Restless Legs Syndrome and Peripheral Movement Disorders





UFHealth
NORMAN FIXEL INSTITUTE FOR NEUROLOGICAL DISEASES

Parkinson's Foundation

Tourette Association of America
Awareness. Research. Support.

Tyler's Hope for a Dystonia Cure

NIH National Institutes of Health

Michael S. Okun, MD

Professor of Neurology
Medical Advisor, Parkinson's Foundation
Director, Norman Fixel Institute for Neurological Diseases

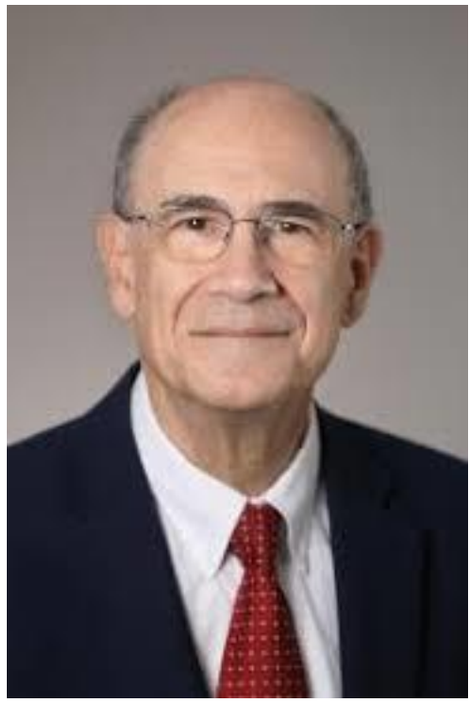
NIH Support

- UH3 NS18-023 Defining Targets for Tic Detection and Suppression in Tourette Syndrome Deep Brain Stimulation NS18-023
- R01NS131342 Thalamic DBS and Voice Tremor
- U01 Automated Image Differentiation of Parkinson's
- R25NS108939 University of Florida R25 Early Research Program for Neurology and Neurosurgery Residents
- R01NS096008 The Human Thalamocortical Network in Tourette Syndrome
- R01NR014852 Mobile Decision Support System for Nurse Management of Neuromodulation Therapy
- R21NS072897 Neural Correlates of Tourette Syndrome
- R21NS119849 Balance and Gait in Essential Tremor
- R34MH080764 Scheduled and Responsive Brain Stimulation for the Treatment of Tourette Syndrome

Special thanks to:

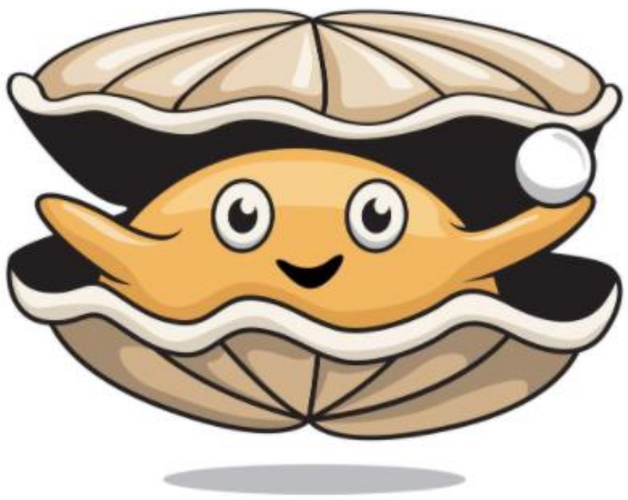








The ‘cypher’ for my talk



Clinical Pearl



New Paper



‘Hot’ Paper

What’s new in RLS?

JAMA

Review

Restless Legs Syndrome
A Review

John W. Winkelman, MD, PhD[1,2]; Benjamin Wipper, MD[3]

Clinical interview for diagnosis of restless legs syndrome (RLS)

Essential diagnostic criteria ("URGED")

- **U**rge to move the limbs (usually legs)
- Urge is present at **R**est
- Symptoms **G**et better with movement
- **E**vening or nighttime onset or worsening of symptoms
- **D**ifferential diagnosis does not explain symptoms

Risk factors

- Female sex (2:1 vs male sex)
- Older age (most do not present until age 50-60 y)
- Relative(s) with RLS (approximately half of patients have a first-degree relative with RLS)
- Use of certain medications (eg, antihistamines, serotonergic antidepressants, dopamine antagonists)

Other common features

- Unpleasant sensations (eg, achy, tingling) often accompanied by an urge to move limbs
- Difficulty falling asleep, staying asleep, or returning to sleep: primary reason patients seek medical care
- Daytime sleepiness (32%)
- Depression (30%)
- Difficulty concentrating (19%)
- Anxiety disorders (17%)

Conditions with high RLS prevalence

- Opioid withdrawal (50%)
- Multiple sclerosis (27.5%)
- End-stage kidney disease (24%)
- Iron deficiency anemia (24%)
- Pregnancy: first trimester (8%), second trimester (16%), third trimester (22%)
- Neuropathy (eg, diabetic, idiopathic [21.5%])
- Parkinson disease (20%)
- Obstructive sleep apnea (16%)

Other assessments for diagnosis of RLS

- Blood testing: low serum ferritin and/or transferrin saturation
- Physical examination: can help rule out RLS mimics (eg, neuropathy)
- RLS screening questionnaires: follow-up interview should be performed
- Polysomnography: can provide information about sleep-related conditions (eg, periodic limb movements of sleep)

Initial management of restless legs syndrome (RLS) after diagnosis

- Evaluate severity and frequency of RLS symptoms
- General measures (eg, limit alcohol use, encourage daytime exercise, promote sleep hygiene)
- Eliminate medications that exacerbate RLS symptoms (eg, antihistamines, serotonergic antidepressants, dopamine antagonists)
- Identify and address comorbidities that may contribute to symptoms (eg, obstructive sleep apnea)

↓

Obtain serum ferritin and transferrin saturation (TSAT) levels

Serum ferritin ≤100 ng/mL[a] or TSAT <20%

↓

First-line therapy: iron supplementation

- Intravenous iron supplementation (eg, ferric carboxymaltose, dextran [1000 mg]) or oral iron (325-650 mg)[b]
- Consider interim use of medication (eg, gabapentinoid) while awaiting response to iron supplementation

If symptoms persist after 1-3 mo of iron supplementation →

Serum ferritin >100 ng/mL[a] and TSAT ≥20%

Patients with bothersome frequent RLS symptoms

↓

First-line therapy: gabapentinoids[c]

Gabapentin, gabapentin enacarbil, or pregabalin

Medication is not effective or is poorly tolerated

↓

Consider other therapies (can be combined)

- Other gabapentinoid medication
- Low-dose opioids (eg, oxycodone, methadone)
- Dipyridamole
- Peroneal nerve stimulation
- Dopamine agonists (eg, pramipexole, ropinirole) with close monitoring for symptoms of augmentation (an iatrogenic worsening of RLS symptoms that requires treatment with increasing doses of dopamine agonists)

Patients with infrequent RLS symptoms

↓

Consider as-needed medication (eg, levodopa, dopamine agonist)

Table 1. Restless Legs Syndrome (RLS) and Common Mimics in Adults[a,b]

Disorder/mimic	RLS	Neuropathy	Anxiety	Arthritides (eg, OA, RA)	Nocturnal leg cramps	Positional discomfort	Akathisia
Description of symptoms	Urge to move legs (and sometimes arms), often with uncomfortable sensations	Pain, numbness, burning, or electrical sensations in legs or arms	Agitation accompanied by worry or unease, without sensory discomfort	Pain, discomfort, or stiffness in joints	Sudden and painful sustained contractions limited to the lower extremities	Extremity "asleep" from compression	Inner whole-body restlessness
Worse at night	Yes	Oftentimes	No	Not typically; may be worse in morning	Yes	No	No
Relieved by movement	Yes, with standing or walking	No	Possibly	Dependent on etiology	Yes, stretching helps	Yes, with simple change in position	Yes
Possible physical examination findings		Abnormal neurologic examination or nerve conduction study result	Tachycardia, tremor, diaphoresis	Joint effusion, erythema; warmth may be present			Body rocking movements, fidgeting
Additional features	PLMS on PSG; family history often present	Can coexist with RLS	May have history of anxiety disorder	Imaging may support diagnosis			Associated with dopamine antagonist use

Abbreviations: OA, osteoarthritis; PLMS, periodic limb movements of sleep; PSG, polysomnography; RA, rheumatoid arthritis.

[a] Ordered left to right based on authors' perceptions of how often these are mistaken for RLS.

[b] Blank cells indicate that there was no pertinent information to include.

