RLS, PLM, PLMD: What does it all mean?

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Objectives

- RLS
- PLM
  - PLMW
  - PLMS
- PLMD

- Deciphering the different terms can often be daunting for the novice health care provider

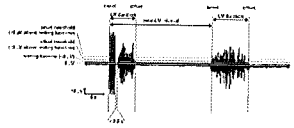
RLS: Restless Legs Syndrome

- Sensorimotor condition whereby patients often complain of uncomfortable sensations associated with an urge to move

PLM: Periodic Limb Movements

- Stereotypical limb movement identified on PSG
- Based on uncalibrated anterior tibialis surface electromyography (EMG)
- Defined as
  - 0.5 to 10 seconds in duration
  - Minimum amplitude of 8 uV above resting baseline EMG
  - Minimum of 4 repetitive eligible limb movements every 5 to 90 seconds
- Separate Channels for each leg preferred

Periodic leg movements during sleep (PLMS) are electromyographic activations recorded from the anterior tibialis muscles, lasting between 0.5 an 10 seconds[1-3]



A PLMS series[1-3] is defined as:

1. minimum number of consecutive LM events is 4
2. period length between LMs (time between onsets of consecutive LMs) 5-90 s
3. leg movements separated by less than 5 seconds are counted as a single leg movement

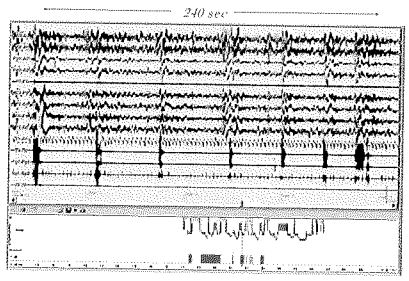
The PLMS index reflects the number of leg movements included in PLMS series per hour of sleep[1-3]

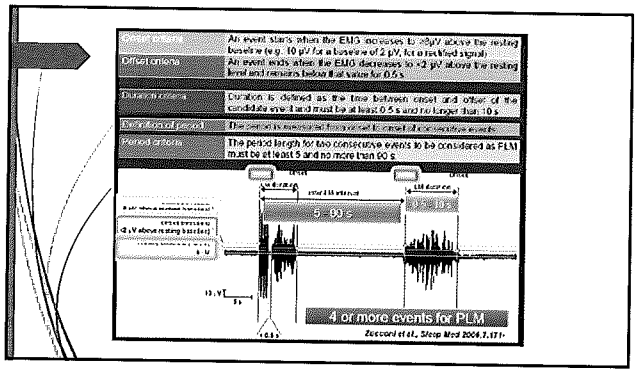
1. Zucconi et al. *Sleep Med* 2006;7:175-183
2. Iber et al. *AASM Manual* 2007
3. Berry et al. *AASM Manual* v 2.2, 2015

PLMS: Special Circumstances

- As Recommended by AASM Scoring Manual
- LM should not be scored if they occur 0.5 seconds before or after an apnea or hypopnea
  - These tend to improve once the sleep disordered breathing events are treated with CPAP
- Arousal and LM should be associated with each other when there is less than 0.5 seconds between the end of one event and onset of the other, regardless of which is first

PERIODIC LEGS MOVEMENT





PLMW: Periodic Limb Movements of Wake

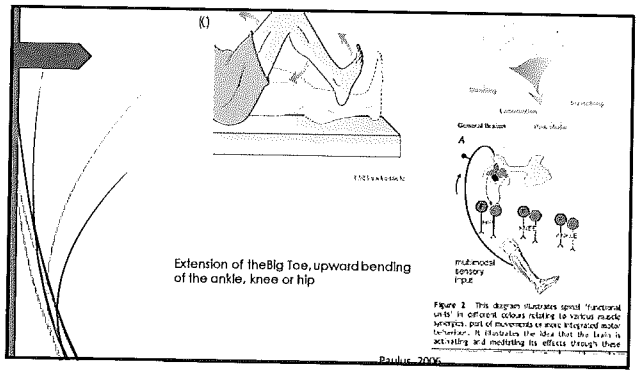
- Same AASM Criteria as PLMS
- However these are scored during Wake portion of the Study
- PLMW are considered more specific for RLS than PLMS and can be more useful when seeking supportive diagnostic information
- ICSD-2 (now outdated, considered PLMW > 5 suggestive of RLS

