



International Parkinson and  
Movement Disorder Society  
European Section



**5<sup>th</sup> Congress of the European Academy of Neurology**

**Oslo, Norway, June 29 - July 2, 2019**

---

**Teaching Course 6**

**EAN/MDS-ES: Movement disorders for general  
neurologists (Level 2)**

**Diagnosis and therapy of restless legs  
syndrome**

**Claudio Bassetti**  
Bern, Switzerland

**Email:** [claudio.bassetti@gmx.net](mailto:claudio.bassetti@gmx.net)

## Restless Legs Syndrome

EAN/MDS-EN

Oslo, June 30, 2019

**Prof. Claudio L. Bassetti**  
Neurology Department  
University Hospital, Bern  
Switzerland



### Conflict of Interest

**In relation to this presentation and manuscript:**

the Author has no conflict of interest in relation to this manuscript.

*“Wherefore to some, when being a Bed they betake themselves to sleep, presently in the Arms and Leggs, Leapings and Contractions of the Tendons, and so great a Restlessness and Tossings of their Members ensue, that the diseased are no more able to sleep, than if they were in a Place of the greatest Torture.”*

De Anima Brutorum, 1672



Thomas Willis, 1621-1675



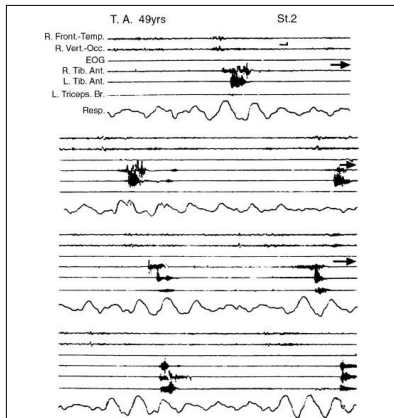
Karl Ekbom, 1907-1977

asthenia crurorum paraesthetica  
asthenia crurorum dolorosa

Acta Med Scand 1944  
Acta Med Scand 1945

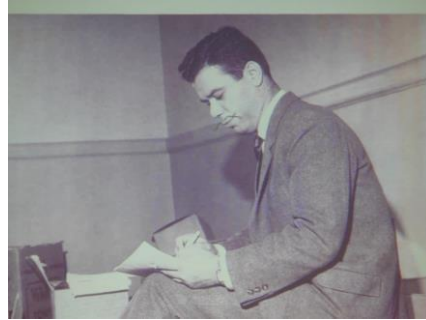
## Myoclonus/PLMS

Symonds, 1953  
Lugaresi, Coccagna 1962



## Levodopa

Arch Neurol 1982



S. Akpınar

Clinical Diagnosis  
Differential diagnosis  
Therapy

## Clinical Diagnosis

Differential diagnosis  
Therapy

## RLS: Epidemiology

- 2-5% (-15%) of the general population  
Europe, North America > Asia
- 10-30% when iron deficiency, pregnancy, renal failure
- F:M = 2:1
- increases with age (onset before age 20 in 20-40%)
- positive family history in ≈50%

Montplaisir, Mov Dis 1997; Bassetti, Eur Neurol 2000, Manconi, Neurology 2004;  
Gamaldo, Chest 2006; Winkelmann, Mov Dis 2007; Ohayon, Sleep Med Rev 2012; Koo, Sleep Med 2015

## RLS: Clinical features I

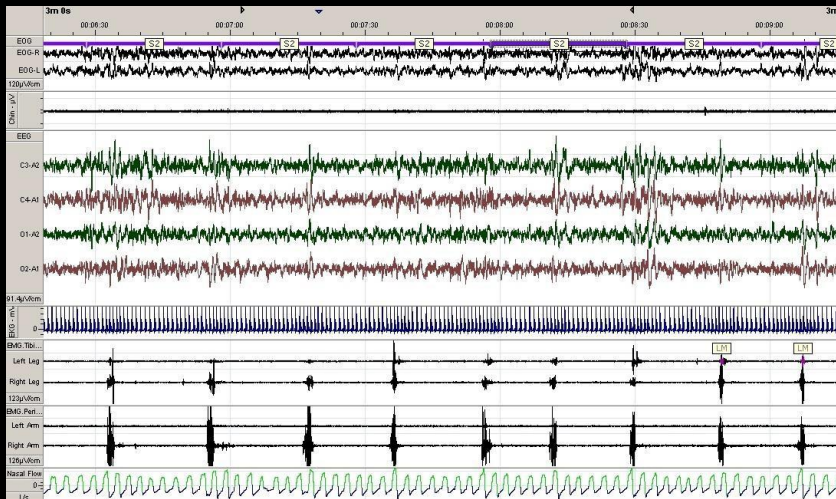
- Unpleasant sensations in the legs/limbs
- Urge to move
- Relieved by movement
- Onset worsening at rest/night
  
