



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

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

---

**Teaching Course 2**

**Treatment of adult and pediatric primary sleep disorders (Level 2)**

**Treatment of sleep-related movement and breathing disorders**

**Ulf Kallweit**  
Hagen, Germany

**Email:** [ulf.kallweit@uni-wh.de](mailto:ulf.kallweit@uni-wh.de)



5th EAN congress  
Oslo, 29 June 2019  
Teaching Course- Level 2

## **Treatment of sleep-related movement and breathing disorders**

Ulf Kallweit  
Center for Narcolepsy & Hypersomnias  
University Witten/Herdecke

- No conflicts of interest



**Sleep-related movement disorders**

Restless legs syndrome

**Sleep-breathing disorders**

Obstructive sleep apnea



**Sleep-related movement disorders**

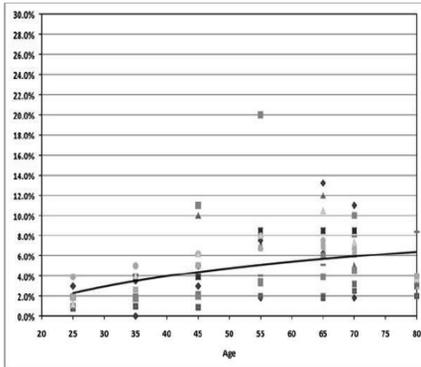
Restless legs syndrome

**Sleep-breathing disorders**

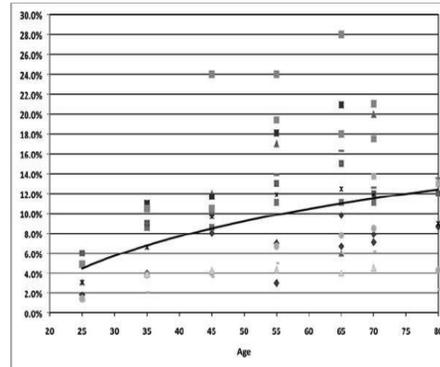
Obstructive sleep apnea

# Epidemiology

- General population: 1-15%
- 1-3% need pharmacotherapy



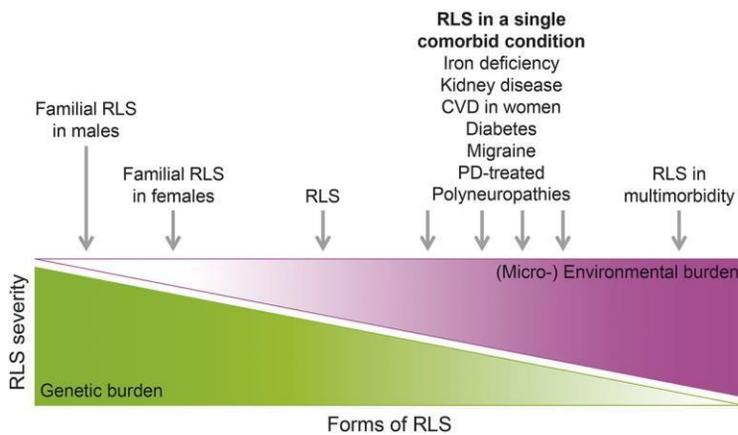
male (n=23,282)



female (n=26,150)

Ohayon, 2012

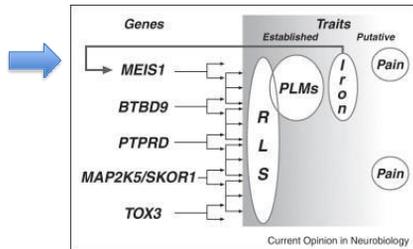
# Etiology/ Pathogenesis



Trenkwalder et al., 2016

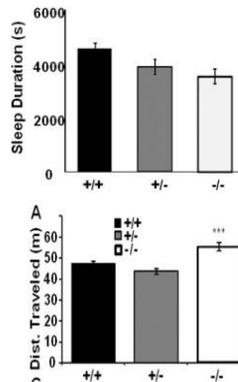
## Genetic predisposition

### Risk genes



MEIS 1 and -2 involved in development of basal ganglia in the human brain

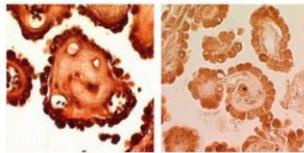
### Altered PTPRD in RLS



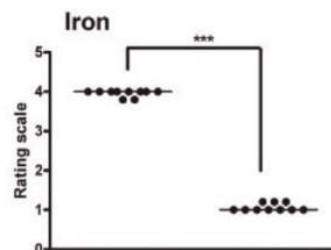
Freemann and Rye, 2013; Drgonova, 2015; Ferré, 2018

## Pathogenesis- dopamine/iron

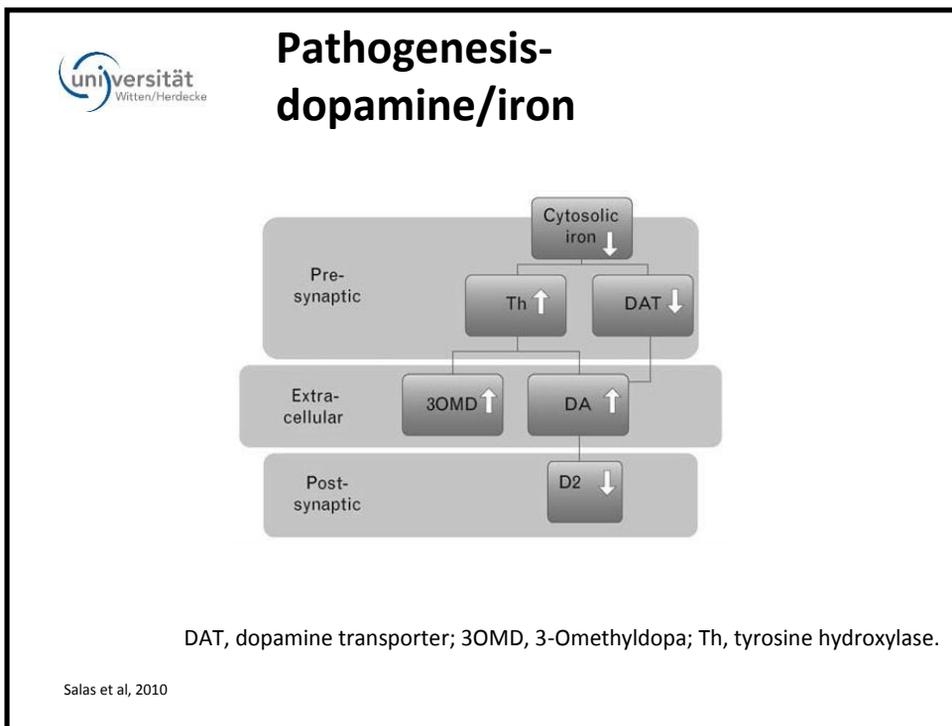
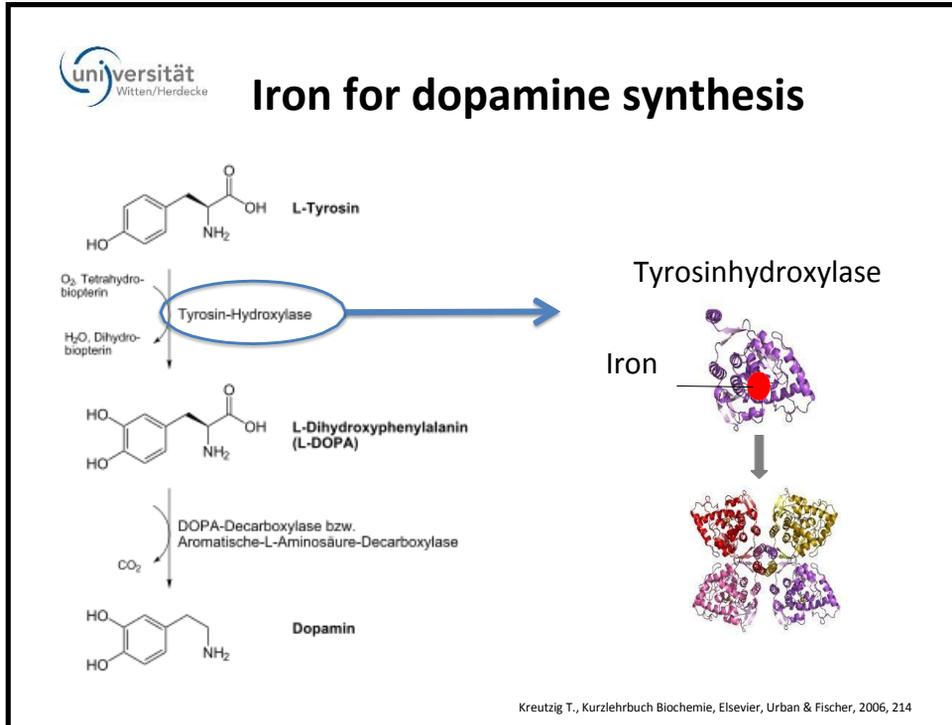
### BID- brain iron deficiency