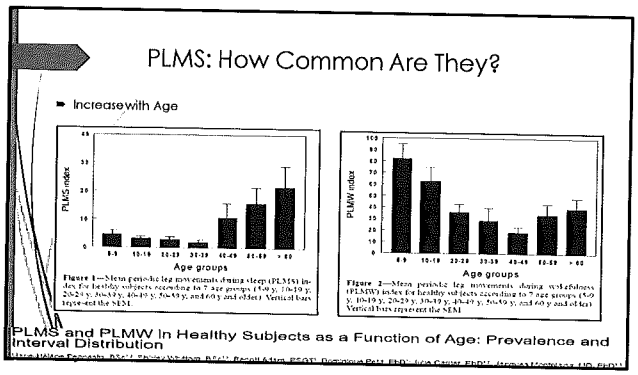
PLMD: Periodic Limb Movement Disorder

- Sleep Disorder characterized by episodes of PLMS
- Often associated with insomnia, non restful sleep, daytime dysfunction that CANNOT BE ACCOUNTED FOR BY ANOTHER SLEEP DISORDER
- Therefore – it is a diagnosis of exclusion!!!

PLMS

- Common in healthy older adults
- Not disease state specific
- Motor sign of RLS (sensitive 80-90%, not specific)
- Associated with HR and BP increases





PLMS: How Common Are They?

- Increasewith Age

Conditions Associated with PLMS

- Aging
- Attention deficit hyperactivitydisorder
- Chronic obstructive pulmonary disease
- Chronic renal failure
- Drugs (ie, neuroleptics and antidepressants)
- Iron deficiency anemia
- Narcolepsy
- Neuropathy
- Parkinson's disease
- Posttraumatic stress disorder
- Pregnancy
- REM behavioral sleep disorder
- Restlessleg syndrome
- Rheumaticdiseases
- Sleep apnea
- Sleep-disordered breathing events
- Spinal cord injury
- Spinal cord lesion

What about PLMS and Cardiovascular Disease

- Most studies are done in the context of PLM in patient with RLSI
- Siddiqui and colleagues reported a significant sleeptime increase of heart rate and systolic blood pressure (SBP) during PLMS associated with RLS, possibly causedby increases in autonomic activation during PLM episodes –8 patients with RLS
- Unruh and colleagues also reported that RLS and PLMS play a factor in nondippingnocturnal BP and sleep-time hypertension seen in renal failure patients– Dialysis patientswho were classifiedas having RLS

Medications that can increase PLM

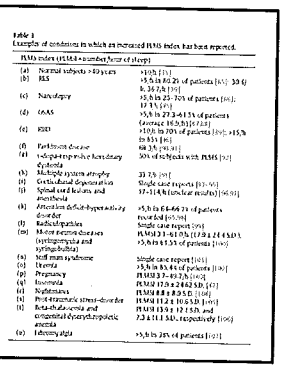
Table 1
Medication aggravators of RLS, PLMS, and PLMD

Type of Drug	Common or Trade Name	Generic
Antidepressants	Elavil	Amitriptyline
	Prozac	Fluoxetine
	Paxil	Paroxetine
Antihistamines	Allegra	Fexofenadine
	Benadryl	Diphenhydramine
	Chlor-Trimeton	Chlorpheniramine
	Claritin	Loratadine
Antiemetics	Compazine	Prochlorperazine
	Reglan	Metoclopramide
Lithium	Eskalith	Lithium carbonate
	Lithobid	
	Lithonate	
	Lithotabs	
Calcium channel blockers	Calan	Verapamil
	Cardizen	Diltazem
	Norvasc	Amlodipine
	Procardia	Nifedipine
Major tranquilizers	Haldol	Haloperidol
	Phenothiazines	Phenothiazines
	Trilafon	Perphenazine
	Thorazine	Chlorpromazine

