
dosage
compared
to placebo

Lancet Neurol
May 2008



ORIGINAL ARTICLE

Comparison of Pregabalin with Pramipexole for Restless Legs Syndrome

Richard P. Allen, Ph.D., Crystal Chen, M.D., Diego Garcia-Borreguero, M.D., Ph.D., Olli Polo, M.D., Sarah DuBrava, M.S., Jeffrey Miceli, Ph.D., Lloyd Knapp, Pharm.D., and John W. Winkelman, M.D., Ph.D.

Table 1. Baseline Characteristics of the Patients.*

	Pregabalin, 300 mg Daily (N=182)	Pramipexole, 0.25 mg Daily (N=178)	Pramipexole, 0.5 mg Daily (N=180)	Placebo (N=179)†
Sex — no. (%)				
Female	123 (67.6)	108 (60.7)	99 (55.0)	111 (62.0)
Male	59 (32.4)	70 (39.3)	81 (45.0)	68 (38.0)
Age — yr				
Mean	54.3±13.0	56.5±12.8	54.2±13.5	53.5±13.3
Range	20–79	25–82	24–80	19–79
BMI				
Mean	28.0±5.0	28.6±5.2	28.2±5.2	28.4±5.3
Range	18.8–49.5	19.5–43.5	18.8–49.6	18.5–49.2
Interval since RLS onset — yr				
Mean	5.0	4.0	4.9	5.9
Range	0.0–52.5	0.0–35.1	0.0–47.9	0.0–35.1

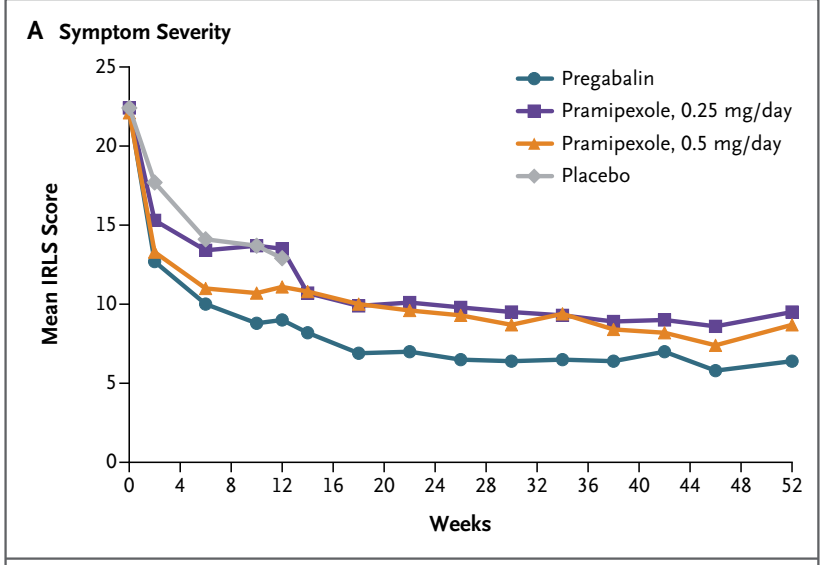


Figure 1. Mean Changes in Symptom Severity and Observed Proportion of Patients with Symptom Improvement, According to Study Group and Number of Weeks in the Study.

Adverse events:

Dizziness, Somnolence: Fatigue:

Discontinuation due to adverse events:
27.5% in pregabaline
28.8% switched from placebo to pregabalin

18.5% in pramipexole
15.3% switched from placebo to ppx

CONCLUSIONS

Pregabalin provided significantly improved treatment outcomes as compared with placebo, and augmentation rates were significantly lower with pregabalin than with 0.5 mg of pramipexole. (Funded by Pfizer; ClinicalTrials.gov number, NCT00806026.)

What do we know about the dosage of dopaminergic drugs 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?