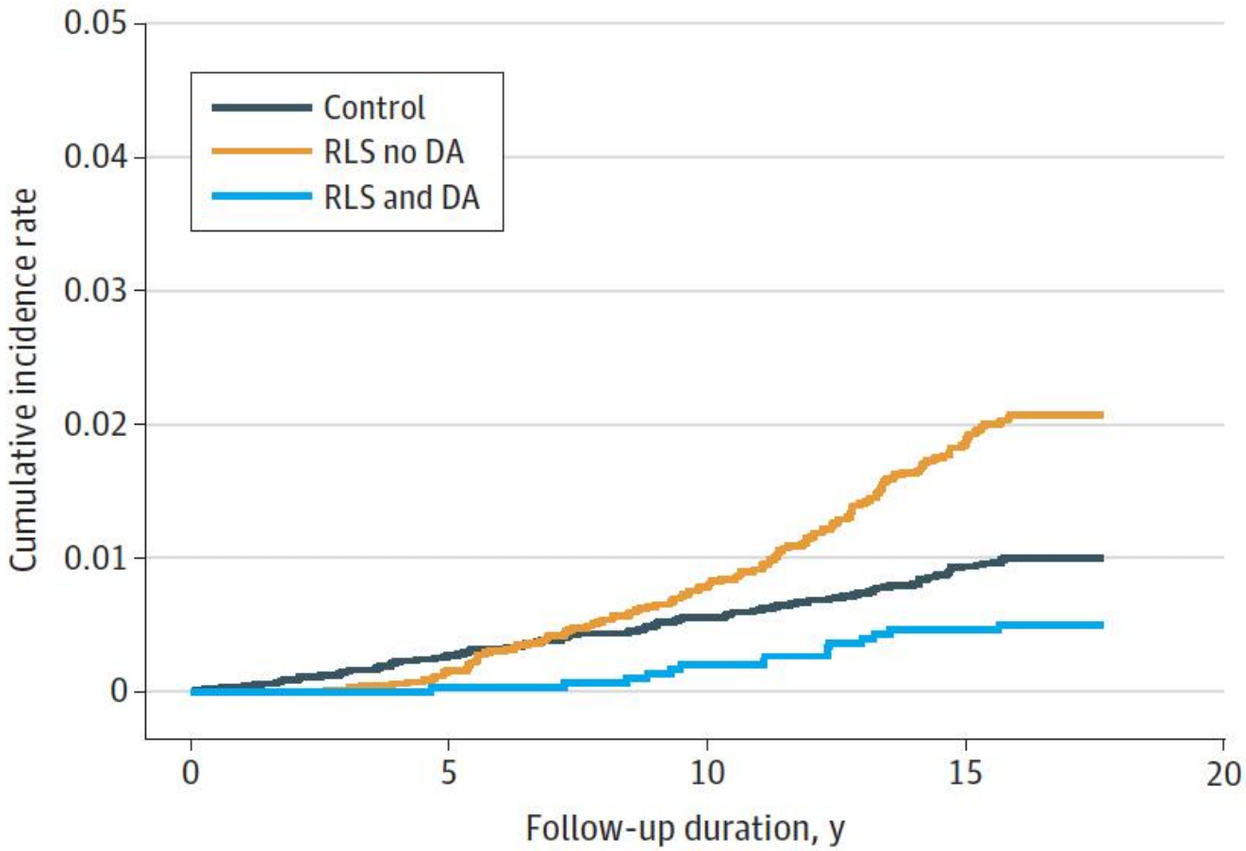
JAMA Network Open

Original Investigation | Neurology

Risk of Parkinson Disease Among Patients With Restless Leg Syndrome

Myeonghwan Bang, MD; Dougho Park, MD, PhD; Jong Hun Kim, MD, PhD; Hyoung Seop Kim, MD, PhD

Figure 2. Cumulative Incidence of the Risk of Parkinson Disease



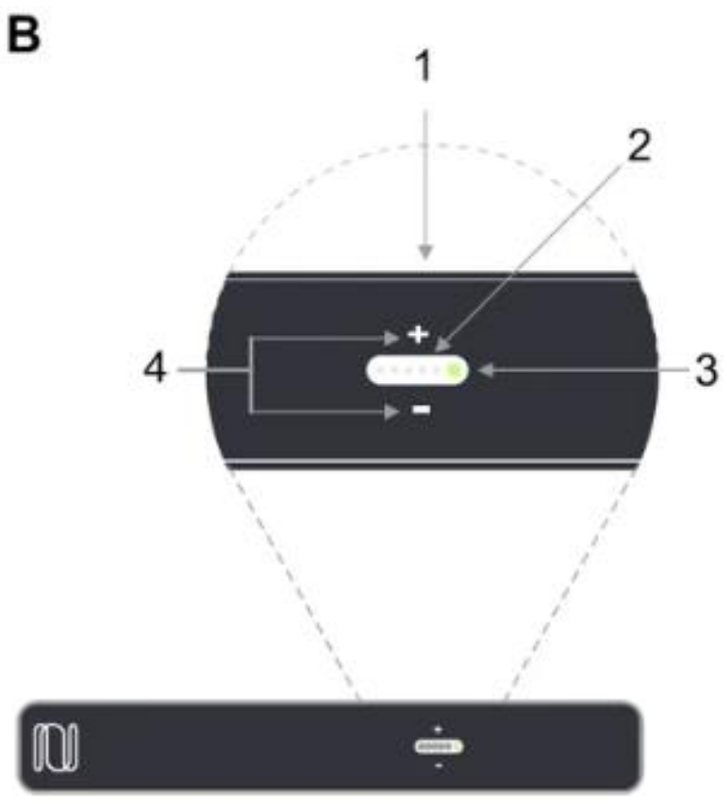
No. at risk				
Control	9919	9718	9165	8555
RLS no DA	6842	6825	6714	6387
RLS and DA	3077	3073	2998	2756

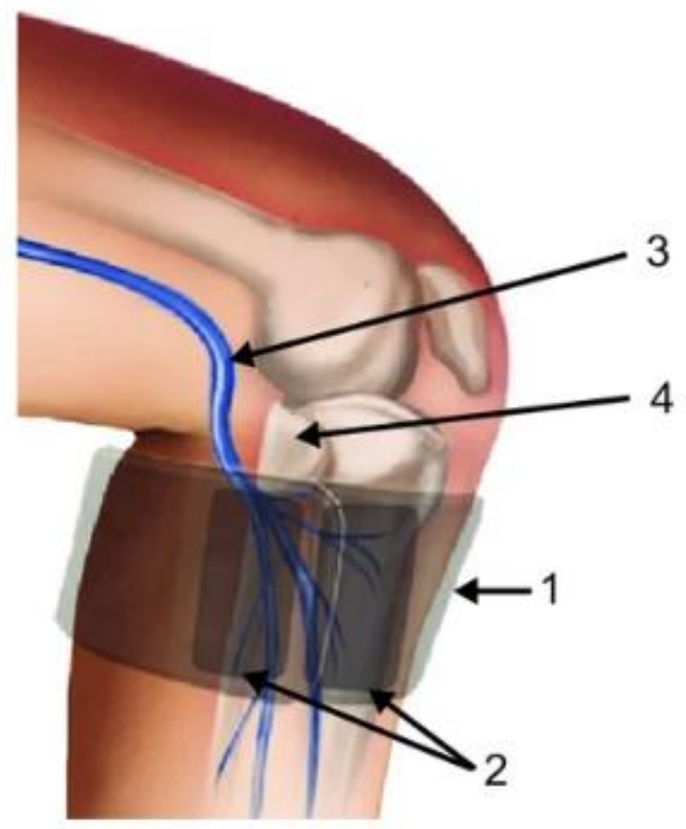
- Five studies; n=252
- 69 monotherapy 183 adjunctive TOMAC therapy
- TOMAC significantly reduced IRLS score both as adjunctive therapy (MD: 3.39, p = 0.0001) and monotherapy (mean difference [MD]: 3.80, p = 0.0047)
- Mild discomfort was the only adverse event with higher prevalence for TOMAC than sham.

sleepmedicine

Efficacy and safety of tonic motor activation (TOMAC) for restless legs syndrome as adjunctive and monotherapy: An individual participant data systematic review and meta-analysis

Elias G. Karroum [a,*], Cornelius G. Bachmann [b,c], Amy Bronstone [d], Leavitt Morrison [e]





SLEEP and Breathing
International Journal of the Science and Practice of Sleep Medicine

Neuromodulation for Restless Legs Syndrome: A Systematic Review and Mechanistic Considerations for Spinal Cord Stimulation

Garrett W. Thrash[1] · Elijah Wang[1] · David Brockington[1] · Colby Rives[1] · Yifei Sun[1] · Anne C. Roberts[1] · Somnath Das[2] · Julie G. Pilitsis[3] · Prasad Shirvalkar[4] · Rocio Vazquez do Campo[5] · Harrison C. Walker[2,5] · Christopher J. Earley[6] · Marshall T Holland[2]