PLM Index

Increased PLM in Wide Variety of Conditions

PLM Alonehave LOW SPECIFICITY for RLS



Ann Neurol 2012; 71: 834-844

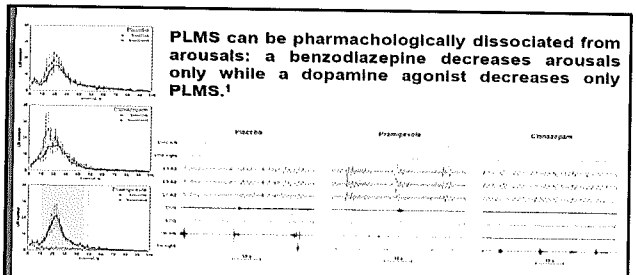
Dissociation of Periodic Leg Movements from Arousals in Restless Legs Syndrome

Mauro Manconi, MD,[1] Raffaele Ferri, MD,[2] Marco Zucconi, MD,[3] Claudio L. Bassetti, MD,[1] Stephany Fulda, PhD,[1] Debora Aricò, PsyD, PhD,[2] and Luigi Ferini-Strambi, MD[1]

Methods

- Prospective, Placebo-controlled, Single-blind, parallelgroup study
- 46 Drug Naïve Patientswith idiopathic RLS
- Each had 2 back toback full night PSG
- Prior to the Second Night:
  - Group 1: 0.25mg pramipexole
  - Group 2: 0.5mg clonazepam
  - Group 3: placebo

PLMS can be pharmachologically dissociated from arousals: a benzodiazepine decreases arousals only while a dopamine agonist decreases only PLMS.[1]



1. Manconi et al. *Ann Neurol.* 2012;71:834-844.

Conclusion

- "These resultsmightweaken the hypothesis of a direct pathologicalrole of PLMS in sleep disruption"

PLMD

PLMD

- Criteria A-D must be met

A. Polysomnographydemonstrates PLMS, as defined in the most recent version of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events.

B. The frequency is >5/hour in children or > 15/hour in adults.

C. The PLMS cause clinicallysignificantsleep disturbance or impairment in mental, physical, social, occupational, educational, behavioral, or other important areas of functioning.

D. The PLMS and the symptoms are not better explained byanother current sleep disorder, medical or neurologicaldisorder, or mentaldisorder (e.g., PLMS occurring with apneas or hypopneasshould not be scored)

PLMD: Footnotes

- The PLMS index must be interpreted in the context of a patient's sleep related complaint. In adults, normative values greater than five per hour have been found in studies that did not exclude respiratory event-related arousals (using sensitive respiratory monitoring) and other causes for PLMS. Data suggest a partial overlap of PLMS index values between symptomatic and asymptomatic individuals, emphasizing the importance of clinical context over an absolute cutoff value.

PLMD: Footnotes

- If PLMS are present without clinical sleep disturbance or daytime impairment the PLMS can be noted as a polysomnographic finding, but criteria are not met for a diagnosis of PLMD.

PLMD: Footnotes

- The presence of insomnia or hypersomnia with PLMS is not sufficient to establish the diagnosis of PLMD. Studies have shown that in most cases the cause of the accompanying insomnia or hypersomnia is something other than the PLMS. To establish the diagnosis of PLMD, it is essential to establish a reasonable cause-and-effect relationship between the insomnia or hypersomnia and the PLMS. This requires that other causes of insomnia such as anxiety or other causes of hypersomnia such as obstructive sleep apnea or narcolepsy are ruled out. PLMS are common, but PLMD is thought to be rare in adults.

PLMD: Footnotes

- PLMD cannot be diagnosed in the context of RLS, narcolepsy, untreated obstructive sleep apnea, or REM sleep behavior disorder; PLMS occur commonly in these conditions but the sleep complaint is more readily ascribed to the accompanying disorder.
- The diagnosis of RLS takes precedence over that of PLMD when potentially sleep disrupting PLMS occur in the context of RLS. In such cases, the diagnosis of RLS is made and the PLMS are noted.

Moving On: RLS!