Treatment of severe RLS with Opioids

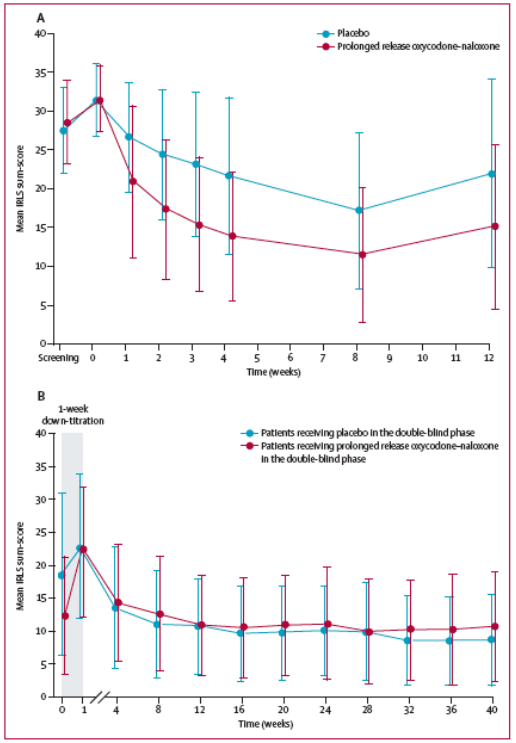
Previous studies with opioids in RLS

- Significant improvement of RLS and PLMS with oxycodon in 11 RLS patients (Walters et al 1993)
- Long-term observation: 36 patients with various opiods up to 23 years (Walters et al 2001)
- 76 RLS patients with methadon therapy, observation of 10 years (Silver et al 20011)

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**

	Double-blind phase			Extension phase (n=197)
	Prolonged release oxycodone–naloxone group (n=132)	Placebo group (n=144)	p value	
CGI-1 score (severity of disease)*				
Baseline	5·24 (0·88)	5·29 (0·85)	..	3·15 (1·62)
End of study phase	2·99 (1·48)	4·10 (1·71)	<0·0001	2·45 (1·23)
CGI-3 score (therapeutic effect)†				
Baseline	..	..	..	1·87 (1·17)
End of study phase	1·73 (1·04)	2·75 (1·29)	<0·0001	1·36 (0·71)
RLS-6 daytime at rest (severity)‡				
Baseline	6·70 (2·19)	6·69 (2·51)	..	2·77 (2·88)
End of study phase	2·50 (2·69)	4·44 (3·30)	<0·0001	1·36 (1·69)



Walters et al Ann Neurol 1993; Walters et al Mov Disord 2001; Silver N et al, Sleep Med 2011; Trenkwalder et al, Lancet Neurol 2013;

Augmentation: Clinical 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

Augmentation is the most important clinical long-term side effect of dopaminergic therapy in RLS patients

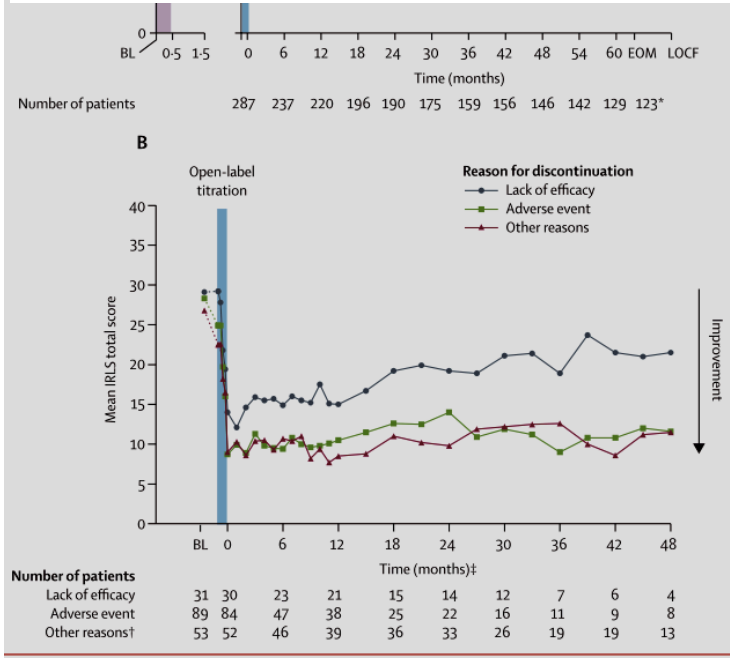
Allen et al 2003, Garcia-Borreguero 2007