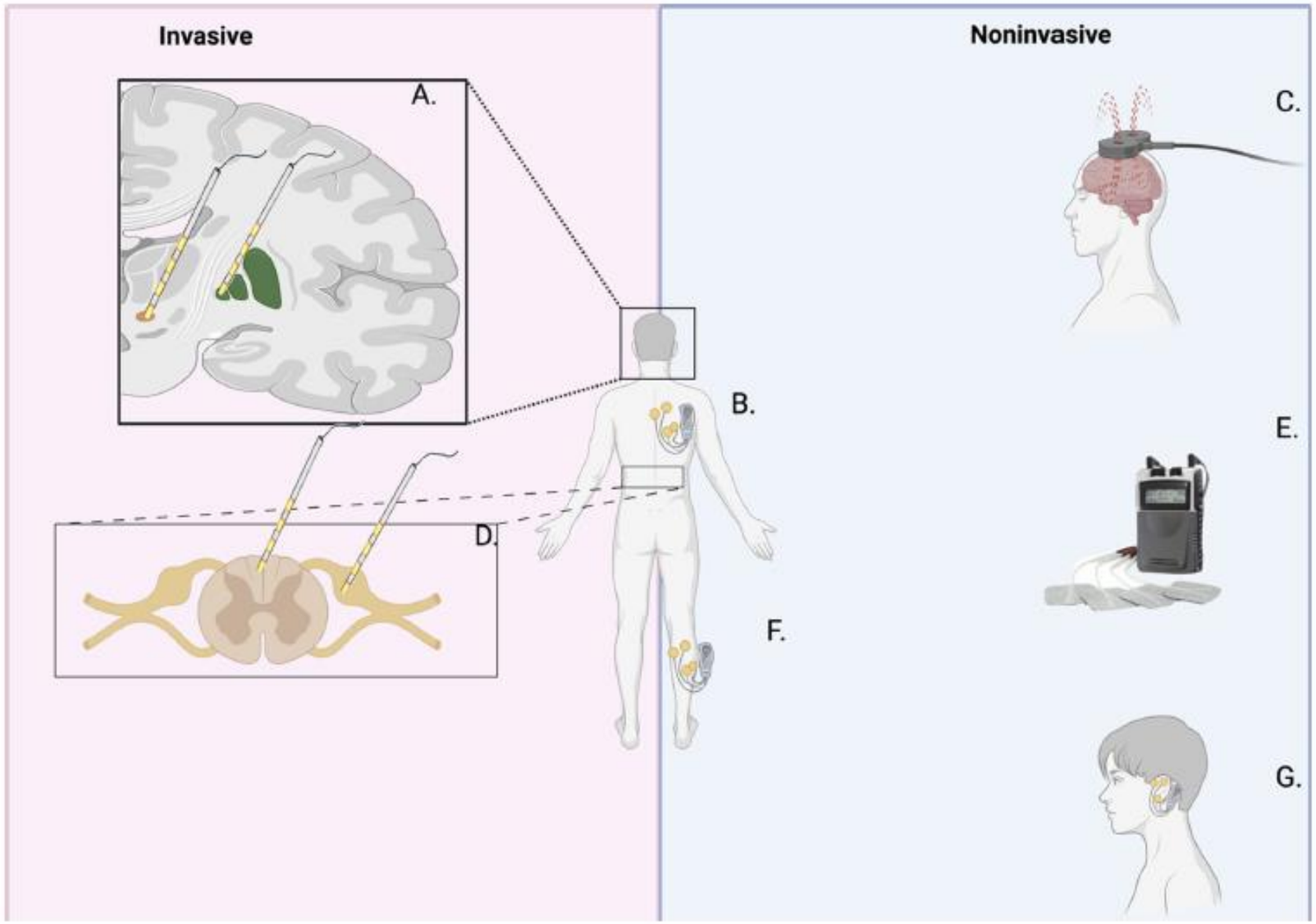
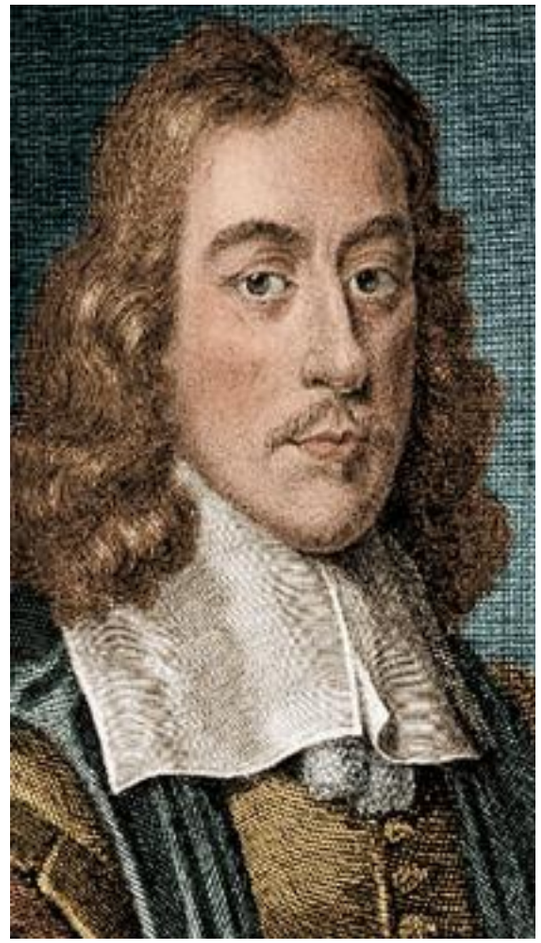


Fig. 1 Illustration of Neuromodulatory modalities to treat RLS. **A** Deep brain stimulation (DBS) in the STN (orange) and GPi of the lentiform nucleus (Green). **B** Transcutaneous spinal direct current stimulation (tsDCS). **C** Transcranial magnetic stimulation (TMS). **D** Dorsal root ganglion (DRG) stimulation and spinal cord stimulation (SCS). **E** Transcutaneous electric stimulation (TENS) of the affected leg. **F** Non-invasive peripheral nerve stimulation (NPNS) of the peroneal nerve. **G** TVNS using an earpiece

"When in bed…they betake (try) themselves to sleep."

"In the arms and legs, leapings and contractions of the tendons,"

"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."



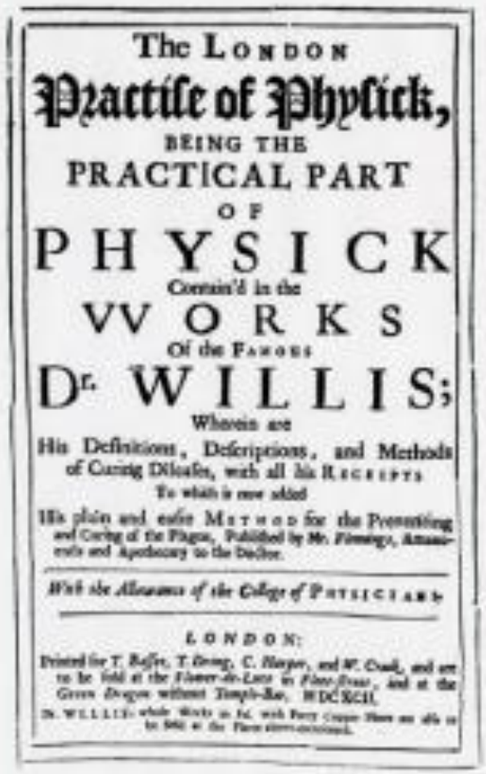
Thomas Willis 1685

-

A BRIEF HISTORY

From "The Watching Evil" to the modern identification of RLS





The LONDON
Practice of Physick,
BEING THE
PRACTICAL PART
OF
PHYSICK
Contain'd in the
VVORKS
Of the FAMOUS
Dr. WILLIS;
Wherein are
His Definitions, Descriptions, and Methods of Curing Diseases, with all his RECEIPTS
To which is now added
His plain and easie METHOD for the Preventing and Curing of the Plague, Published by Mr. Pinnegar, Almanack-maker and Apothecary to the Doctor.
With the Allowance of the College of PHYSICIANS
LONDON:
Printed for T. Basset, T. Dring, C. Harper, and W. Crook, and are to be Sold at the Flower-de-Luce in Fleet-street, and at the Green Dragon without Temple-Bar. MDCXCII.

Wherefore to ſome, when being a Bed they betake themſelves to ſleep, preſently in the Arms and Legs, 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.

A condition like a torture that prevented its sufferers' sleep was first described by Dr. Thomas Willis in 1685. "The Watching Evil," or insomnia, was the result of "a great restlessness" of the arms and legs. While the disorder was given its modern title, Restless Legs Syndrome, by Karl-Axel Ekbom in a Swedish journal in 1945, it remains largely undiagnosed today.



7% of the population
More common with aging

Prospective study of restless legs syndrome and mortality among men

Yanping Li, PhD
Wei Wang, MD, PhD
John W. Winkelman, MD, PhD
Atul Malhotra, MD
Jing Ma, MD, PhD
Xiang Gao, MD, PhD

ABSTRACT

Objective: To prospectively examine whether men with restless legs syndrome (RLS) had an increased risk of mortality.

Method: This was a prospective cohort study of 18,425 US men free of diabetes, arthritis, and renal failure in the Health Professionals Follow-up Study (HPFS). In 2002, RLS was assessed using a set of standardized questions. Deaths were identified from state vital statistics records, the National Death Index, family reports, and the postal system

Men have a slightly higher mortality

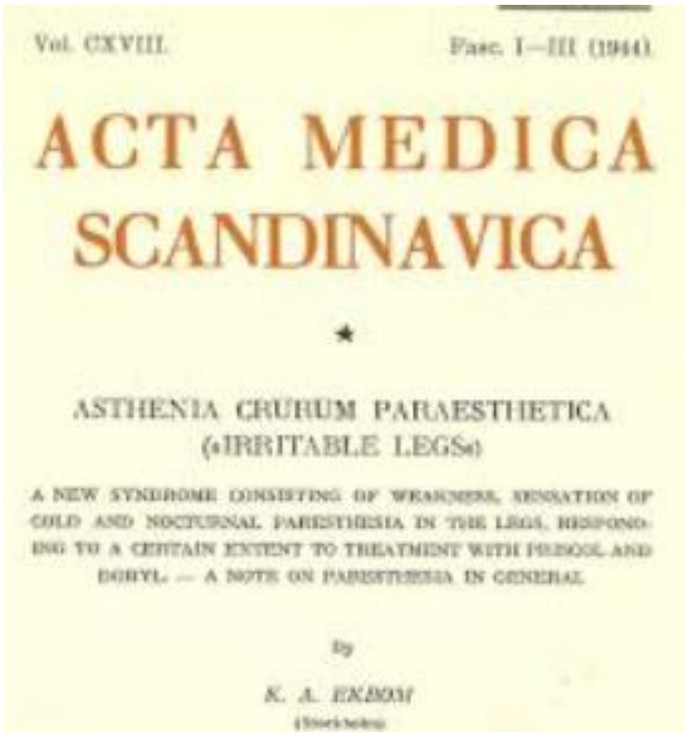
Willis-Ekbom Disease



Thomas Willis
1621-1675



Karl Axel Ekbom
1907-1977



Vol. CXVIII. Fasc. I—III (1944)