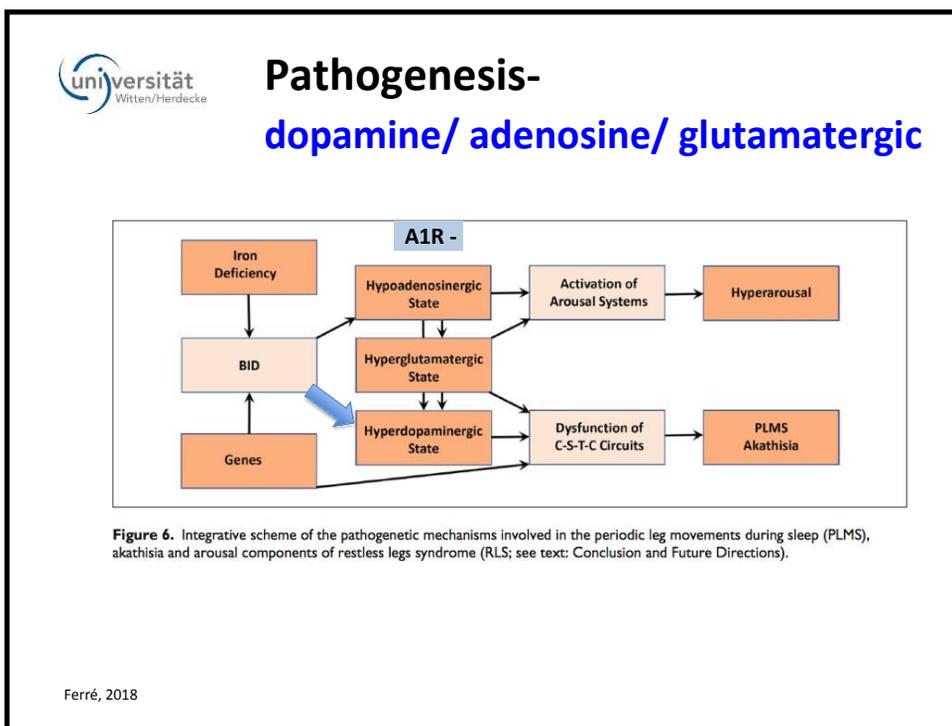
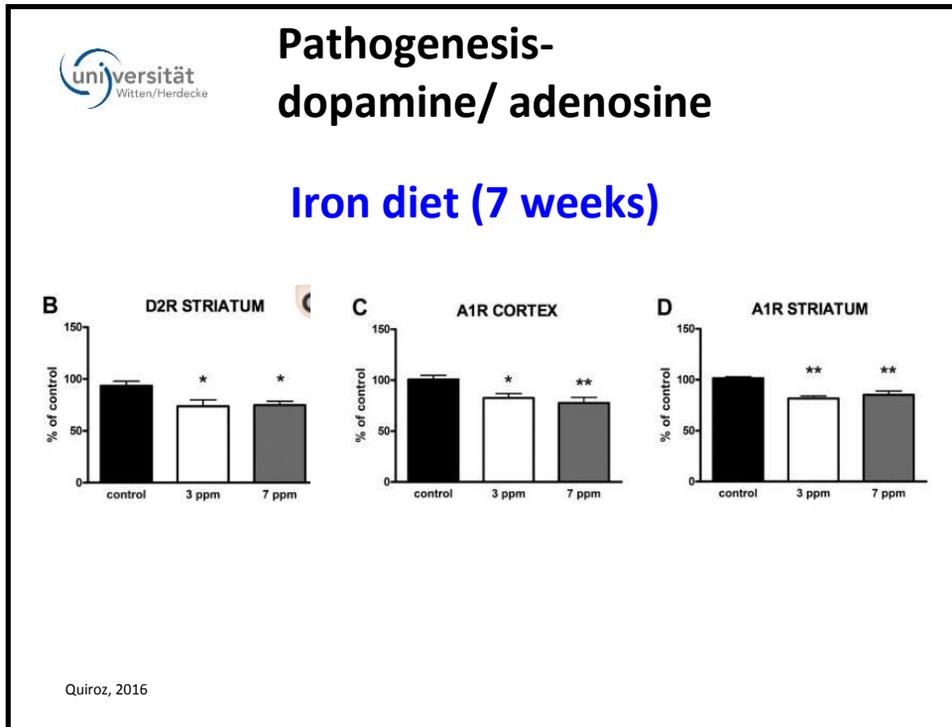


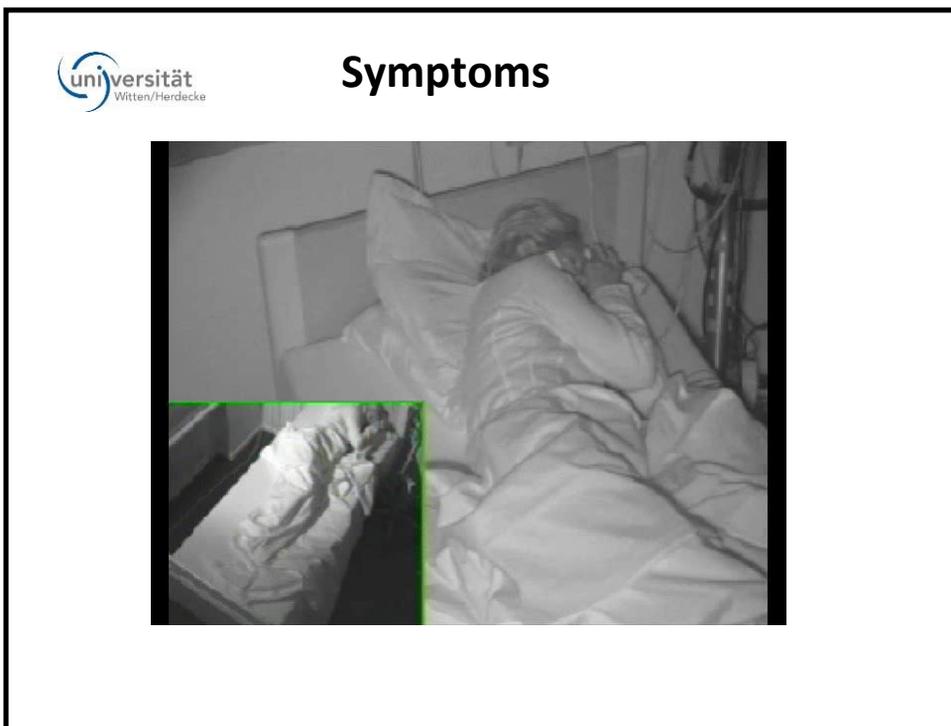
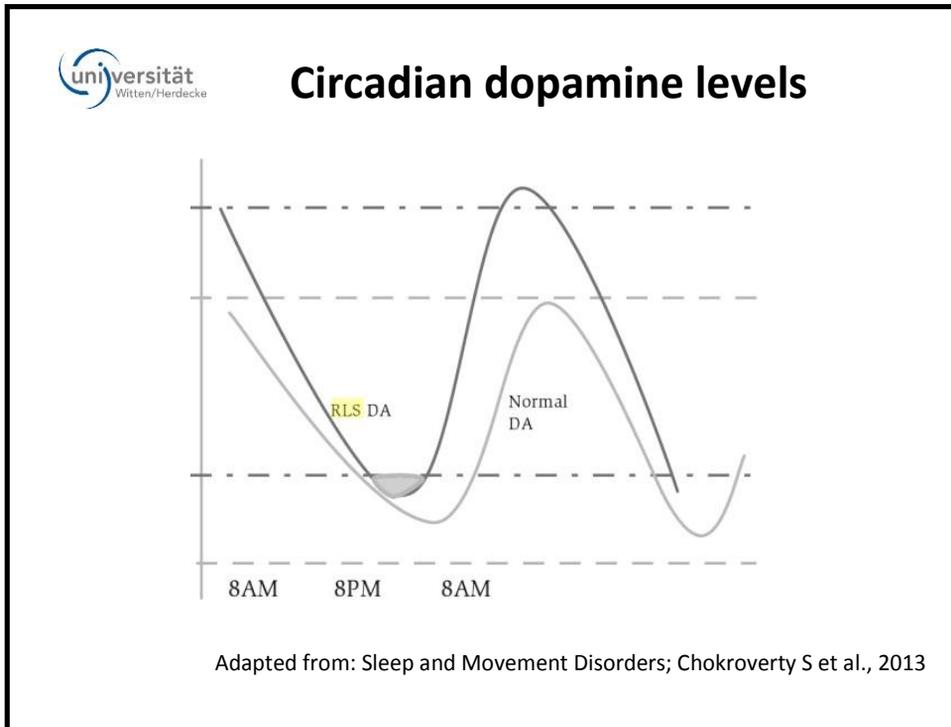
Iron transport dysregulation- BBB  
-> acquisition of iron in the brain low