Augmentation in long-term therapy of RLS

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

First Long-term study for 5-year duration

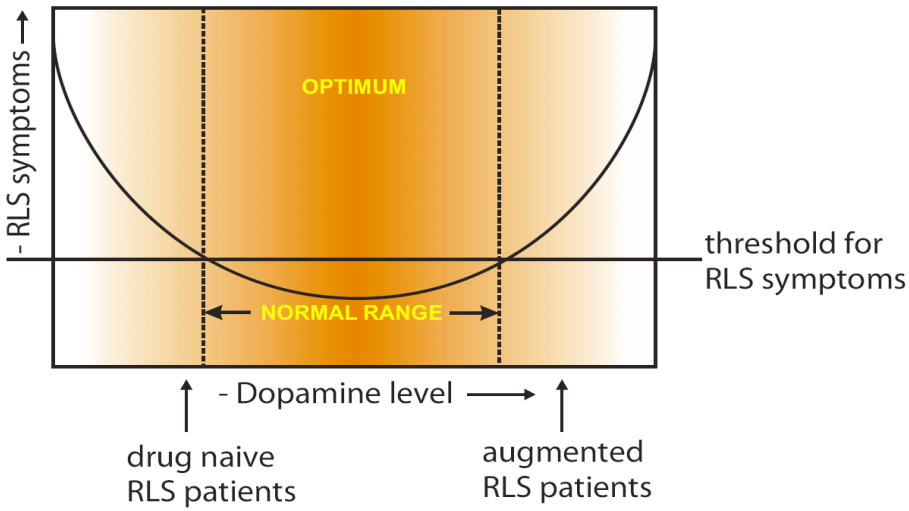
Augmentation rate for rotigotine 3mg: 5%, 4mg: 8%



Less is more: pathophysiology of dopaminergic-therapy-related augmentation in restless legs syndrome