ACTA MEDICA SCANDINAVICA

★

ASTHENIA CRURUM PARAESTHETICA
(»IRRITABLE LEGS«)

A NEW SYNDROME CONSISTING OF WEAKNESS, SENSATION OF COLD AND NOCTURNAL PARESTHESIA IN THE LEGS, RESPONDING TO A CERTAIN EXTENT TO TREATMENT WITH PERVOL AND DORYL — A NOTE ON PARESTHESIA IN GENERAL

by

K. A. EKBOM

Ekbom, Acta Medica Scandinavica, 1945

Restless legs syndrome diagnostic criteria from the international RLS Study Group (2011)

Essential

An urge to move legs usually but not always accompanied by or felt to be caused by uncomfortable sensations in the legs

The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting

The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, as long as that activity continues

The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day

The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioural condition (eg, myalgia, venous stasis, leg oedema, arthritis, leg cramps, positional discomfort, habitual foot tapping)

Australian Doctor 2013

Descriptors of restless legs syndrome sensations

Samantha Kerr [a,b,*], Warrick McKinon [b], Alison Bentley [a]

Sleep Medicine 13 (2012) 409–413

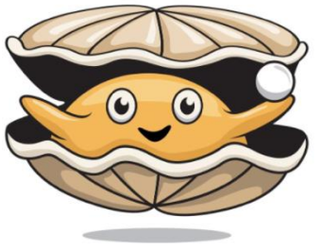
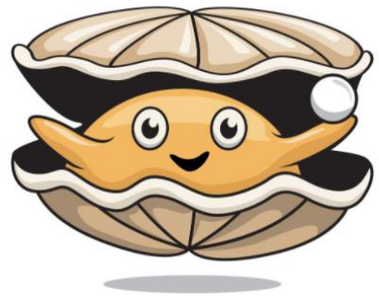


Table 2

The eight most frequent words given by RLS participants ($n = 41$) when asked to describe their RLS sensations spontaneously, prompted with words from a literature derived list of RLS descriptors, and asked to choose words from the McGill Pain Questionnaire (MPQ).

TOP "8" words (% of participants that offered/chose the word)					
Spontaneous words (%)		Prompted words (%)		MPQ words (%)	
Irritating	17	Restless	88	Tingling	56
Painful	17	Uncomfortable	78	Jumping	54
Crawling	15	Twitchy	63	Nagging	51
Uncomfortable	15	Unpleasant	59	Tiring	44
Discomfort	12	Irritating	56	Annoying	41
Restless	10	Nagging	56	Tugging	39
Tingling	10	Fidgety	46	Dull	34
Twitching	10	Jerky	46	Gnawing	29

Restless Legs Syndrome



“Can’t get comfortable”

“Can’t fall asleep”

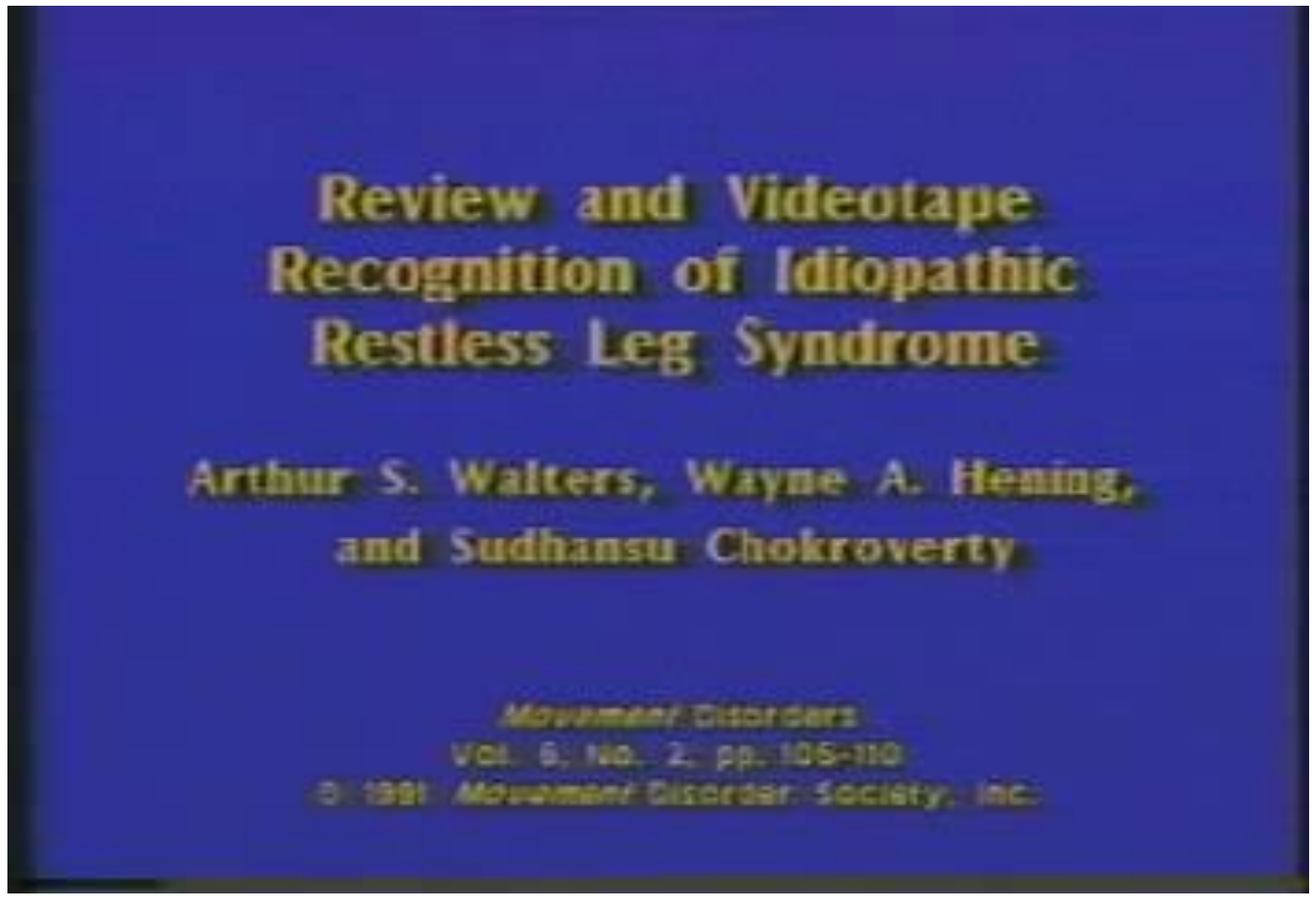
Wake up and feel “antsy”

“Crampy, itchy calves”

“Tingling in legs”

“Dread going to bed at night”

Avoid long car rides or airplanes



Allen R, et al. Sleep Med 2003, 4:101–119.

Brain Iron Content in RLS

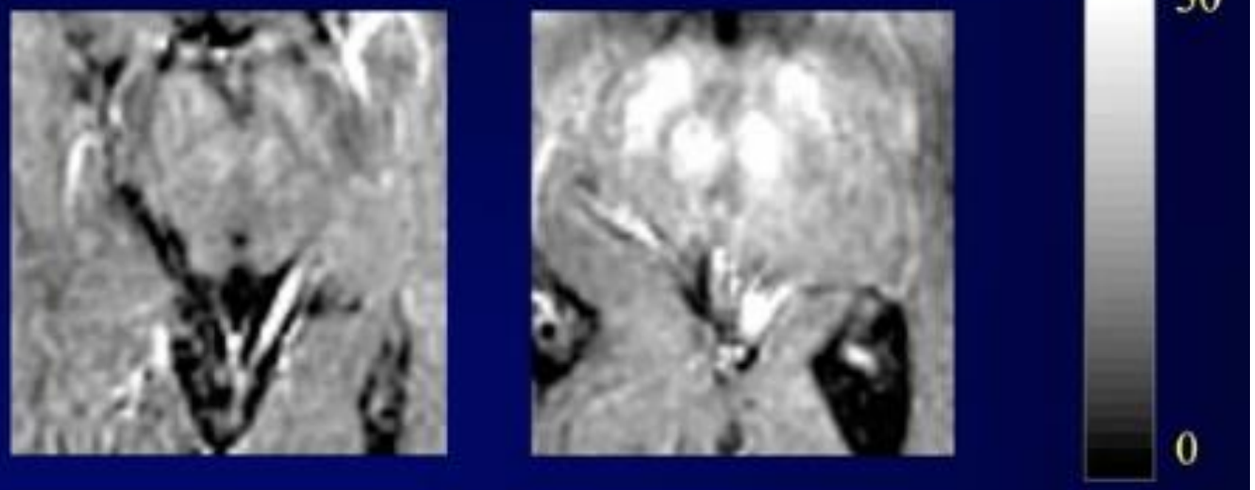
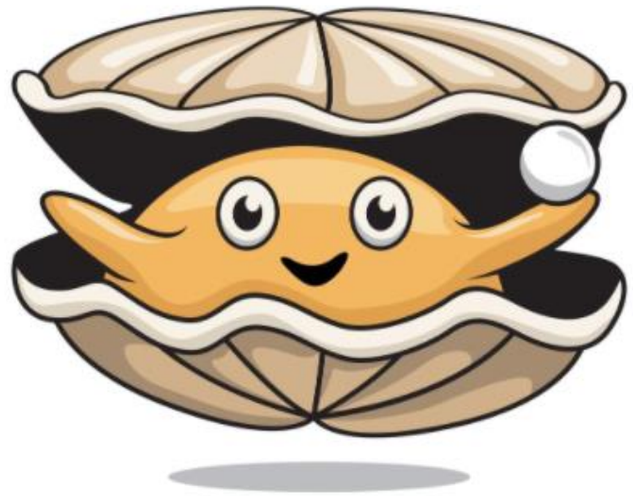


Figure 2. R2* images in (A) a 70 year old RLS patient and (B) a 71 year old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both red nucleus and substantia nigra. (Allen RP, Earley CJ and Barker P Johns Hopkins Univ.