- Daytime „myoclonus“ (dyskinesias while awake“)
- Periodic limb movements in sleep (90%)

S.T., 34y



RLS-Score >30, severe insomnia, PLMS > 80/h  
good response to pramipexol + oxycodon

R.S., 60y



## RLS: Clinical features II

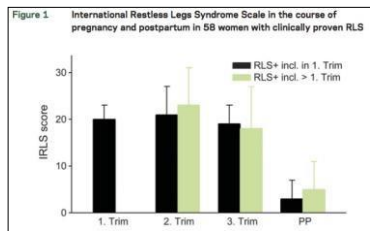
- acute forms (blood loss, myelopathy,...)
- remittent forms (pregnancy, anesthesia, anemia,...)
- chronic forms
  
- unilateral RLS
- focal (pelvic/genital) RLS

## RLS in pregnancy

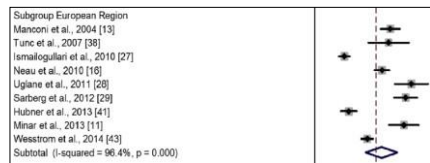
prospective study  
12% of 501 women

meta-analysis, 28 studies  
21% pooled prevalence

40% severe, 37% familial



Hübner, Neurology 2014



Chen, Sleep Med Rev 2018

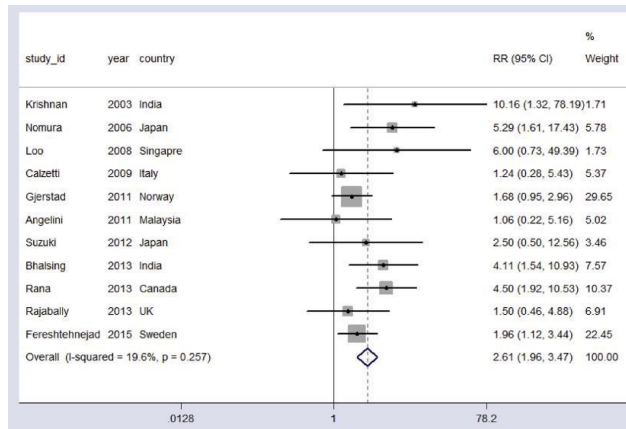
## RLS: Clinical associations/comorbidities

- **insomnia**
- excessive daytime sleepiness
- **neurologic comorbidity**
  - migraine, Parkinson
  - stroke, tic disorder, multiple sclerosis,...
- **psychiatric comorbidity**
- **cardiovascular comorbidity (?)**
- others