Walter Paulus, Claudia Trenkwalder

Lancet Neurol 2006; 5: 878–86



Augmentation is a dopaminergic overstimulation

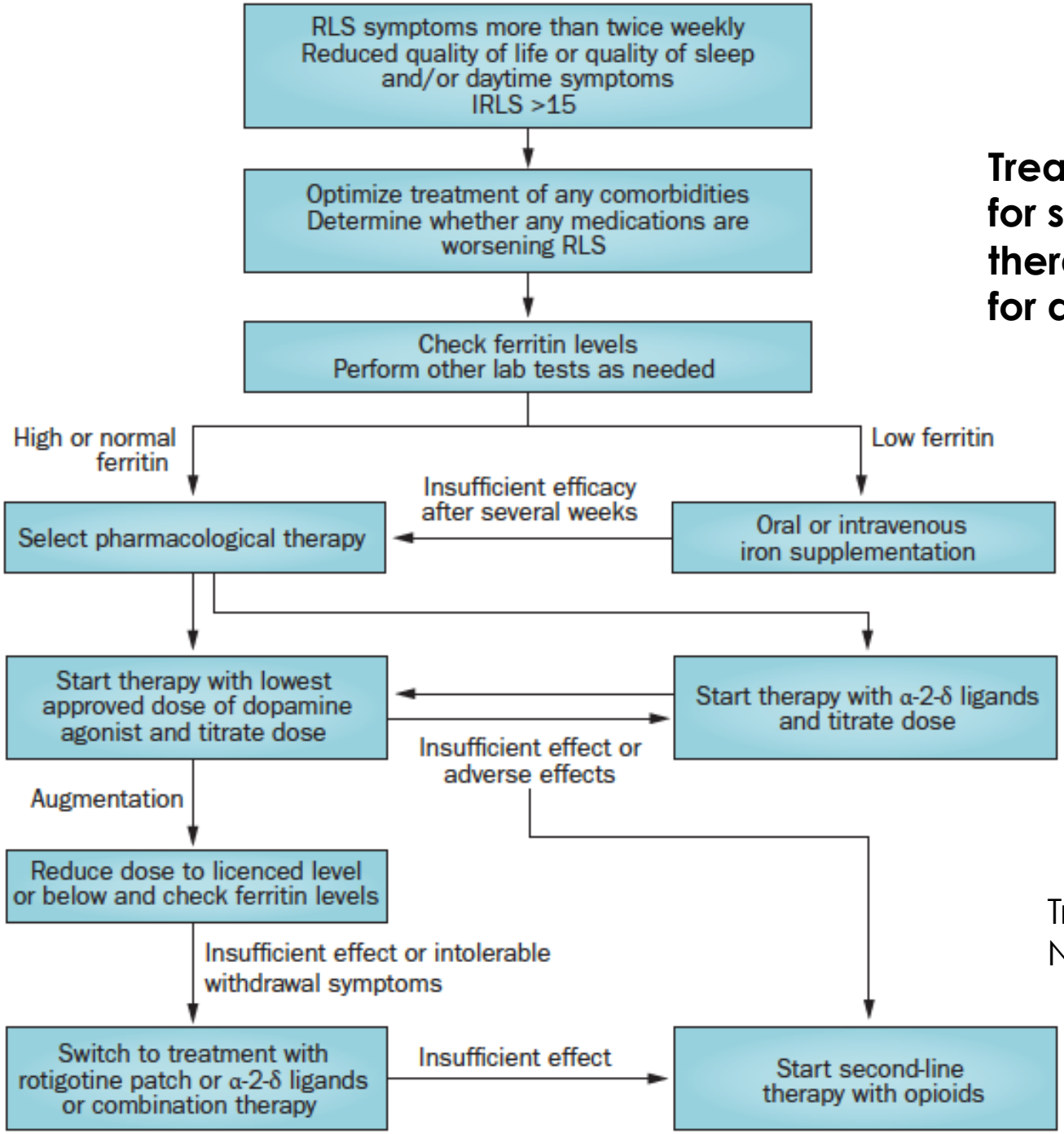
Oertel , Trenkwalder et al, Lancet Neurol 2010, Paulus and Trenkwalder, Lancet Neurol 2006; Earley et al, Sleep 2013

General Management of Augmentation

- **Risk Factor for developing augmentation:**
  - High dosages of dopaminergic therapy
  - Pulsatile dopaminergic therapy
  - Possibly: low ferritin
- **If a dopamine agonist leads to augmentation:**
  - Reduce the dopamine agonist to the lowest level possible (only licensed dosages)
  - Switch to a long-acting dopamine agonist (i.e. rotigotine patch)
  - Give iron i.v. if ferritin is below 50
  - If augmentation is severe: Switch to an opioid for long-term treatment