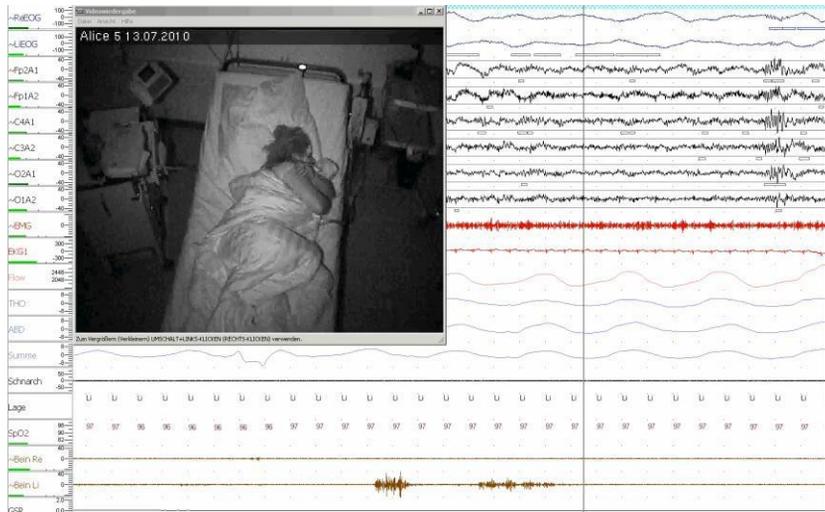
Earley, 2014







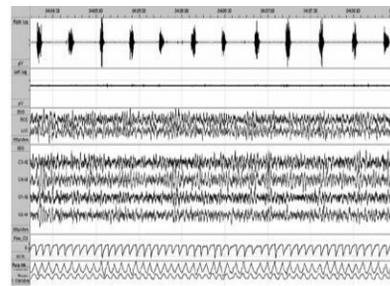
## Symptoms



## Symptoms

### Periodic limb movements

- Periodic limb movements in sleep consist of flexion movements at the ankles, knees and hips, and sometimes the arms, recurring every 5 to 90 seconds
- Usually bilateral (>90%),
- rarely unilateral



## Symptoms

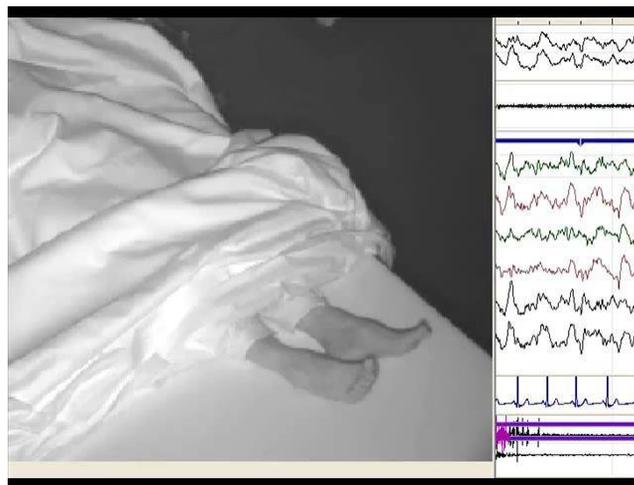
### Periodic limb movements

- PLM often associated with arousal (defined as separated less than 0.5 sec.)
- In >85% of RLS



## Symptoms

### Periodic limb movements



## Symptoms / Diagnosis

### Box 2 | The URGE acronym

Wayne Hening coined the acronym 'URGE' as a convenient reminder of the key features of restless legs syndrome:<sup>4</sup>

- U = urge to move the legs, usually associated with unpleasant leg sensations
- R = rest induces symptoms;
- G = getting active (physically and mentally) brings relief
- E = evening and night make symptoms worse

**Table 12** Diagnostic criteria for restless legs syndrome (RLS; adapted from ICSD-3)

Criteria A–C must be met

- A. 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
- B. The above features are not solely accounted for as symptoms of another medical or a behavioural condition (e.g. leg cramps, positional discomfort, myalgia, venous stasis, leg oedema, arthritis, habitual foot-tapping)
- C. The symptoms of RLS cause concern, distress, sleep disturbance or impairment in mental, physical, social, occupational, educational behavioural or other important areas of functioning

Trenkwalder, 2013; European Sleep Textbook, 2014

## Differentialdiagnosis

**Table 1.** Characteristics That Differentiate the Most Common Conditions That Mimic RLS From RLS<sup>15,38</sup>

Disorder	Characteristics
Hypotensive akathisia	Occurs in patients with orthostatic hypotension; does not normally occur while lying down
Radiculopathy	No urge to move the legs; no response to dopamine agonists
Vascular claudication;	Pain intensity in legs worsens with movement; pain intensity in legs lessens with rest; no urge to move legs; no circadian rhythmicity
neurogenic claudication	
Neuroleptic-induced akathisia	History of neuroleptic use; no relief with leg movement
Neuropathy	Typically reported as numbness, burning, pain; no urge to move the legs; present mostly during the day, infrequent at night; no relief with sustained movement; no response to dopamine agonists
Chronic pain syndrome	Symptoms may be present with movement
Nocturnal leg cramps	No urge to move the legs; often experienced as sudden and painful muscle contractions in calf
Hypnic jerks	Sudden movements/sensations often described as falling or electric shocks
Fibromyalgia	No circadian rhythmicity; no response to dopamine agonists; not relieved by movement
Positional discomfort	No circadian rhythmicity; can be relieved by simple change in position; usually does not return with position change
Arthritis	Discomfort with movement and mostly in joints; no response to dopamine agonists; no circadian rhythmicity
Varicose veins	Some relief with inactivity or massage

**Abbreviation:** RLS, restless legs syndrome.

Bogan, 2013

# Questionnaires

## Box 3 | Scales for assessing RLS

### Severity scales

- IRLS (International RLS Study Group Severity Scale)<sup>161</sup>
- RLS-6<sup>162</sup>
- Johns Hopkins Severity Scale (JHSS)<sup>27</sup>

### Quality of life scales

- RLS QoL questionnaire by Kohlen<sup>163</sup>
- RLS QoL questionnaire by Allen<sup>47</sup>
- RLS-QLI instrument<sup>48</sup>
- SF-36 (Short-Form 36 Health Survey)<sup>164</sup>

### Other scales for RLS

- Clinical Global Impression (CGI), Patient Global Impression (PGI)<sup>165</sup>
- RLS diagnostic index (RLS-DI)<sup>7</sup>
- Augmentation Severity Rating Scale of the European RLS study group (ASRS)<sup>136</sup>

Abbreviation: RLS, restless legs syndrome. Reprinted from Sleep Med. 4, Högl, B. & Gschliesser, V. RLS assessment and sleep questionnaires in practice—lessons learned from Parkinson's disease, S7–S12, © (2007), with permission from Elsevier.