Ondo 2023

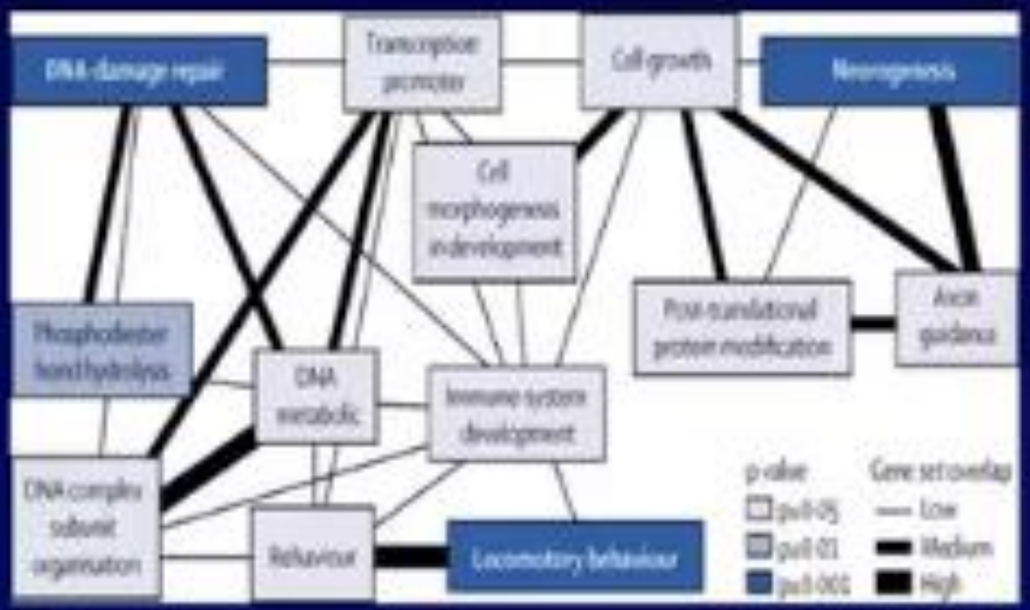
Dopamine PET / SPECT Studies

NO EVIDENCE OF DOPAMINE DEFICIENCY

SOME EVIDENCE FOR INCREASED DOPAMINE TURNOVER

- Dopamine transporter protein
  - 3 SPECT normal studies, one PET abnormal
- ^{18}F-dopa PET
  - 2/3 Studies : mild striatal reduction
- ^{11}C-raclopride
  - mild striatal reduction
- ^{123}I-iodobenzamide SPECT
  - ½ studies: mild reduced striatal D_2 binding

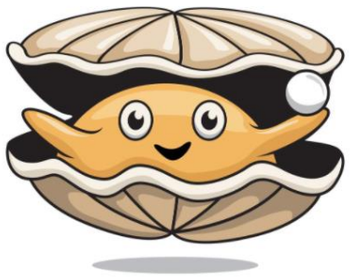
What Do These Genes Do?



- Mostly in CNS
- CNS development
- Synaptic and Axon Formation / Control/ Guidance
- DNA repair

MEIS1 Knock-out losses circadian pattern and hyperactive

Ondo 2023



Is it primary RLS or secondary RLS?

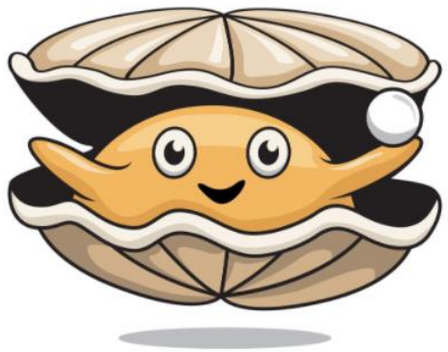
- Very common to be a primary central nervous system related disease.
- Familial 25-75%
- Can have autosomal dominant or recessive pattern
- If in the family, usually presents before age 45
- Familial has slower disease progression.

Table 1: Secondary causes of RLS	
Patient	**Prevalence in patient population**
General population	7%
Pregnancy	13.5%
Iron deficiency anaemia	31%
Renal failure	21%
Polyneuropathies	20%
Parkinson's disease	20%
Rheumatoid arthritis/systemic sclerosis	25%
Coeliac disease	31%
Multiple sclerosis	29%
Spinocerebellar ataxia (SCA3)	45%
Medications such as SSRIs, TCAs, lithium, anticonvulsants, metoclopramide, antipsychotics	-

Australian Doctor 2013

Table 2: Mimics	
Condition	**Distinguishing features**
Nocturnal leg cramps	Calves only, painful. Urge to move legs is confined to stretching out the cramp. More sudden in onset and brief duration
Radiculopathy	One-sided, positional not just with rest, radiation from back
Painful neuropathy	Can be nocturnal, sensory symptoms or numbness. Neurological signs include loss of vibration and ankle jerks
Akathisia	Motor restlessness. Related to neuroleptic exposure, absence of pain, affects whole body and present throughout day
Vascular/neurogenic claudication	Opposite pattern, worse with walking/ standing. Nil circadian pattern
Venous insufficiency	Evidence of venous hypertension — discolouration, varicose veins, oedema. Present throughout day and preference for leg elevation
Pressure-related symptoms	Short duration, relief with change in position. Affects arms as well as legs. Often unilateral. Normal phenomenon
Others: Inflammatory arthritis, erythromelalgia, complex regional pain syndrome	Difficult to confuse with RLS. Continuous in nature

Australian Doctor 2013



Associated features

Dopaminergic responsiveness

Presence of periodic limb movements in sleep or in wakefulness

Positive family history

Usually progressive clinical course

Normal neurological examination in the idiopathic form

Sleep disturbance

Australian Doctor 2013

Sensations in Restless Legs Syndrome

Table 2
Reported verbal descriptors for the restless legs syndrome sensations ($n = 56$ patients).

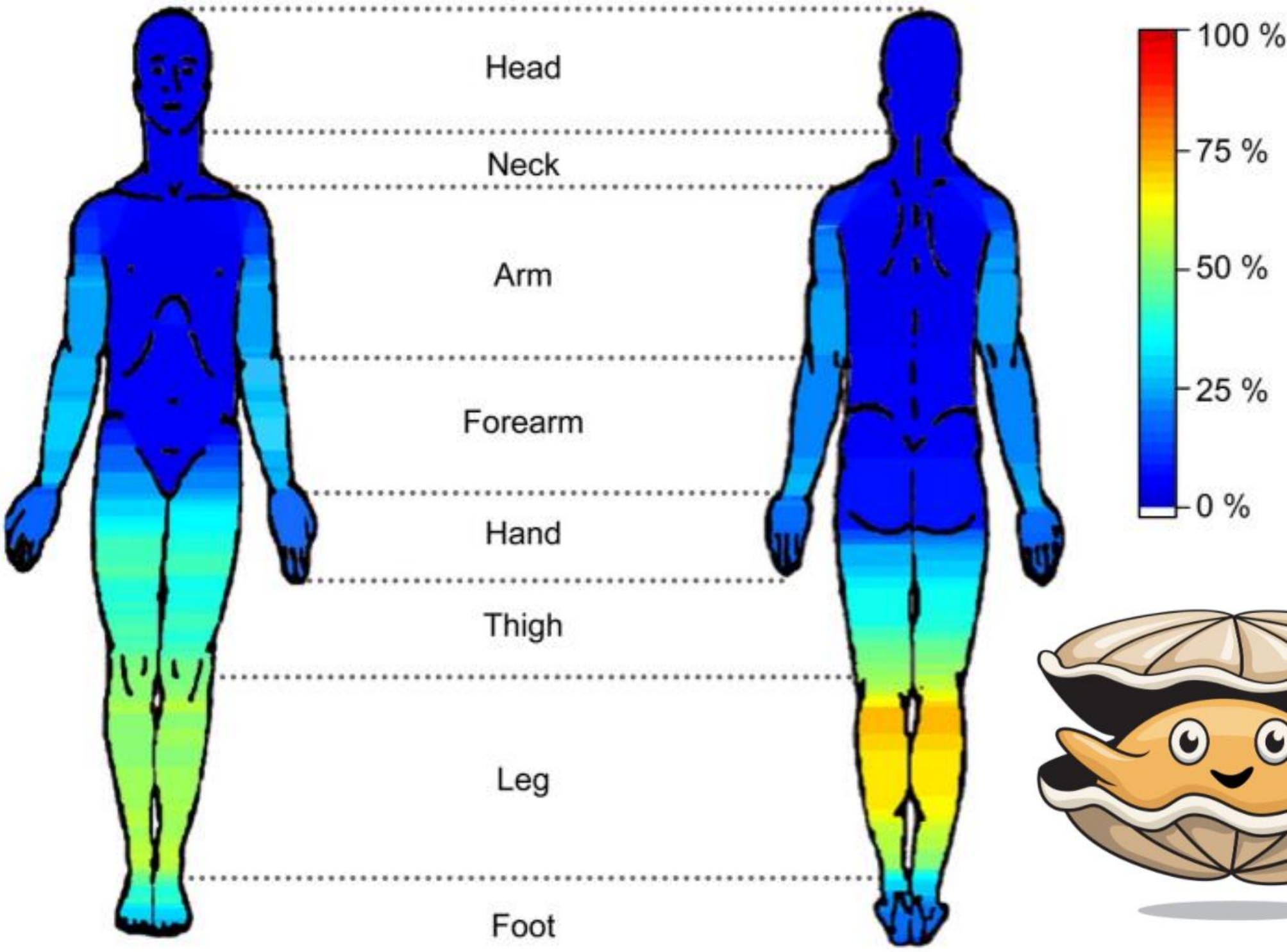
French descriptors Descriptifs sensoriels	English translation Sensory descriptors	Percentage (frequency) 95% (53)
Electriques	Electrical	43% (24)
Picotements	Prickling	30% (17)
Brûlure	Burning	29% (16)
Fourmillement	Tingling	27% (15)
Démangeaisons	Itching	14% (8)
Contraction	Contraction	9% (5)
Lourdeur	Heaviness	7% (4)
Pression	Pressure	7% (4)
Tension	Tenseness	7% (4)
Tiraillement	Tugging	7% (4)
Chaleur	Heat	5% (3)
Courbatures	Aching	5% (3)