RLS

- Sensorimotor condition whereby patients often complain of uncomfortable sensations associated with an urge to move

RLS: Essential Diagnostic Criteria

- 1. Uncomfortable Sensations with an urge to move the legs
- 2. Sensations worsen during periods of rest or inactivity
- 3. Sensations are relieved by movement, such as walking or getting up
- 4. Sensations are worse in the evening or at the night

Mnemonic: URGE

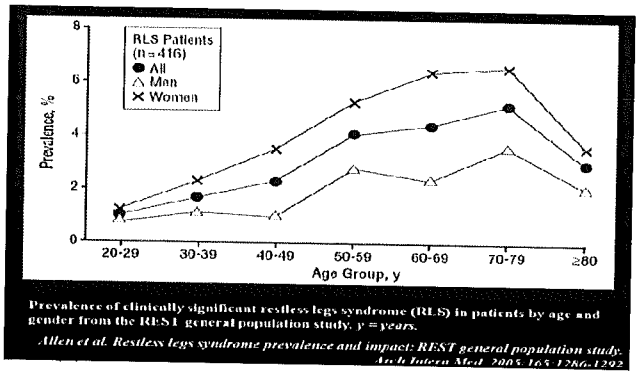
- Uncomfortable Sensations that occur in the lower extremity
- Rest, gets worse
- Gets better with activity
- Evening

Supportive features

- Positive Family History of RLS
- Positive response to dopaminergic agents
- Presence of PLMS on PSG

Rule Out Mimics!!

RLS Mimics	Distinction from RLS
Positional Discomfort	Brief, relieved by changing positions
Leg cramps	Presence of Muscle Contractions, cramp, not relieved by movement
Akathesia (inner sense of restlessness)	Typically seated, no circadian pattern does not cause sleep disturbance
Peripheral Neuropathy	Less restlessness lack of relief with movement
Arthritis Pain	In joint, lack of circadian pattern



Prevalence of clinically significant restless legs syndrome (RLS) in patients by age and gender from the REST general population study. *y = years.*

Allen et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med. 2005; 165:1286-1292

Prevalence of RLS in Primary Care

- 10% of patients meet diagnostic criteria
- 3% with severe RLS
  - 88% of these patients had at least 1 sleep related complaint

"REST Primary Care Study" Sleep Medicine 2004;5:237-46.

Genetics of RLS

- 60% of patients with RLS will have a family member with RLS
- Genetic studies have identified 5 genes and 10 different risk alleles for RLS

Sakas et al Current Opinion in Neurology 2010;23:401-06.

Useful Statistics

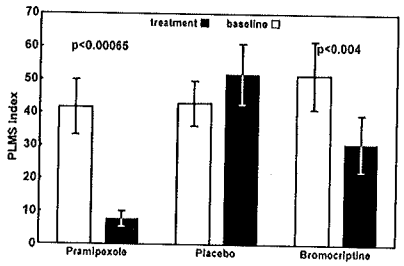
- 80-90% of individuals with RLS have PLMS
- Only 30% of individuals with PLM have RLS
- Therefore the presence of PLM alone does not warrant the diagnosis of RLS!!!!

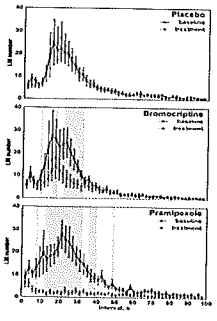
Dopamine Receptors

- A placebo-controlled, prospective, single-blind investigation was carried out on 45 drug-naive patients with Idiopathic RLS.
- Each patient underwent 2 consecutive full night polysomnographic studies.
- The first night was performed without medication.
- Prior to the second night, one group received a single oral dose of 0.25 mg pramipexole while a second group received a single oral dose of 2.5 mg bromocriptine and the remaining patients received placebo.