## IRLSSG- rating scale

**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

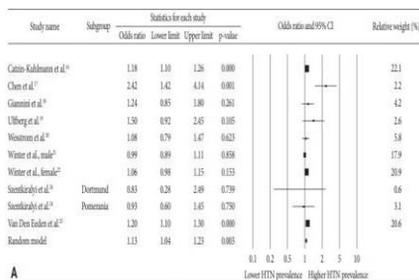
**In the past week...**  
 (3) Overall, how much relief of your RLS arm or leg discomfort did you get from moving around?  
 – (4) No relief  
 – (3) Mild relief  
 – (2) Moderate relief  
 – (1) Either complete or almost complete relief  
 – (0) No RLS symptoms to be relieved

**In the next week...**

Trenkwalder, 2010

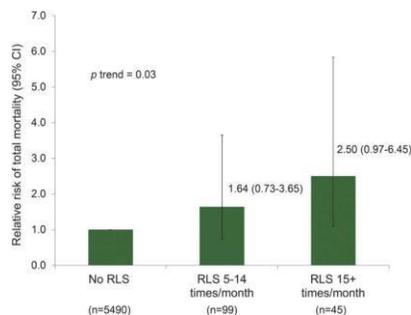
# Associated symptoms/ disorders Cardiovascular diseases

Increased risk for hypertension  
OR 1,12-2,5



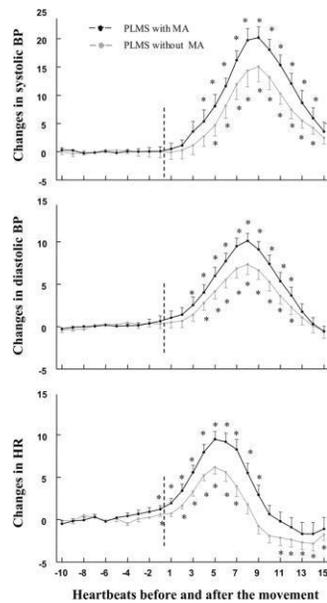
Hwang et al., 2018; Innes, 2012

Association between RLS severity and mortality among relatively healthy men



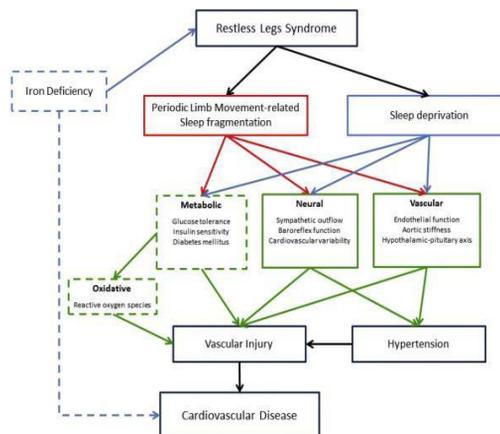
Li, 2013

## Autonomic/sympathetic activation- PLM



Pennestri, 2007

## Model RLS/PLMS – cardiovascular disorders



Gottlieb et al., 2017

## Associated symptoms/ disorders

### Psychiatric disorders

Increased risk for depression and anxiety  
OR 2-4

**Table 2** Lifetime prevalence rates and odds ratio of depressive disorders, panic attacks and anxiety disorders in RLS patients and the GHS-MHS control group (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ ) (RLS restless legs syndrome; MDE major depressive episode; w weighted; OR odds ratio; CI confidence interval)

	RLS (n = 130)			Controls (n = 2265)			RLS vs. Controls		RLS > 65 years (n = 108)		
	N	%	95% CI	N	%w	95% CI	OR	95% CI	N	%	95% CI
#Any MDE	48	36.9	29.0–45.6	398	15.2	13.7–16.8	3.30***	2.1–5.0	21	19.4	13.0–28.1
MDE	30	23.0	16.6–31.2	348	13.4	11.9–14.9	1.98**	1.2–3.0	17	15.7	10.0–23.9
Dysthymia	7	5.3	2.5–10.9	108	3.8	3.1–4.7	1.10	0.4–2.5	4	3.7	1.3–9.5
Panic Attack	20	15.38	10.1–22.7	198	7.2	6.2–8.4	2.11**	1.2–3.6 <sup>a</sup>	8	7.4	3.7–14.2
#Any Panic Disorder	15	11.4	7.0–18.3	92	3.4	2.7–4.2	3.64***	1.8–6.9 <sup>a</sup>	5	4.6	1.9–10.7
Panic Disorder	15	11.4	7.0–18.3	87	3.2	2.5–4.0	4.13***	2.1–8.0 <sup>a</sup>	5	4.6	1.9–10.7
Pattern of comorbidity											
Anxiety & Depression	25	19.2	13.3–27.0	173	6.0	5.1–7.1			9	8.3	4.3–15.3
Panic & Depression	9	6.9	3.6–12.8	47	1.6	1.2–2.3	4.57***	1.9–10.7	2	1.9	0.4–7.2

#Including patients with the disorder due to a general medical condition according to DSM-IV

<sup>a</sup>OR adjusted for mean control group = 4.6 for panic attack (95% CI = 2.2–9.5), 8.5 for panic attack due to medical condition (95% CI = 3.9–18.3), and 9.1 for panic disorder (95% CI = 4.2–19.5)

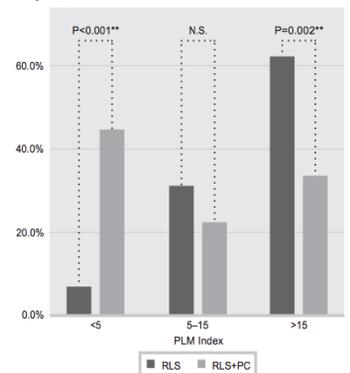
Hornyak, 2010

## Prospective study: RLS-Psy-Co

A psychiatric disorder was found in 39% of RLS patients

Psychiatric disorder	N
Major depression	8 (16.3%)
Anxiety disorder	6 (12.2%)
Somatoform disorder *	9 (18.3%)
* Subtyp psychogenic pain disorder	8/9
Post- traumatic stress disorder (PTSD)	2 (4.1%)
Eating disorder	1 (2%)

**FIGURE 2.** PLM Index in Patients With RLS Versus Patients With RLS Plus Psychiatric Comorbidity, According to PLM Index Categories\*



\*PC, psychiatric comorbidity; PLM, periodic limb movement; RLS, restless legs syndrome.

Kallweit et al., 2016

## Medication inducing or deteriorating RLS

### Antidepressants (SSRI, SNRI)

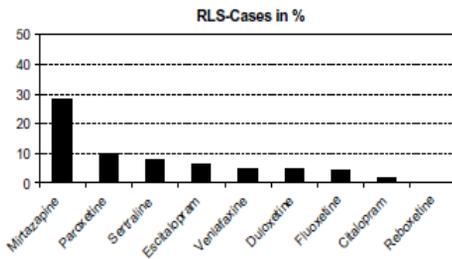


Fig. 2. Percentage frequency of new RLS cases with reference to individual medication.

### Other

*Cimetidin*  
*Metoclopramid*  
*Clozapin, Haloperidol, Olazapin,*  
*Quetiapin, Risperidon*  
*Lithium*  
*Simvastatin*  
*Tramadol*  
*Interferon α*  
*Phenytoin, Methsuximid*

Hoque et al., 2010

## Therapy

Acta Medica Scandinavica. Vol. CXLV, fasc. VI, 1953.

From the Medical Clinic of the University of Upsala, Sweden (Chief: Professor E. Ask-Upmark, M. D.)

### Therapy in Restless Legs.

By

NILS BRAGE NORDLANDER.

(Submitted for publication January 7, 1953.)

transusions. In the patient with chronic nephritis the paresthesia occurred several times. In cases of sideropenia without anemia where restless legs occurred, they have been cured by iron therapy per os (3). Since then I have tried intravenous iron therapy with »Intrafer» (identical with »Ferrivenin» and containing a 2 per cent colloidal solution of saccharated oxide of iron) in patients with restless legs. As the result of one or two injections the paresthesia as a rule disappeared after a day and remained absent for a long time. Thus 10 patients with iron-deficiency-

Nordlander BG; Acta Med Scand 1953;145(6):453-457

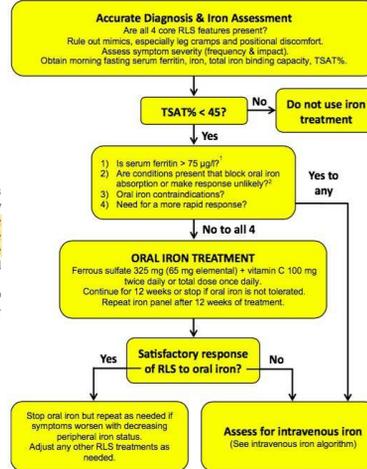
# Iron therapy

Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report

Richard P. Allen <sup>a,\*</sup>, Daniel L. Picchetti <sup>b</sup>, Michael Auerbach <sup>c</sup>, Yong Won Cho <sup>d</sup>, James R. Connor <sup>e</sup>, Christopher J. Earley <sup>f</sup>, Diego Garcia-Borreguero <sup>g</sup>, Suresh Kotagal <sup>h</sup>, Mauro Manconi <sup>b</sup>, William Ondo <sup>i</sup>, Jan Ulfberg <sup>j</sup>, John W. Winkelman <sup>k</sup>, On behalf of the International Restless Legs Syndrome Study Group (IRLSSG)

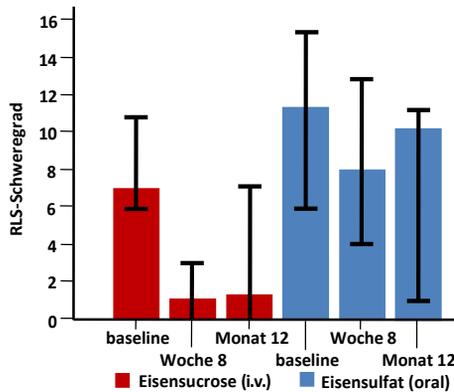
**Results:** A total of 299 papers were identified, of these 31 papers met the inclusion criteria. Four studies in adults were given a Class I rating (one for IV iron sucrose, and three for IV ferric carboxymaltose); only Class IV studies have evaluated iron treatment in children. Ferric carboxymaltose (1000 mg) is effective for treating moderate to severe RLS in those with serum ferritin <300 µg/l and could be used as first-line treatment for RLS in adults. Oral iron (65 mg elemental iron) is possibly effective for treating RLS in those with serum ferritin <75 µg/l. There is insufficient evidence to make conclusions on the efficacy of oral iron or IV iron in children.