## RLS and M. Parkinson

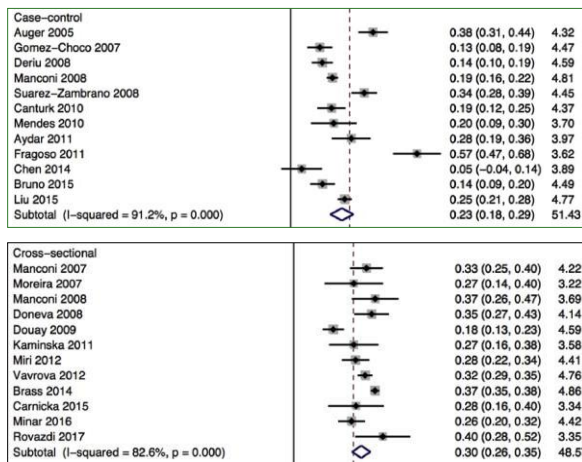
11 publications, odds ratio 2.9



Yang, Sleep Med 2018

## RLS and multiple sclerosis

24 publications, pooled prevalence 26%, odds ratio 3.9



Ning, Sleep Med 2018

## RLS and cardiovascular diseases

### CV events in older men with RLS and PLMS

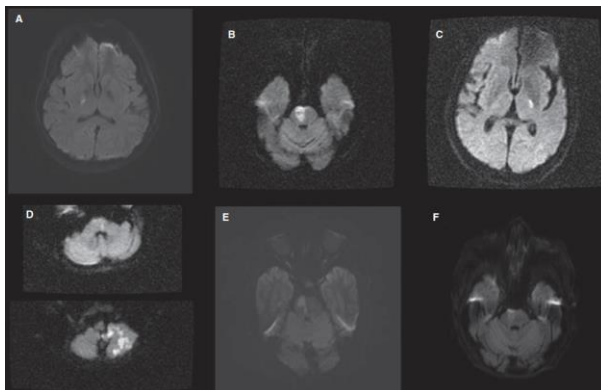
Incident event	N (%) of Events	Hazard ratio (95% Confidence interval)			
		Model 1	Model 2	Model 3	Model 3 + PLMI
Cardiovascular disease	826 (29.26)	1.31 (0.87, 1.97)	1.15 (0.76, 1.74)	1.15 (0.76, 1.74)	1.14 (0.75, 1.73)
Fatal cardiovascular disease	140 (5.02)	1.21 (0.45, 3.31)	1.29 (0.46, 3.59)	1.25 (0.45, 3.48)	1.22 (0.44, 3.40)
Coronary heart disease	560 (19.89)	1.44 (0.90, 2.30)	1.21 (0.75, 1.97)	1.21 (0.74, 1.96)	1.19 (0.73, 1.93)
Stroke or transient ischemic attack	261 (9.30)	1.42 (0.70, 2.89)	1.41 (0.69, 2.90)	1.41 (0.69, 2.90)	1.44 (0.70, 2.95)
Stroke	181 (6.46)	1.75 (0.82, 3.75)	1.80 (0.83, 3.91)	1.81 (0.83, 3.94)	1.83 (0.84, 3.97)
Myocardial infarction	199 (7.10)	2.32 (1.22, 4.40)	2.05 (1.06, 3.97)	2.02 (1.04, 3.91)	1.93 (0.99, 3.75)

Characteristic	No RLS diagnosis (N = 2761)	RLS diagnosis (N = 62)	p
Polysomnography data:			
Apnea-hypopnea index	11.49 ± 12.77	16.76 ± 16.35	.005
Periodic leg movements/hour of sleep (PLMI)	35.37 ± 37.21	46.21 ± 42.95	.04
PLMI ≥ 15	1641 (59.43)	42 (67.74)	.19