Karroum et al. *Sleep Medicine* 2012;13:402

Topography of the sensations in primary restless legs syndrome

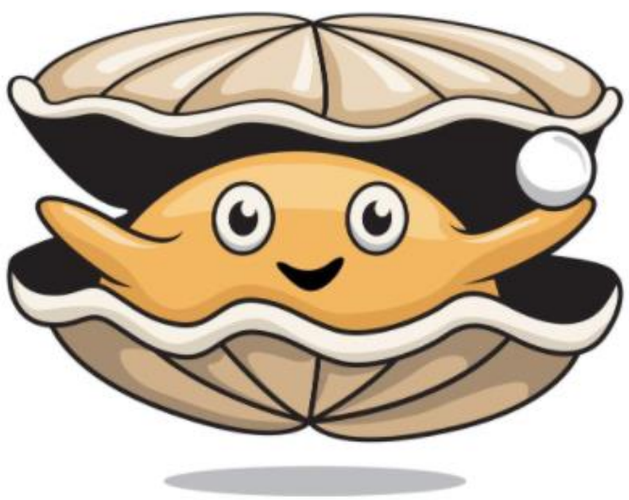
Elias Georges Karroum, Smaranda Leu-Semenescu, Isabelle Arnulf *

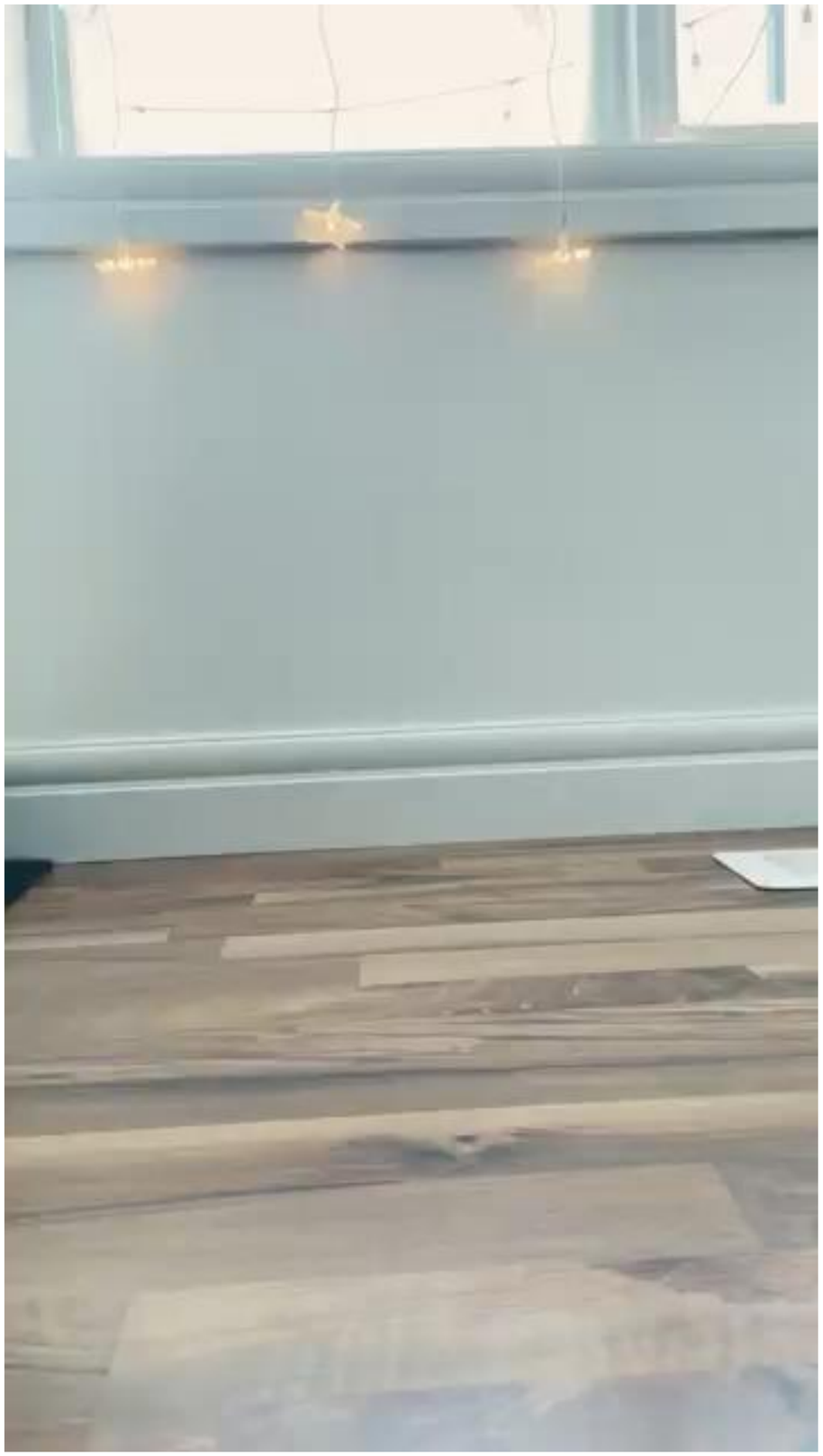
Journal of the Neurological Sciences xxx (2012) xxx–xxx



RLS is not **akathisia**

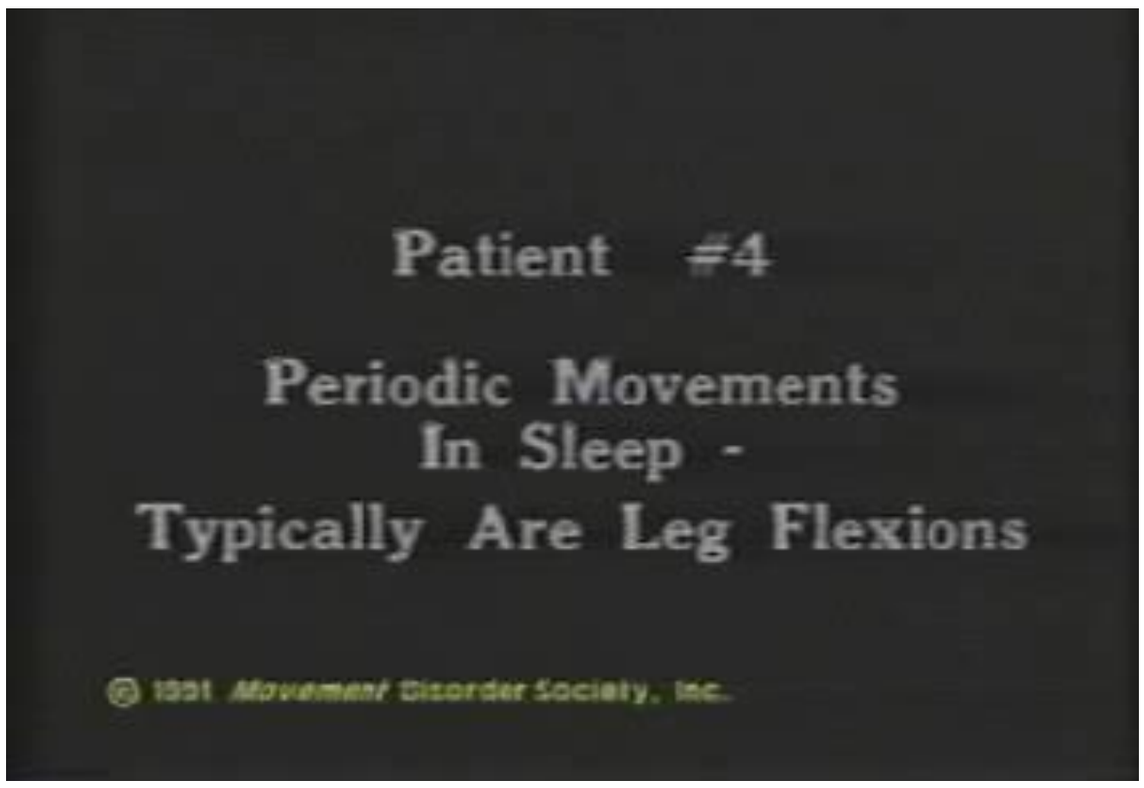
Pure restlessness
Not leg discomfort
Not (predominantly) at night
Common w/ drugs