**Conclusions:** Consensus recommendations based on clinical practice are presented, including when to use oral iron or IV iron, and recommendations on repeated iron treatments. New iron treatment algorithms, based on evidence and consensus opinion have been developed.



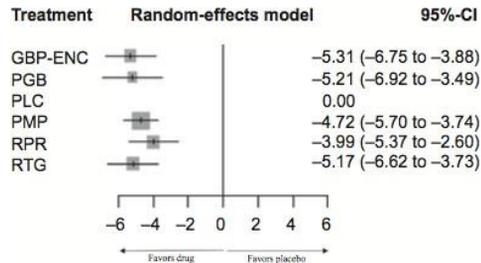
<sup>1</sup>Serum ferritin can be falsely elevated in the presence of acute or chronic inflammation.  
<sup>2</sup>Such as a heavy uterine bleeding, bariatric surgery, malabsorption syndrome, inflammatory bowel disease, rheumatic diseases, etc.

## Oral vs. iv. iron therapy



i.v. iron therapy more effective (p=0.0022)

## RLS- Therapy



**Gabapentin encarbil, pregabalin and rotigotine are equally effective in restless legs syndrome: a comparative meta-analysis.**

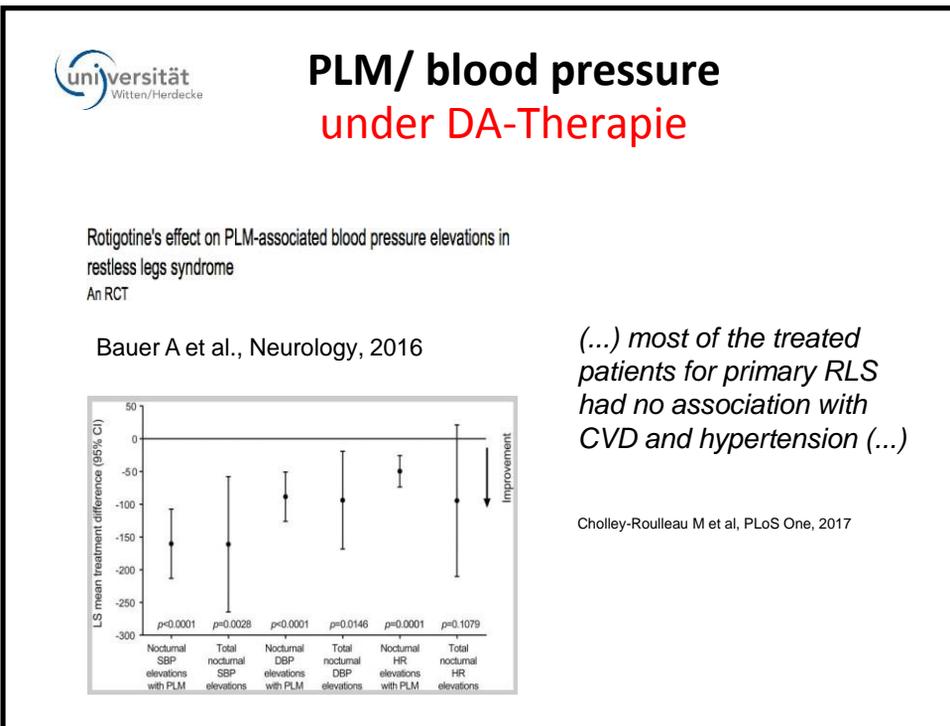
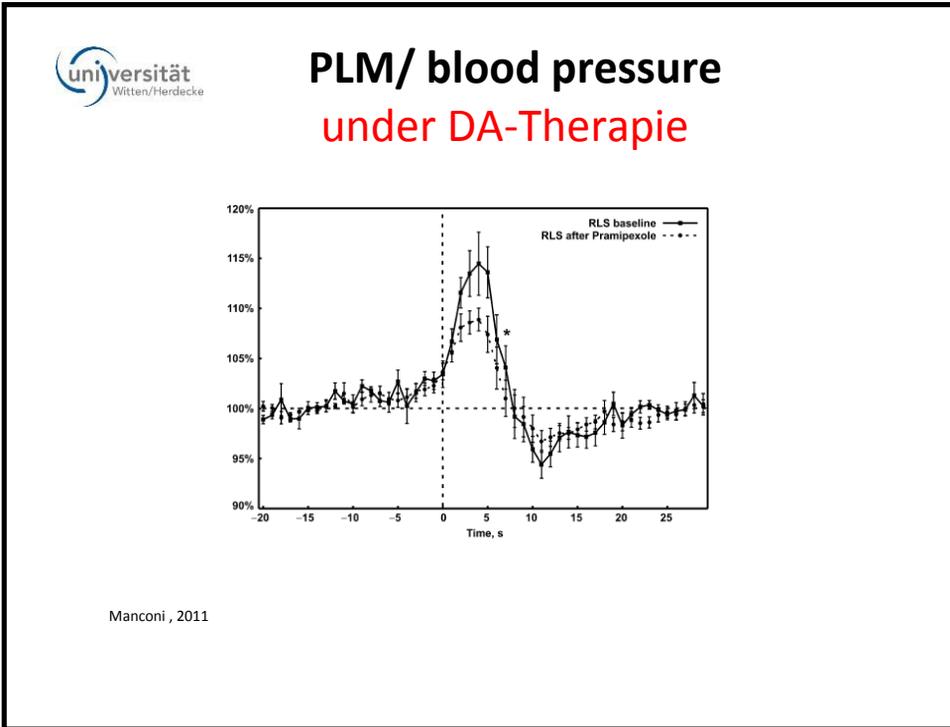
Iftikhar IH, Alghothani L, Trotti LM. Eur J Neurol. 2017;24:1446-1456.

## RLS – therapy

**Table 1.** Levels of evidence of the principal pharmacologic treatment of RLS/WED.

Drug	Level of evidence
<b>Dopamine agonists</b>	
Pramipexole	Level A
Rotigotine	Level A
Cabergoline	Level A, not FDA-approved
Ropinirole	Level B
Levodopa	Level C, not FDA-approved
<b>Alpha-2-delta calcium channel ligands</b>	
Gabapentin encarbil	Level A
Pregabalin	Level B, not FDA-approved
Gabapentin	
<b>Opioids</b>	
Oxycodone/naloxone	Level C, not FDA-approved
<b>Iron</b>	
Oral iron	Level B, not FDA-approved
Ferric carboxymaltose	Level B, not FDA-approved

Abbreviation: FDA = US Food and Drug Administration.



## DA-therapy improves depression in RLS

J Neurol (2011) 258:1046–1054  
DOI 10.1007/s00415-010-5879-7

ORIGINAL COMMUNICATION

### Ropinirole improves depressive symptoms and restless legs syndrome severity in RLS patients: a multicentre, randomized, placebo-controlled study

Heike Benes · Wolfgang Mattern · Ines Peglau · Tillmann Dreykluft ·  
Lars Bergmann · Corinna Hansen · Ralf Kohlen · Norbert Banik ·  
S. W. Schoen · Magdalena Hornyak

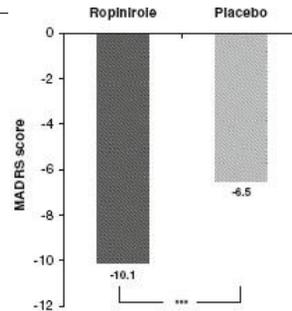


Fig. 3 Change of the Montgomery-Åsberg Depression Rating Scale (MADRS). Adjusted mean treatment difference from baseline to end of the study (day 85). \*\*\*Indicates  $P < 0.001$

## RLS- Augmentation

### Definition

- main complication of dopaminergic treatment of RLS (levodopa > dopamine receptor agonists).