Trenkwalder et al 2015

Treatment Algorithm for starting RLS therapy and for augmentation



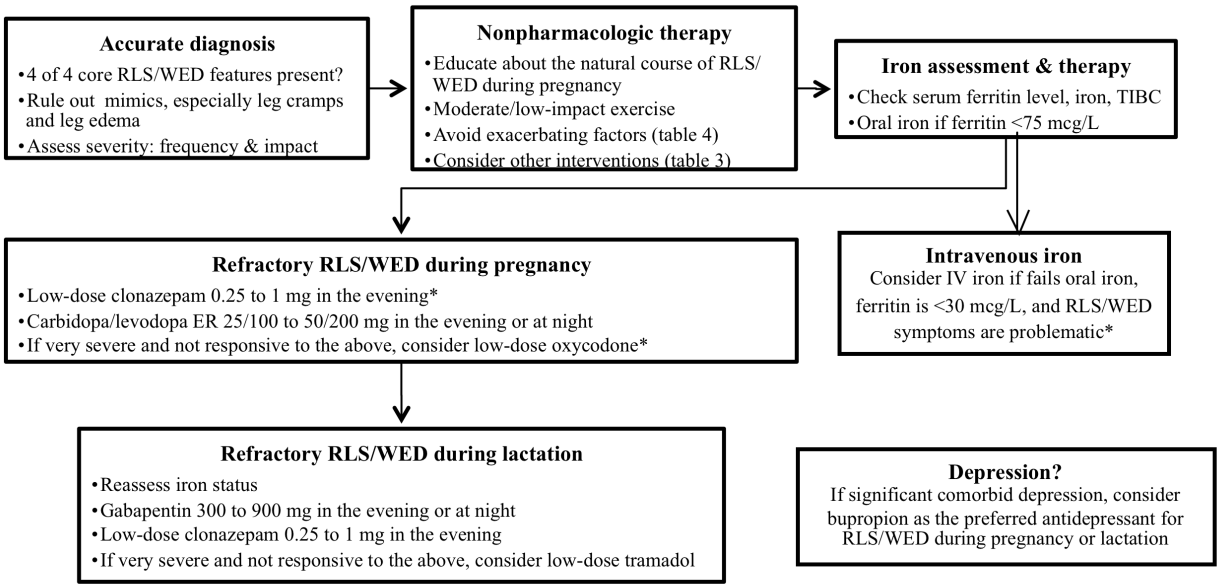
Trenkwalder et al,
Nat Rev Neurol 2015

Clinical Practice Guidelines for the Diagnosis and Treatment of Restless Legs Syndrome/Willis-Ekbom Disease During Pregnancy and Lactation

Daniel L. Picchietti[a,], Jennifer G. Hensley[b], Jacquelyn L. Bainbridge[c], Kathryn A. Lee[d], Mauro Manconi[e], James A. McGregor[f], Robert M. Silver[g], Claudia Trenkwalder[h], and Arthur S. Walters[i]*
On behalf of the International Restless Legs Syndrome Study Group (IRLSSG)