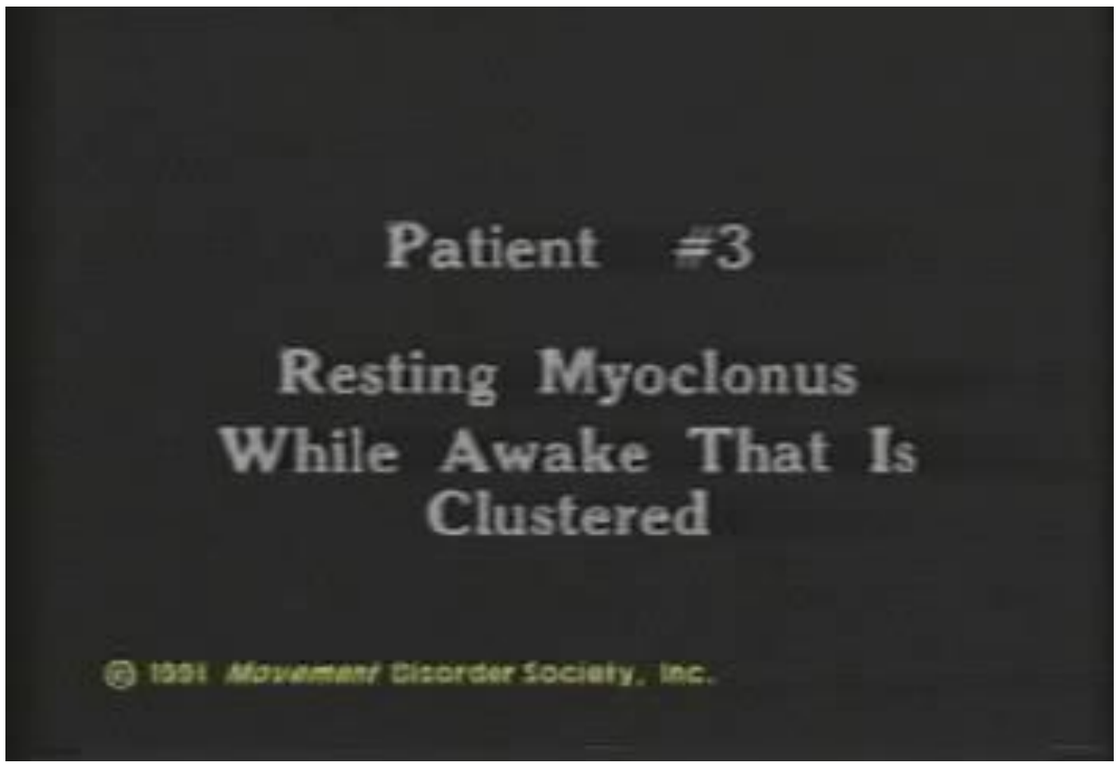




Living Well with Schizophrenia
https://www.youtube.com/watch?v=BvcvzdJS5FM&ab_channel=LivingWellwithSchizophrenia

Periodic Limb Movements in Sleep





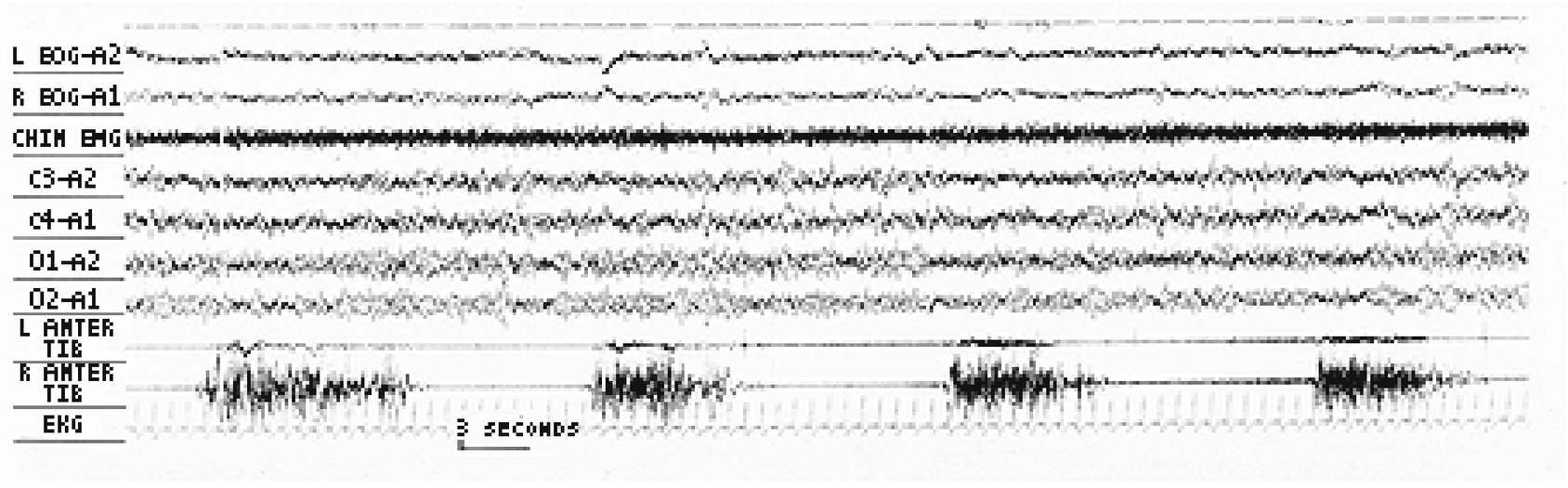


Table 2. Similarities between Restless Legs Syndrome and Periodic Limb Movements during Sleep

	Restless Legs Syndrome	Periodic Limb Movements During Sleep
Pathophysiology	• Possibly involvement of A11 dopaminergic system, which is located in the spinal cord.[19] • Decreased dopamine-2 receptor expression in putamen.[22]	• Emerge likely spinal cord generator as evidenced by pattern of recruitment of muscles, which is rostral to caudal or caudal to rostral in lumbar and sacral myotomes.[17] • Decreased urinary dopamine.[23]
Pharmacology	• Symptoms of RLS are decreased by dopamine agonists.[24] • D3-receptor agonists more effective than D2-receptor agonists.[27] • Symptom worsening by antidepressants.[30]	• PLMS are decreased by dopamine agonists.[25,26] • D3-receptor agonists more effective than D2-receptor agonists.[27] • PLMS become more frequent with antidepressants.[28]
Genetics	• Associated with BTBD9.[31] • TOX3/BC034767.[32] • MEIS1.[32] • MAP2K5/SKOR1.[32] • PTPRD.[33]	• Associated with BTBD9.[31] • TOX3/BC034767.[34] • MEIS1.[34] • MAP2K5/SKOR1.[34] • PTPRD.[34]
Epidemiology	• Around 10% prevalence.[36] • More common in older individuals	• Around 10% prevalence.[4] • More common in older individuals

Abbreviations: MAP2KD, Mitogen-Activated Protein Kinase Kinase 5; PLMS, Periodic Limb Movements during Sleep; PTPRD, Protein Tyrosine Phosphatase Receptor Type D; RLS, Restless Legs Syndrome.



Periodic Limb Movements of Sleep (PLMS)

- Periodic movements in sleep (PMS)
- Periodic limb movement disorder (PLMD)
- Periodic leg movements (PLM)
- Nocturnal myoclonus

Heartbeat International

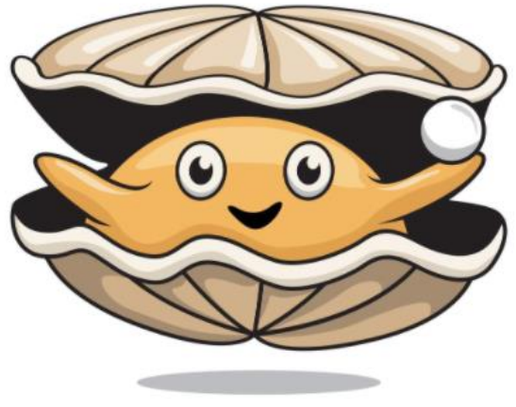
PLMS Pearls

* In 80% of folks with RLS
* 30% of population over 50

- Flexion hips, knees and ankles
- Flexion lasts 0.5-5.0 secs
- Dorsiflexion big toe and/or foot
- Unilateral or bilateral
- Intervals can range 5-90 secs
- ~20-40 secs is most common
- Daytime somnolence, ‘kicking sleep’

RLS, Iron and iron therapy in one slide

- Can’t measure iron stores in blood well
- Measure serum ferritin
- Measure percentage transferrin saturation
- Want iron level above 75mcg/dL



- Don’t administer iron more than once a day and maybe consider every other day (improve absorption)
- IV iron (Why: low iron stores, iron deficient, malabsorption, intolerant to oral iron, severe RLS needing to replenish fast)

- Strongest evidence ferric carboxymaltose infusion (do not use iron sucrose IV)
- Many experts use oral ferrous gluconate, ferrous sucrose

Received: 5 January 2024 | Revised: 23 February 2024 | Accepted: 4 March 2024
DOI: 10.1002/ajh.27290

RESEARCH ARTICLE

A randomized double-blind pilot study to evaluate the efficacy, safety, and tolerability of intravenous iron versus oral iron for the treatment of restless legs syndrome in patients with iron deficiency anemia

Vanessa Short[1] | Richard Allen[2†] | Christopher J. Earley[2] | Huzefa Bahrain[3] | Stella Rineer[3] | Kiumarce Kashi[4] | Jesse Gerb[3] | Michael Auerbach[3,5]



Oral ferrous sulfate vs IV ferumoxytol

No difference between IV or oral iron replacement

IV had self-limited musculoskeletal symptoms
the day following the infusion.