Winkelmann, Sleep 2017

## RLS and PLMS post-stroke

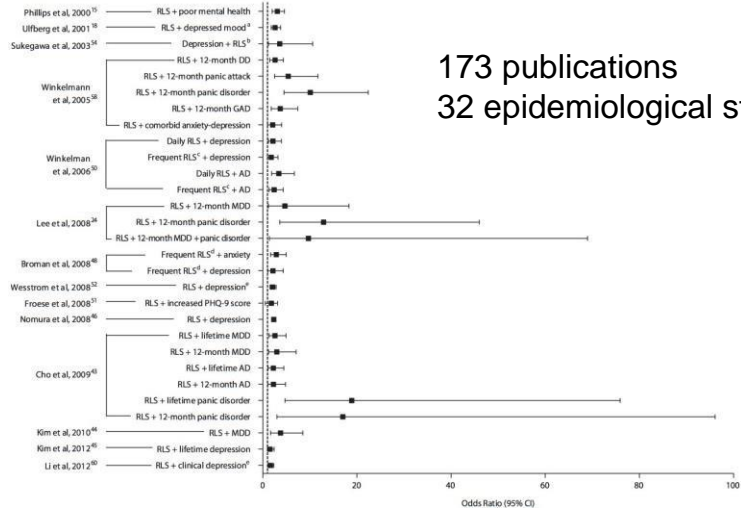
6 own cases, 30 cases from literature



unilateral/transient phenotypes possible

Woo, Acta Neurol Scand 2017

## RLS and psychiatric comorbidities

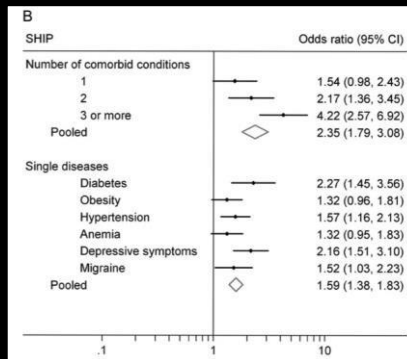
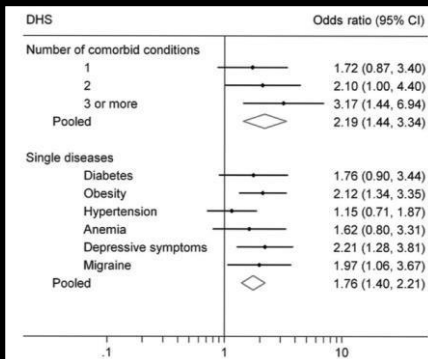


Becker, J Clin Psychiat 2014

## RLS risk increases with multimorbidity

Dortmund Health Study  
n=1312, follow-up 2 y

Study of Health in Pomerania  
n=4308, follow-up 5 y



Stentikaralyi, Neurology 2014

# RLS: Diagnosis I

## Essential criteria

1. urge to move accompanied by uncomfortable sensations
2. onset/exacerbation at rest
3. partial/total relief with movement
4. onset/worsening in the evening/at night
  
5. exclude mimics (myalgia, venous stasis, leg edema/cramps,...)

Allen, Sleep Med 2003  
Walters, J Clin Sleep Med 2014

Original Article

The four diagnostic criteria for Restless Legs Syndrome are unable to exclude confounding conditions ("mimics")

Wayne A. Hening<sup>a</sup>, Richard P. Allen<sup>b,c</sup>, Mysterina Washburn<sup>b</sup>, Suzanne R. Lesage<sup>c</sup>, Christopher J. Earley<sup>b</sup>

## RLS severity score

**Table 2** The international restless legs syndrome severity scale

1. Overall, how would you rate the RLS discomfort in your legs or arms?	6. Overall, how severe is your RLS as a whole?
4. Very severe	4. Very severe
3. Severe	3. Severe
2. Moderate	2. Moderate
1. Mild	1. Mild
0. None	0. None
2. Overall, how would you rate the need to move around because of your RLS symptoms?	7. How often do you get RLS symptoms?
4. Very severe	4. Very often (6-7 days a week)
3. Severe	3. Often (4-5 days a week)
2. Moderate	2. Sometimes (2-3 days a week)
1. Mild	1. Occasionally (1 day a week or less)
0. None	0. Never
3. Overall, how much relief of your RLS arm or leg discomfort do you get from moving around?	8. When you have RLS symptoms how severe are they on an average day?
4. No relief	4. Very severe (8 h per 24 h or more)
3. Slight relief	3. Severe (3-6 h per 24 h)
2. Moderate relief	2. Moderate (1-3 h per 24 h)
1. Either complete or almost complete relief	1. Mild (less than 1 h per 24 h)
0. No RLS symptoms to be relieved	0. None
4. Overall, how severe is your sleep disturbance due to your RLS symptoms?	9. Overall, how severe is the impact of your RLS symptoms on your ability to carry out your daily affairs, e.g. carrying out a satisfactory family, home, social, school or work life?
4. Very severe	4. Very severe
3. Severe	3. Severe
2. Moderate	2. Moderate
1. Mild	1. Mild
0. None	0. None
5. How severe is your tiredness or sleepiness during the day from your RLS symptoms?	10. How severe is your mood disturbance from your RLS symptoms - e.g. angry, depressed, sad, anxious or irritable?
4. Very severe	4. Very severe
3. Severe	3. Severe
2. Moderate	2. Moderate
1. Mild	1. Mild
0. None	0. None

Scoring criteria are: mild (sum of score 1-10); moderate (score 11-20); severe (score 21-30); very severe (score 31-40)

Rate your symptoms for the following 10 questions. Unless otherwise instructed, you should rate the average symptoms that you have experienced for the most recent 2-week period.

RLS, restless legs syndrome.