### RLS symptoms

- appear earlier in the afternoon or evening
- have a quicker onset after rest
- are more intense
- are spread to different parts of the body
- shorter duration of medication effect

## RLS- Augmentation

**Table 3.** The MPI Diagnostic Criteria for Augmentation<sup>102</sup>

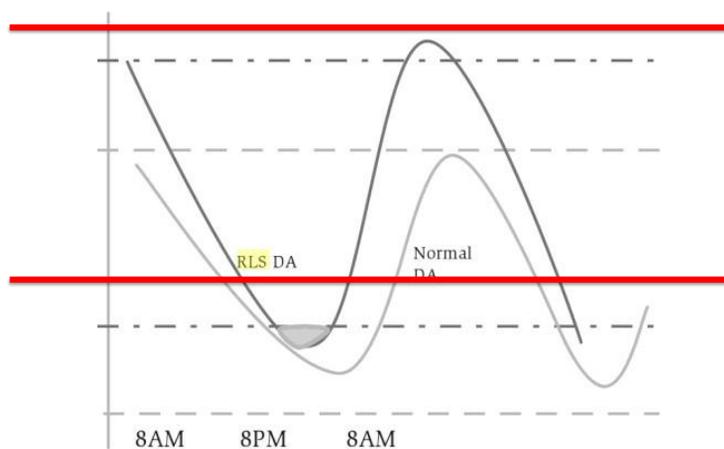
**Augmentation requires that criteria A + B, A + C, or A + B + C are met:**

- A) Basic features (all of which need to be met):**
1. The increase in symptom severity was experienced in 5 of 7 days during previous week.
  2. The increase in symptom severity is not accounted for by other factors, such as a change in medical status, change in lifestyle, or the natural progression of the disorder.
  3. It is assumed that there has been a prior positive response to treatment.
- B) Persisting (although not immediate) paradoxical response to treatment: RLS symptom severity increases some time after a dose increase and improves some time after a dose decrease.**
- C) Earlier onset of symptoms:**
1. Earlier onset by  $\geq 4$  hours  
or
  2. Earlier onset (between 2–4 hours) occurs with 1 of the following compared with symptom status before treatment: a) shorter latency to symptoms when at rest; b) extension of symptoms to other body parts; c) greater intensity of symptoms (or increase in PLMs); or d) shorter duration of relief from treatment.

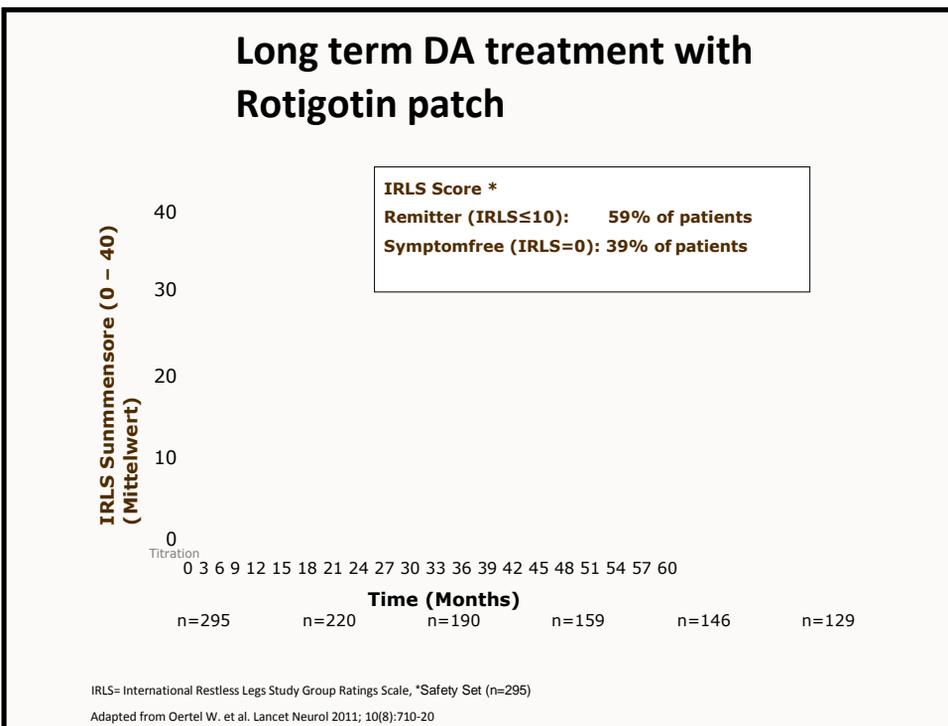
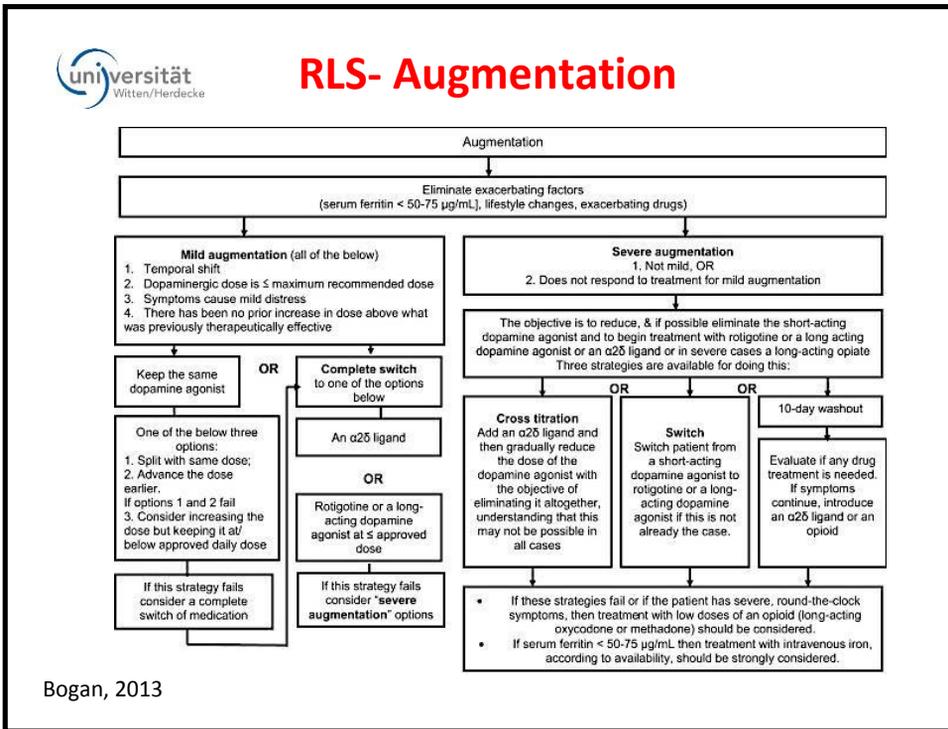
**Abbreviations:** MPI, Max Planck Institute; PLM, periodic leg movement; RLS, restless legs syndrome.