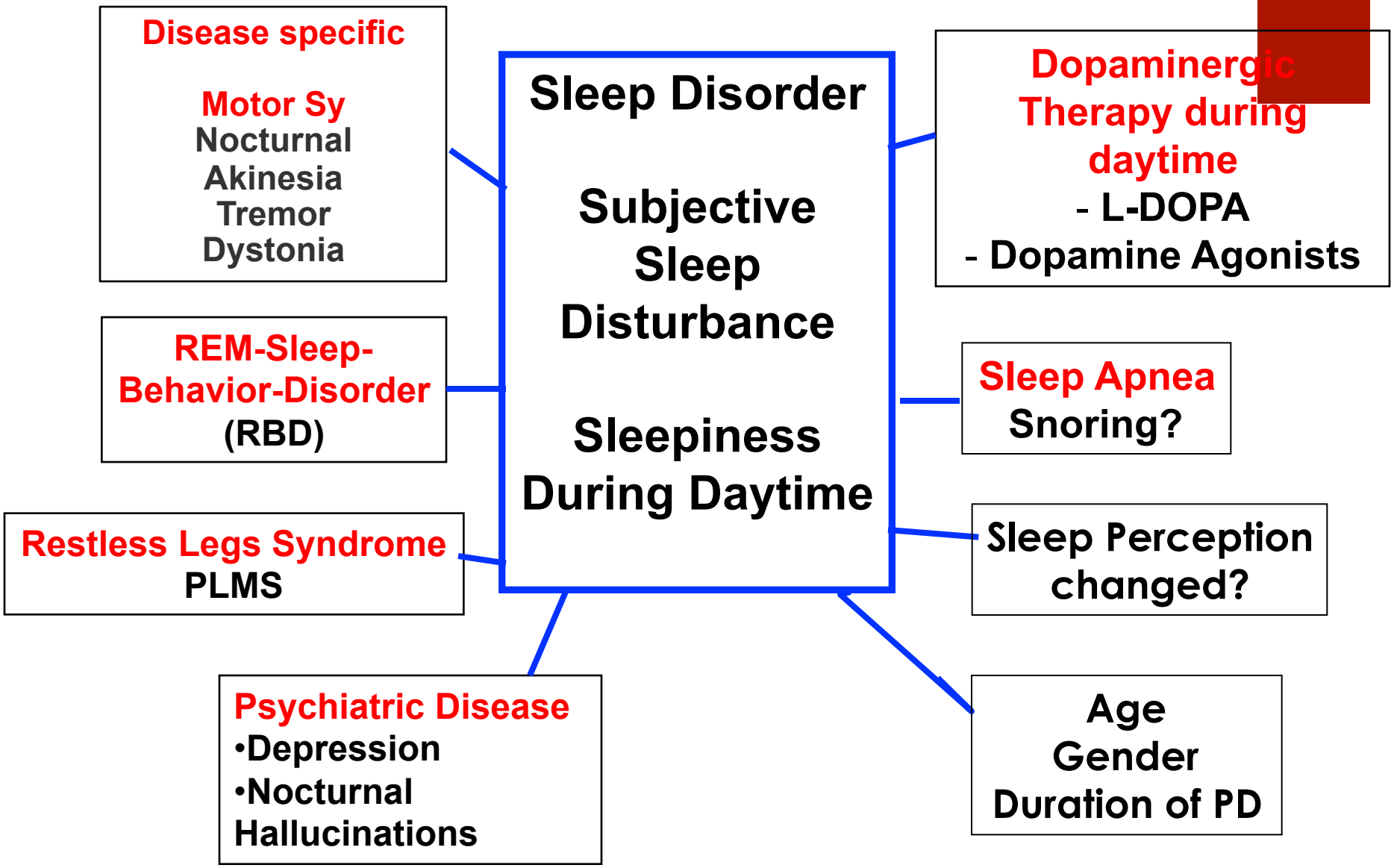
Sleep Med Reviews (2014)

Figure 1. Algorithm for the diagnosis and management of RLS/WED during pregnancy and lactation.



*After 1st trimester
Abbreviations: RLS, restless legs syndrome; WED, Willis-Ekbom disease; TIBC, total iron binding capacity; ER, extended release.
Refractory: an inadequate response to at least one non-pharmacologic intervention tried over an adequate period of time.
Very severe, refractory: a score of >30 on the IRLS rating scale and failure to respond to iron, at least one other non-pharmacologic treatment, and one non-opioid pharmacologic treatment.

Sleep Disturbance in Parkinson Disease - contributing factors



Developing Sleep Measures in PD: PDSS-2

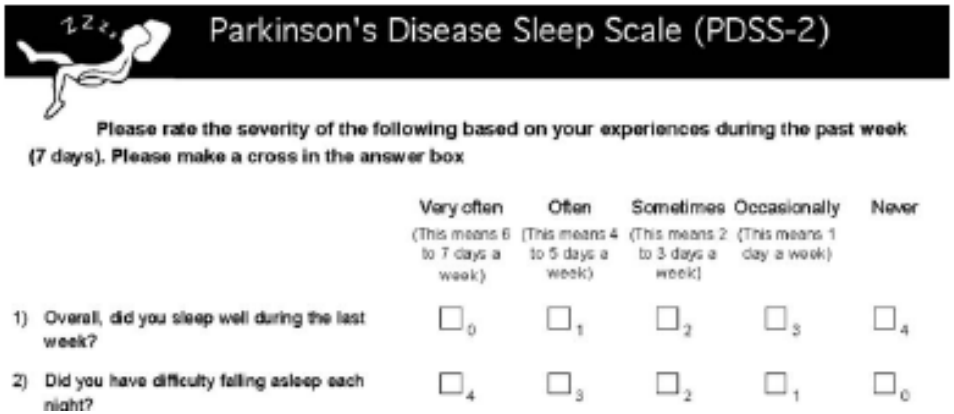
The Parkinson's Disease Sleep Scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease: 15 questions, specific for nocturnal disturbances in PD patients (2011)