## RLS: **Diagnosis II**

### Supportive criteria

positive family history  
periodic limb movements in sleep (PLMS)  
improvement with dopaminergic agents

### Laboratory tests

iron, ferritin  
renal/liver tests, vitamin B12, TSH

Clinical Diagnosis  
**Differential diagnosis**  
Therapy

## „RLS mimics“

### limb paresthesias/pain

polyneuropathies/-radiculopathies  
myelopathies  
burning feet syndrome  
venous/arterial insufficiency  
muscle cramps  
„growing pains“

### restlessness/urge to move

akathisia  
hypotensive akathisia  
wearing off (Parkinson)  
tic disorder  
anxiety/psychiatric disorders

### involuntary movements

painful legs/moving toes  
hypnic jerks  
hypnagogic foot tremor  
pain-fasciculations syndrome

## Venous insufficiency



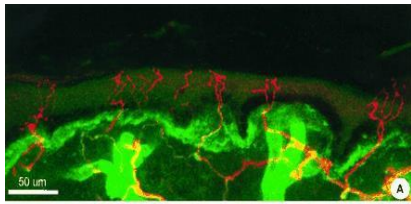
V.W., 59y

chronic venous insufficiency  
venous stripping 1993-4

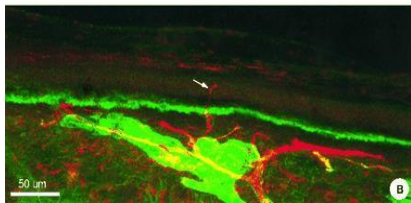
Sensory paresthesias since 1980's

- worse sitting
- worse in the evening
- worse when legs swollen
- better when recumbent (1h)

## Sensory polyneuropathy/Burning feet syndrome



skin biopsy:  
normal subject



skin biopsy:  
small fiber sensory neuropathy

*green= basal lamina*  
*red=nerve fibers (epidermis)*

Neurology 2000; 55: 1641-7



A.C., 51y

## Painful and moving toes

- constant, deep, burning pain
- toe movements  
    seated > standing  
    in sleep
- after peripheral tissue, nerve,  
    root, spinal injury
- improved by sympathetic blockade

Brain 1971; 94: 541-56; Mov Dis 1994; 9: 13-21



E.R., 73y



## Akathisia („not to sit“)

- continuous motor restlessness
- felt in the whole body
- not relieved by movement
- occasionally daytime dyskinesias/dystonia

Arch Gen Psychiatry 1985; 42: 874-8; Sleep 1991; 14: 339-45

Clinical Diagnosis  
Differential diagnosis  
Therapy

**EFNS/ENS/ESRS GUIDELINES**

European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society

Diego Garcia-Borreguero<sup>a</sup>, Luigi Ferini-Strambi<sup>b</sup>, Ralf Kohnen<sup>c</sup>, Shaun O'Keefe<sup>d</sup>, Claudia Trenkwalder<sup>e,f</sup>, Birgit Högl<sup>g</sup>, Heike Benes<sup>h</sup>, Poul Jennum<sup>i</sup>, Markku Partinen<sup>j</sup>, Danyal Fer<sup>a</sup>, Pasquale Montagna<sup>k,t</sup>, Claudio L. Bassetti<sup>l</sup>, Alex Iranzo<sup>m,n,o</sup>, Karel Sonka<sup>p</sup> and Anne-Marie Williams<sup>a</sup>

**TREATMENT OF RLS AND PLMS DISORDER IN ADULTS: PRACTICE PARAMETERS**

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

R. Nisha Aurora, MD<sup>1</sup>; David A. Kristo, MD<sup>2</sup>; Sabin R. Bista, MD<sup>3</sup>; James A. Rowley, MD<sup>4</sup>; Rochelle S. Zak, MD<sup>5</sup>; Kenneth R. Casey, MD, MPH<sup>6</sup>; Carin I. Lamm, MD<sup>7</sup>; Sharon L. Tracy, PhD<sup>8</sup>; Richard S. Rosenberg, PhD<sup>9</sup>

## RLS: Treatment I

**Triggers's removal** alcohol, caffeine, nicotine  
neuroleptics, antidepressants, -epileptics  
iron deficiency, sleep apnea/deprivation

**Pharmacology** placebo-effect  
dopaminergics („levodopa test“)  
pregabalin, gabapentin, enacarbil  
opioids (oxycodone-naloxone)

Akpinar, Arch Neurol 1982; Fulda, Brain 2008; Oertel, Lancet Neurol 2011;  
Garcia-B., Eur J Neurol 2012; Trenkwalder, Lancet Neurol 2013; Garcia-B., Sleep Med 2013;  
Allen, NEJM 2014; Hornyak, Sleep Med Rev 2014