Preferential D2 or preferential D3 dopamine agonists in restless legs syndrome. Manconi et al. Neurolo

PLMS index before and after treatment in the three different groups of patients





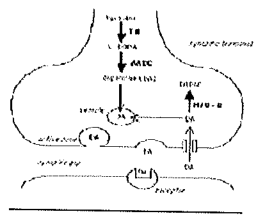
Distribution curve of the inter-LM intervals before and after treatment, in the three groups of patients

Conclusion

- PRA is significantly more effective than BRO in reducing PLMS in patients with a high level of PLMS index at baseline.
  - In patients with a PLMS index over 80, PRA suppressed more than 80% of events, while BRO decreased up to 50%.
  - After PRA treatment, the PLMS index decreased in all patients, while after BRO an increase of PLMS index was observed in 2 patients out of 15.
- Considering the distribution of inter-LM intervals, treatment with PRA completely abolished the dopaminergic peak, which persist after BRO
- **The results presented in this clinical study focus on the D3 receptor subtype as a possible preferential target of DA in RLS**
- The involvement of other possible dopaminergic or non-dopaminergic neuronal circuits cannot be excluded

Pathophysiology of RLS

- Iron-dopamine hypothesis
  - Low CNS iron in RLS Patients
  - Iron is a substrate in the rate limiting step of dopamine synthesis



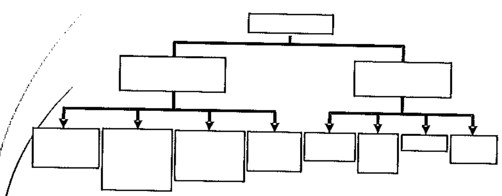
Adverse Effects of RLS

- Poor quality of life
- Insomnia
- Depression/Anxiety
- Cardiovascular disease – association, not necessarily causation

Common Exacerbating Factors

- Alcohol
- Nicotine
- Caffeine
- Cold Medications especially 1st generation antihistamines
- Antidepressants
- Sleep disordered breathing
- Low ferritin (< 50)

Algorithm for the management of intermittent restless legs syndrome (RLS)



Silber et al. Mayo Clin Proc. 2004;79(7):916-922.

Iron Replacement Therapy

- Serum ferritin <50-75 μg/L
  - 325 mg tid, 1 hour AC with 100 mg Vitamin C
- Oral iron therapy concerns
  - GI problems (constipation, abdominal pain)
  - Absorption- 20-30% with ferritin <5 μg/L
    - 2% with ferritin 60-80 μg/L

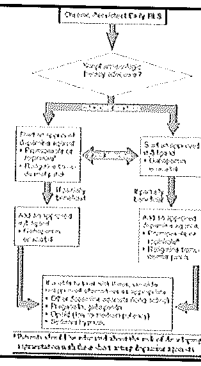
A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. Davis BJ, Rajput A, Rajput ML, Aul EA, Eichhorn GR. Eur Neurol. 2000;43(2):70-5.
Efficacy of oral iron in patients with restless legs syndrome and a low-normal ferritin: A randomized, double-blind, placebo-controlled study. Wang J, O'Reilly B, Venkataraman R, Mysliwiec V, Mysliwiec A. Sleep Med. 2009 Oct;10(9):973-5.

Intermittent RLS Medication Treatment

Type of RLS problem	Suitable drugs
Bedtime RLS, infrequent	Benzodiazepines Opioids Carbidopa/levodopa
Bedtime RLS, ≥ 4-5 nights per week	Consider regular dopamine agonists or alpha 2 delta drugs
Daytime RLS, expected	Opioids Carbidopa/levodopa Dopamine agonists
Daytime RLS, unexpected	Opioids Carbidopa/levodopa

Chronic Persistent/Daily RLS

- Symptoms when not treated would occur on average at least twice a week for the past year but usually more frequent and often daily
- Symptoms are typically more severe and tend to impact social, occupational or educational aspects of life



Augmentation – NIH Criteria

- Worsening RLS symptoms after starting DA therapy (usually months to years)
- Earlier onset by at least 2 hours
- Increase in intensity of symptoms
- Quicker onset of symptoms with rest
- Medication effect does not last as long
- Spread of symptoms to other body parts
- PLMW occur for the first time or are worse

Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. Sleep Med 2003;4:101-19.

Max Planck Institute Criteria

A: Basic features (all of which need to be met):

1) The increase in symptom severity was experienced on five out of seven days during the previous week;
2) The increase in symptom severity is not accounted for by other factors such as a change in medical status, lifestyle or the natural progression of the disorder;
3) It is assumed that there has been a prior positive response to treatment.