Bogan, 2013

## Circadian dopamine levels



Aus: Sleep and Movement Disorders; Chokroverty S et al., 2013



## Sleep-related movement disorders

Restless legs syndrome

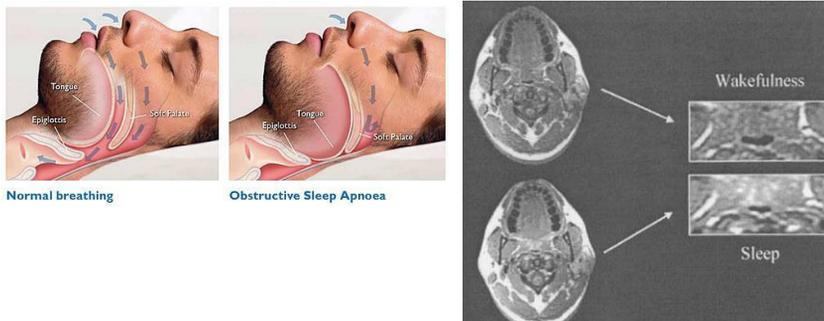
## Sleep-breathing disorders

Obstructive sleep apnea

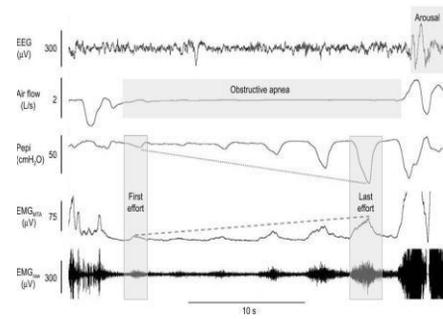
Phenotyping

Residual sleepiness

## OSA Pathophysiology



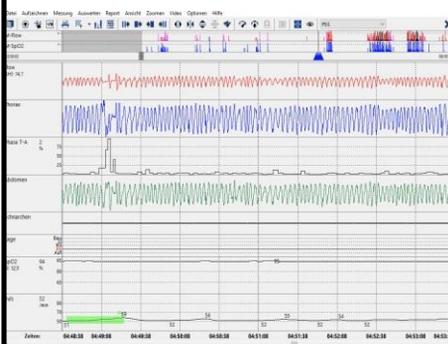
# Apnoea



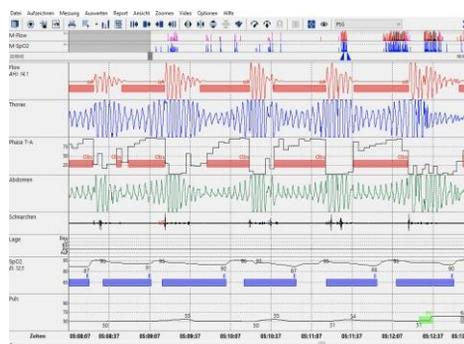
Osman, 2018

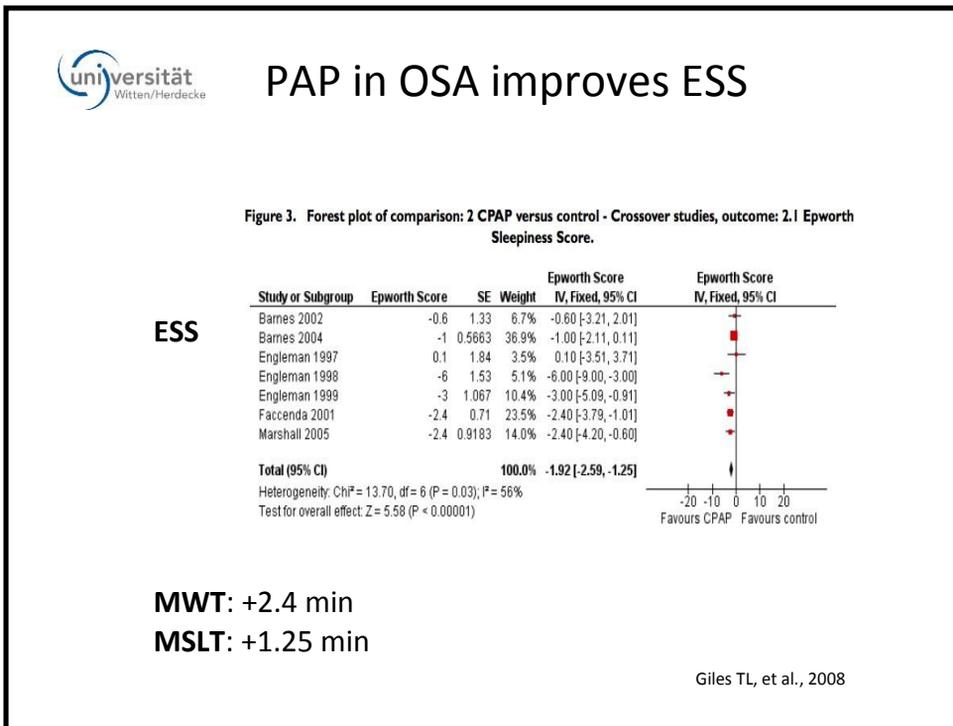
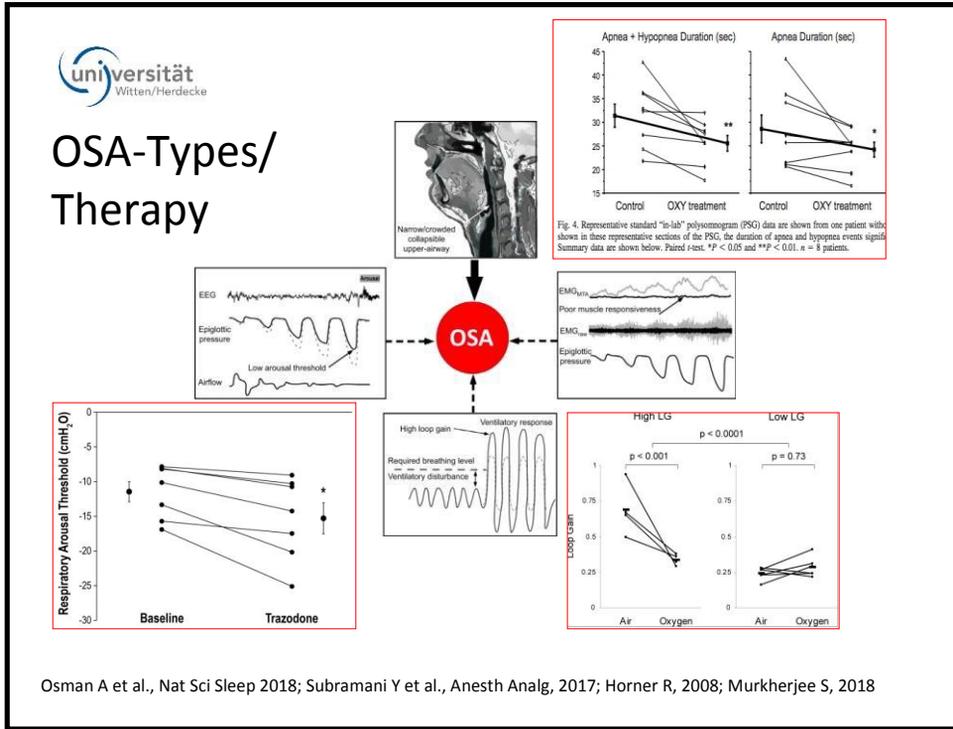
# Apnoea

## Normal respiration



## Apnoea



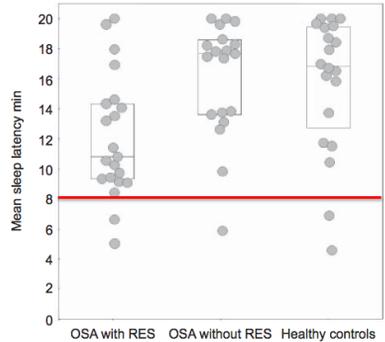


# “Residual” sleepiness in Obstructive Sleep Apnea (OSA)

**5-15%** R-EDS in OSA (ESS >10)

Characteristic	OSA with RES	OSA without RES
Usual sleep duration h:min	7:02±1:53	7:06±1:09
Multiple awakenings	25.0	45.0
Early awakening	45.0	30.0
Nocturnal micturitions	35.0	50.0
Restless legs symptoms, treated	30.0	15.0
Nonrefreshing night	60.0 <sup>†</sup>	5.0
Sleep drunkenness	0.0	0.0
Morning headache	45.0 <sup>†</sup>	20.0
Sleep paralysis	20.0	0.0
Hypnagogic hallucinations	0.0	0.0
Tired on awakening	55.0 <sup>†</sup>	15.0
Tired during daytime	95.0 <sup>†</sup>	20.0
Nonrefreshing nap	50.0 <sup>†</sup>	35.0
Home-Ostberg score	57.4±7.5	58.3±8.1

Data are presented as mean ± SD or %, unless otherwise stated. <sup>†</sup> p<0.05 for OSA patients with versus without RES controls.