RESEARCH ARTICLE

Rotigotine Effects on Early Morning Motor Function and Sleep in Parkinson's Disease: A Double-Blind, Randomized, Placebo-Controlled Study (RECOVER)

Claudia Trenkwalder, MD,[1]* Bryan Kies, FCNeurol (SA),[2] Monika Rudzinska, MD,[3] Jennifer Fine, FCP (SA) Neurology,[4] Janos Nikl, MD,[5] Krystyna Honczarenko, MD,[6] Peter Dioszeghy, MD,[7] Dennis Hill, MD,[8] Tim Anderson, FRACP,[9] Vilho Myllyla, MD,[10] Jan Kassubek, MD,[11] Malcolm Steiger, FRCP,[12] Marco Zucconi, MD,[13] Eduardo Tolosa, MD,[14] Werner Poewe, MD,[15] Erwin Surmann, MSc,[16] John Whitesides, PhD,[17] Babak Boroojerdi, MD,[16] Kallol Ray Chaudhuri, DSc[18] and the RECOVER Study Group

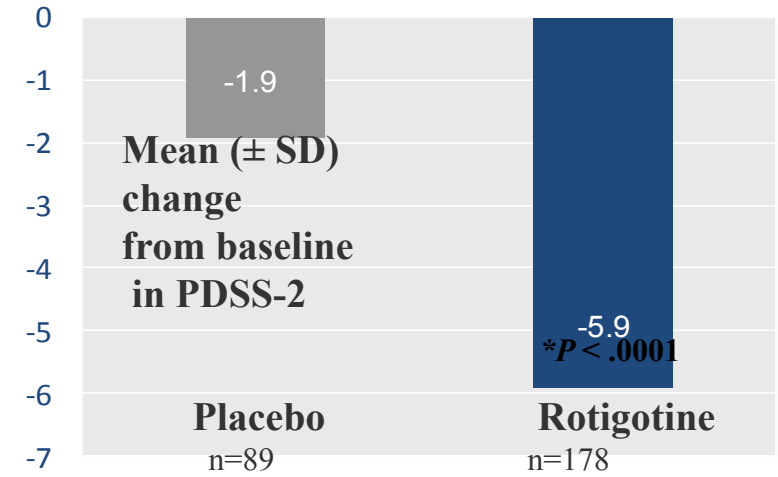
PARKINSON'S DISEASE SLEEP SCALE



Parkinson's Disease Sleep Scale (PDSS-2)