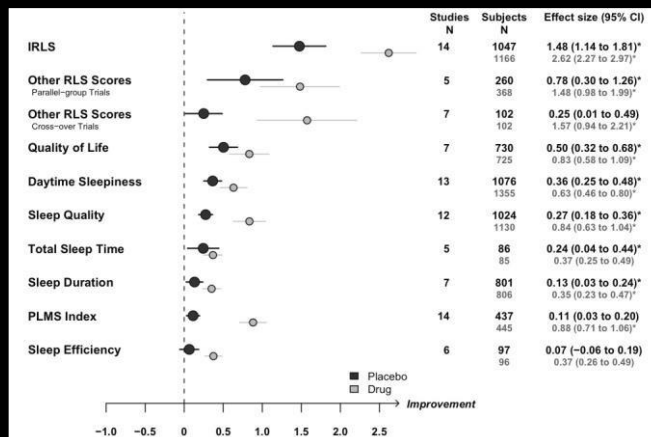
## Drug-induced RLS

Neuroleptics	Antidepressants	Antiepileptics
Aripiprazole (1)	Mirtazapine (11)	Zonisamide (2)
Olanzapine (14)	Fluoxetine (1)	Topiramate (4)
Clozapine (4)	Citalopram (1)	
Quetiapine (18)	Sertraline (1)	
Risperidone (1)	Paroxetine (2)	
Asenapine (1)	Escitalopram (1)	
Lurasidone (1)	Nefazodone (1)	
Aloperidole (1)	Duloxetine (1)	
	Lithium (2)	
	Venlafaxine (2)	

Patatanian, Neuropharmacology 2018

## Placebo effect in restless legs syndrome

### meta-analysis of 36 trials

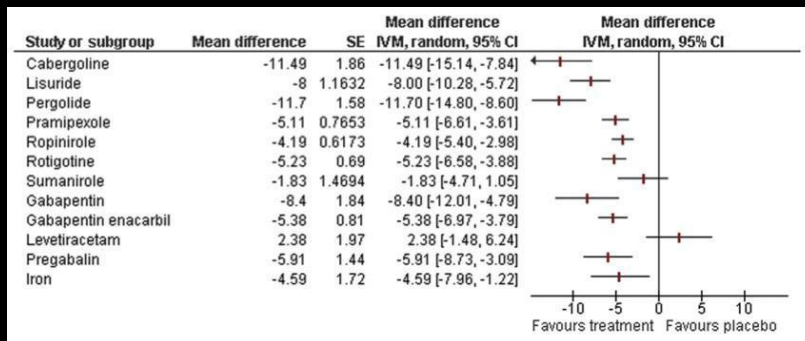


Fulda and Wetter, Brain 2008

## Meta-analysis of RLS-treatments

46 randomized control trials (RCT)  
 (DA=31, levodopa=2, anticonvulsants 11, iron 4, opioid 1)

### Improvement of RLS-Score



Hornyak, Sleep Med Rev 2014

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



2014

Claudia Trenkwalder, Heike Benet, Ludger Grote, Diego Garcia-Borreguero, Birgit Högl, Michael Hopp, Björn Besse, Alexander Olsche, Karen Reimer, Juliane Winkelmann, Richard P Allen, Rolf Kohnen, for the RELOXYN Study Group\*

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

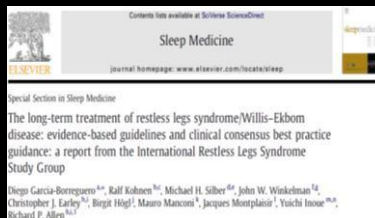
### Comparison of Pregabalin with Pramipexole for Restless Legs Syndrome

2014

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.

## RLS: Treatment II

Side effects of dopaminergics	augmentation dysregulation excessive daytime sleepiness
Special situations	psychiatric comorbidity pregnancy children
Special issues	rebound longterm control



**Table 4**

Evidence from clinical trials has shown the following commonly used drugs to be effective or probably effective for at least these durations.

Drug	Effective	Probably effective
Pramipexole	6 mo	1 y
Ropinirole	6 mo	1 y
Rotigotine	6 mo	5 y
Levodopa	- <sup>a</sup>	2 y
Gabapentin enacarbil	-	1 y
Pregabalin	1 y	-
Gabapentin	-	-

2013

Clinical Diagnosis  
Differential diagnosis  
Therapy