In addition, either B or C or both have to be met:

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) An earlier onset by at least four hours

or

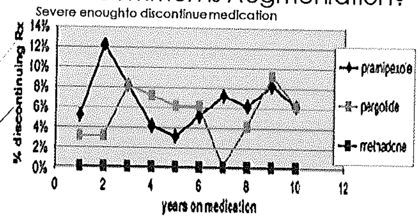
2) An earlier onset (between two and four hours) occurs with one of the following compared to symptom status before treatment:
   a) Shorter latency to symptoms when at rest;
   b) Spreading of symptoms to other body parts;
   c) Intensity of symptoms is greater (or increase in periodic limb movements (PLM) if measured by polysomnography (PSG) or the suggested immobilization test (SIT);
   d) Duration of relief from treatment is shorter

Augmentation requires criteria A + B or A + C or A + B + C to be met)

Garcia-Borreguero D, Allen RP, Kohnen R, Hogl B. Diagnostic standards for dopaminergic augmentation of restless legs syndrome: report from a World Association of Sleep Medicine–IRLSSG consensus conference at the Max Planck Institute. Sleep Med 2007;8:520-

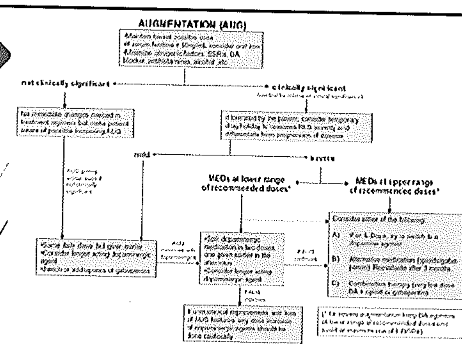
How Common is Augmentation?

Severe enough to discontinue medication

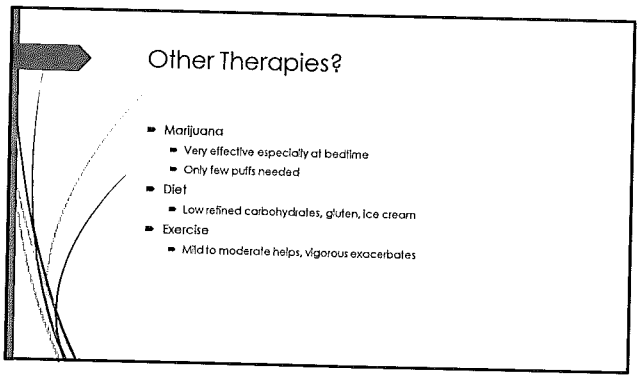


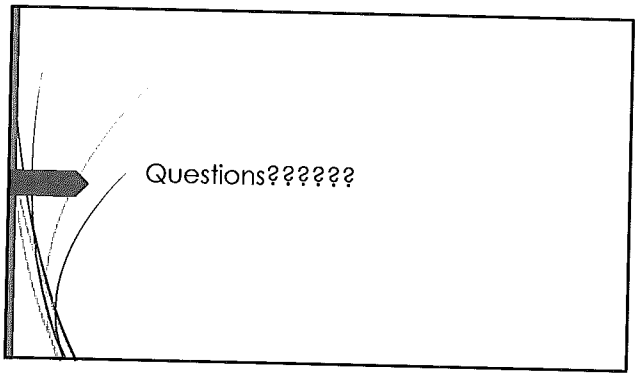
Pramipexole (1.3 mg): 7% per year, Pergolide (.5 mg): 5% per year

Silver N, Allen RP, Senerth J, Earley CJ. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med. 2011 May;12(5):440-4.



Garcia-Borreguero D, Williams AM. Dopaminergic augmentation of restless legs syndrome. Sleep Med Rev. 2010 Oct;14(5):339-46.


Other Therapies?
Marijuana
Very effective especially at bedtime
Only few puffs needed
Diet
Low refined carbohydrates, gluten, ice cream
Exercise
Mild to moderate helps, vigorous exacerbates


Questions??????