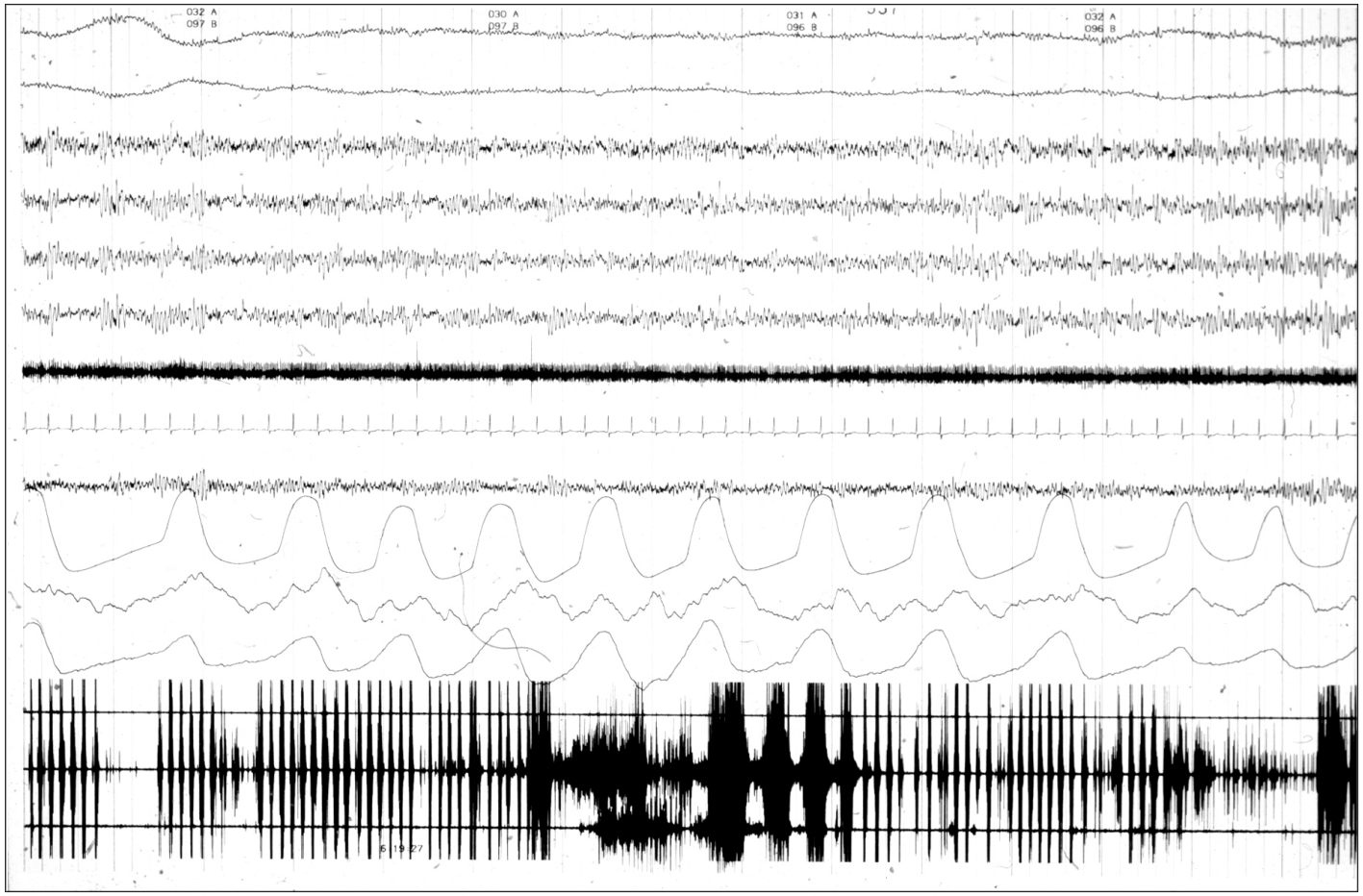
Please rate the severity of the following based on your experiences during the past week (7 days). Please make a cross in the answer box

	Very often (This means 6 to 7 days a week)	Often (This means 4 to 5 days a week)	Sometimes (This means 2 to 3 days a week)	Occasionally (This means 1 day a week)	Never
1) Overall, did you sleep well during the last week?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2) Did you have difficulty falling asleep each night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0



Chaudhuri et al, JNNP 2002; Trenkwalder et al, MovDisord 2011 (PDSS-2); Trenkwalder et al Mov Disord 2011 (RECOVER)

Parkinson tremor in sleep: tremor of left leg



EMG
M.tib.ant li

Therapy of nocturnal /sleep problems in PD patients

- Nocturnal akinesia, tremor, RLS and pain:
  - Increase dopaminergic therapy at night
  - Add long-acting dopamine agonist or patch
  - Add sustained release levodopa (not evidence based)
- RLS at sleep onset or during the night, nocturnal pain:
  - Add either dopaminergic therapy or opioids (oxycodon/naloxone)
- REM sleep behavior disorder:
  - Add low dose clonazepam (or melatonine
- Sleep-onset Insomnia
  - Reduce high dosages of doapmine agonists
  - Add mirtazapine, quetiapine (not evidenced based)