Guilleminaut & Philip, 1996; Koutsourelakis I et al., 2009; Pepin JL et al., 2009; Vernet I et al., Eur Respir J, 2011

# Differential diagnosis of sleepiness in OSA

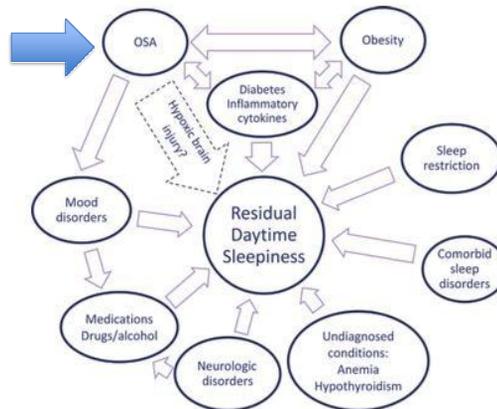
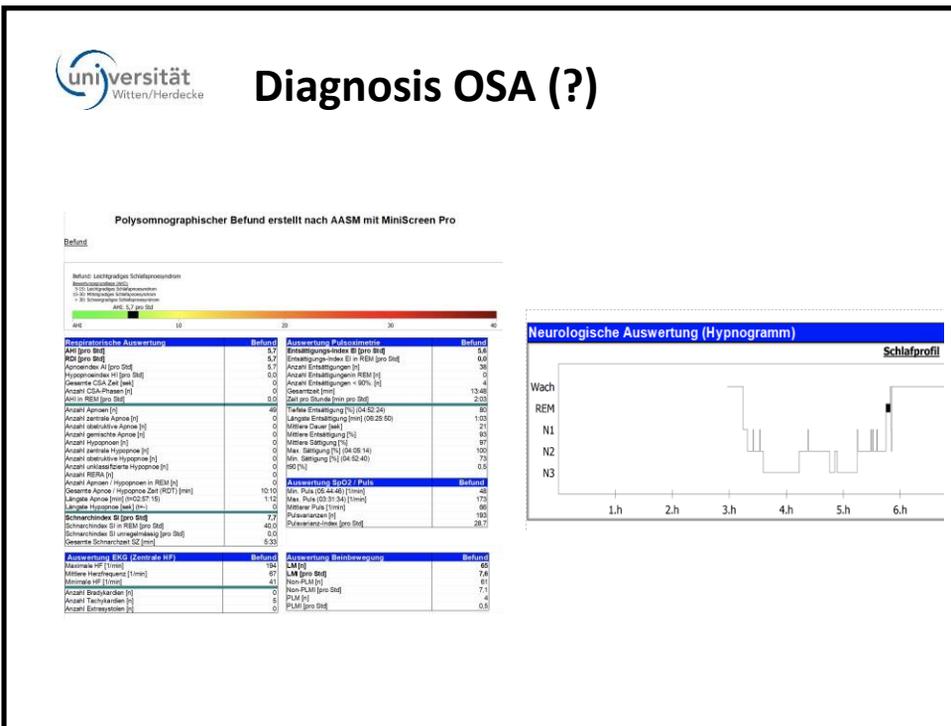
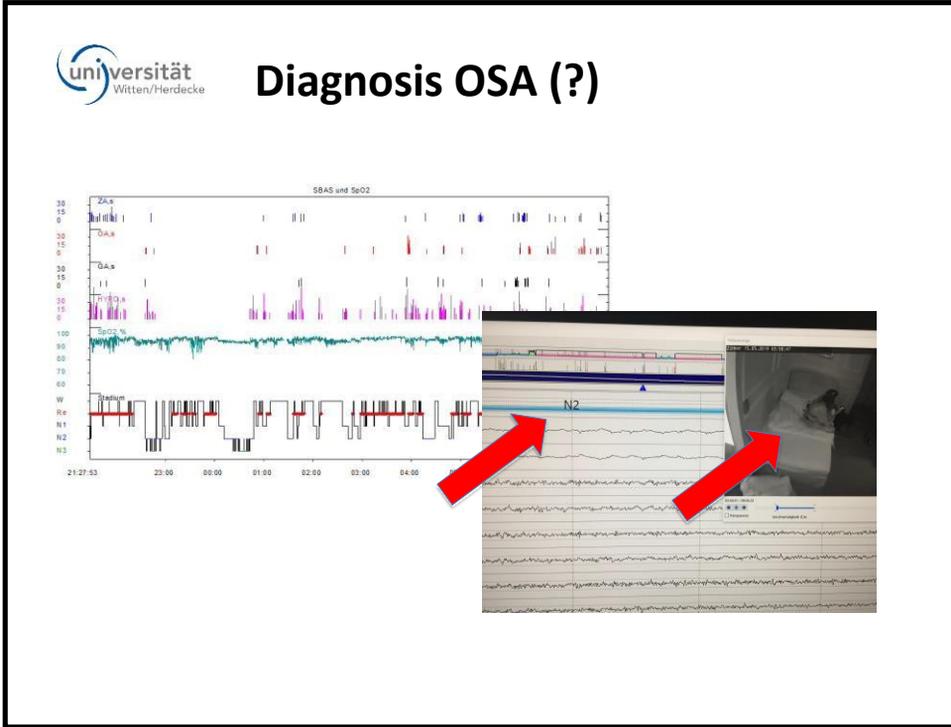


Fig. 1. Factors in ovals are potential contributing factors to the cause of residual daytime sleepiness in OSA. Arrows represent the direction of effects.

Chapman et al., Sleep Med, 2011



## Differential diagnosis of sleepiness in OSA

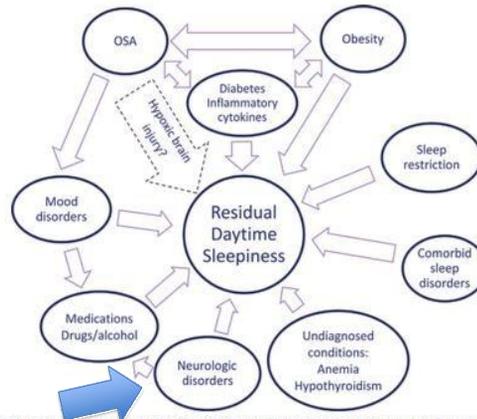


Fig. 1. Factors in ovals are potential contributing factors to the cause of residual daytime sleepiness in OSA. Arrows represent the direction of effects.

Chapman et al., Sleep Med, 2011

## Therapy besides of PAP

### Hypoglossal nerve stimulation

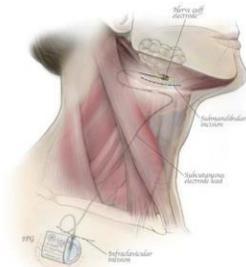
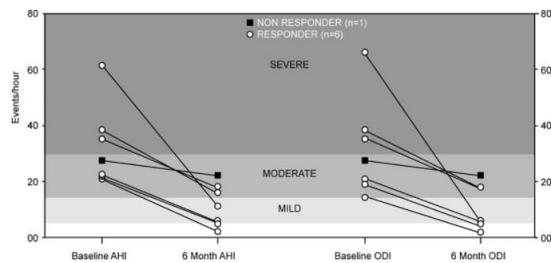


Fig. 1. Targeted hypoglossal nerve system; IPG = implantable pulse generator. [Color figure can be viewed in the online issue, which is available at [www.laryngoscope.com](http://www.laryngoscope.com).]



Friedmann, 2016

## Outlook

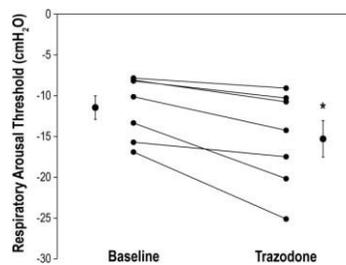
### Pharmacological management

#### Treatment for EDS in OSA

Solriamfetol  
(under review EMA)  
Other

#### Treatment of OSA - according phenotype

#### Change of arousal threshold



Eckert D, et al. 2014

## Outlook

### Pharmacological management

#### Treatment of OSA - according phenotype

#### Activation of muscle tone

Ondansetron +  
Fluoxetine (5-HT<sub>2</sub>/3 / Serotonin)

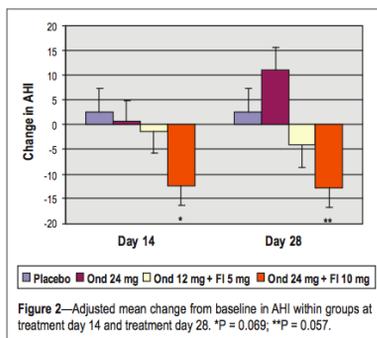


Figure 2—Adjusted mean change from baseline in AHI within groups at treatment day 14 and treatment day 28. \*P = 0.069; \*\*P = 0.057.

Prasad et al., 2010



## Sleep neurology at EAN Oslo

### Sunday, 30 June

**Time:** 8:00 – 9:30 h

**Room:** Jan Mayen 1

**Activity:** *Focussed Workshop 10:*  
Disturbances of consciousness and  
sleep-wake functions: The lessons  
from brain damaged patients.

**Time:** 17:00 – 18:30 h

**Room:** Budapest

**Activity:** *Oral session:* Sleep disorders

### Monday, 1 July

**Time:** 8:00 – 9:30 h

**Room:** Lisbon

**Activity:** *Interactive Session 5:* What can  
movement in sleep tell us about the disease?

**Time:** 13:30 – 14:15 h

**Room:** Poster Screen B12

**Activity:** Poster session Sleep 2

**Time:** 15:45 – 16:45 h

**Room:** VIP Room, exhibition, blue area

**Activity:** **Sleep Panel Business Meeting**