Oral group: tended to have more gastrointestinal perturbations.

	IV iron mean (SD)	Oral iron mean (SD)	*p*-Value[a]
Change in IRLSS score	$n = 48$	$n = 46$	.27
	−7.9 (8.7)	−10.1 (10.4)	
CGI-I score at Week 6	$n = 28$	$n = 28$	.70
	2.0 (1.2)	1.9 (1.3)	
Change in PGI-S score	$n = 30$	$n = 27$	.35
	−1.7 (1.8)	−2.1 (1.8)	
Change in hemoglobin, g/dL	$n = 36$	$n = 32$	.22
	1.2 (1.3)	1.7 (1.8)	
Change in MCV, fL	$n = 36$	$n = 33$	.10
	4.0 (5.9)	6.5 (6.4)	
Change in iron, μg/dL	$n = 35$	$n = 31$	.87
	36.8 (21.8)	35.3 (50.3)	
Change in ferritin, μg/L	$n = 34$	$n = 33$	<.0001
	200.3 (133.0)	23.3 (21.2)	
Change in TSAT, %	$n = 35$	$n = 33$	.17
	16.5 (7.5)	12.2 (16.3)	
Change in TIBC, μg/dL	$n = 35$	$n = 32$	.004
	−105.7 (60.4)|	−64.3 (52.5)	

Jadidi *et al.*
BMC Complementary Medicine and Therapies (2023) 23:1
https://doi.org/10.1186/s12906-022-03814-8

BMC Complementary
Medicine and Therapies

RESEARCH Open Access

Therapeutic effects of magnesium and vitamin B6 in alleviating the symptoms of restless legs syndrome: a randomized controlled clinical trial

Ali Jadidi[1,2*], Alireza Rezaei Ashtiani[3], Ali Khanmohamadi Hezaveh[4] and Seyed Mohamad Aghaepour[4]



- Single-blind for at least three months.
- 75 patients
- 40 mg vitamin B6 or 250 mg magnesium oxide or placebo.
- No difference in sleep quality and disease severity at month 1.
- Month 2: significant improvement.
- Safe dose for adults 60-80mg maximum (remember to include amount in a multi-vitamin).



2023

sleepmedicine

Ferric carboxymaltose effects on restless legs syndrome and on brain iron in patients with iron deficiency anemia

Hyoeun Bae [a], Yong Won Cho [b, *], Keun Tae Kim [b], Xu Li [c, d], Christopher J. Earley [e]

- Randomized, double-blind placebo-controlled.
- 1500 mg FCM vs. placebo.
- 18 RLS patients for 6 weeks
- RLS improved
- MRI Imaging: R2* techniques showed a treatment effect for the thalamus and the QSM technique for both the substantia nigra and pulvinar

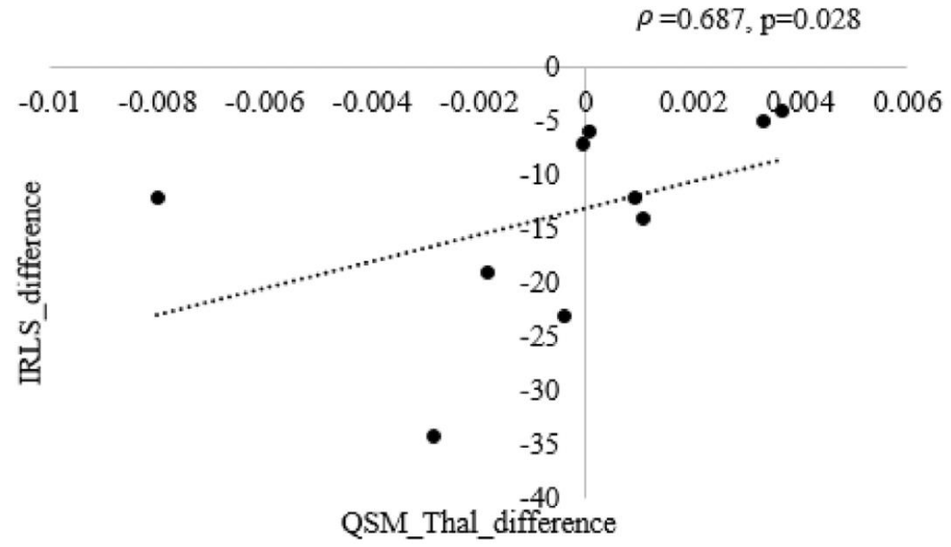


Fig. 1. Correlation of IRLS difference and QSM measured thalamus difference in FCM group.

JAMDA
The Journal of Post-Acute and Long-Term Care Medicine

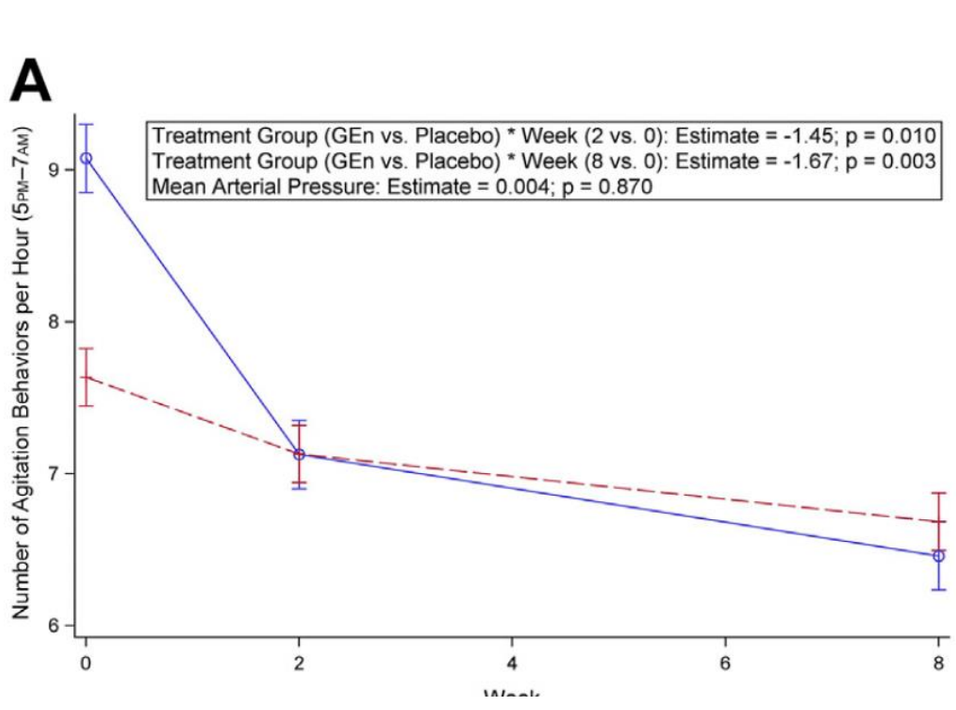


Original Study

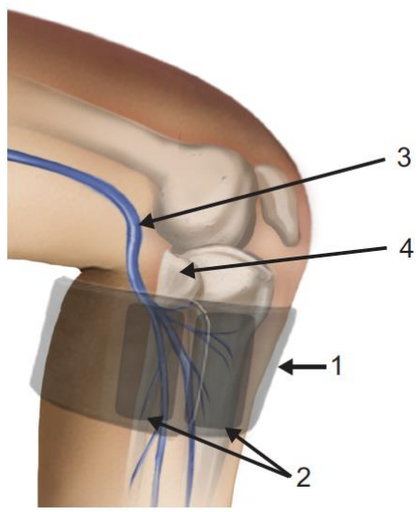
Treatment of Restless Legs Syndrome Improves Agitation and Sleep in Persons with Dementia: A Randomized Trial

Kathy C. Richards PhD, RN [a,*], Liam M. Fry MD [b], Alicia J. Lozano MS [c], Wenyan Ji MA [c], Janet D. Morrison PhD, RN [a], Katherine C. Britt PhD, RN [d], Donald L. Bliwise PhD [e], Nalaka S. Gooneratne MD, MSc [f], Alexandra L. Hanlon PhD [c]

- Double-blind and placebo-controlled in dementia + RLS
- Gabapentin enacarbil (GEn) (Horizant) or placebo
- Baseline to 8 weeks in nighttime agitation on the Cohen-Mansfield Agitation Inventory Index
- Nighttime agitation, by group over time significant at 2 and 8 weeks
- Observed nighttime wake by group over time significant at 2 and 8 weeks
- GEn group trended toward more falls



SLEEP, 2023, 46, 1–11
https://doi.org/10.1093/sleep/zsad190
Advance access publication 17 July 2023
Original Article



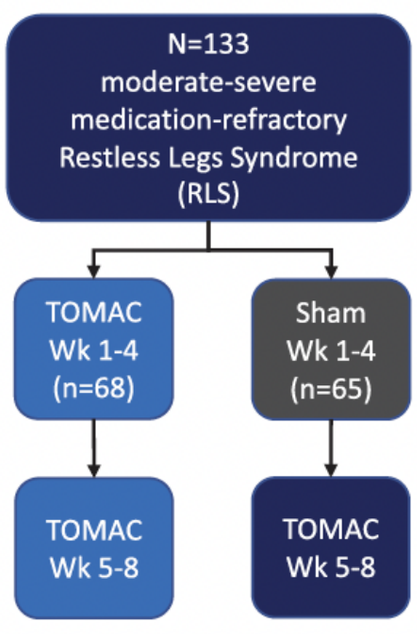


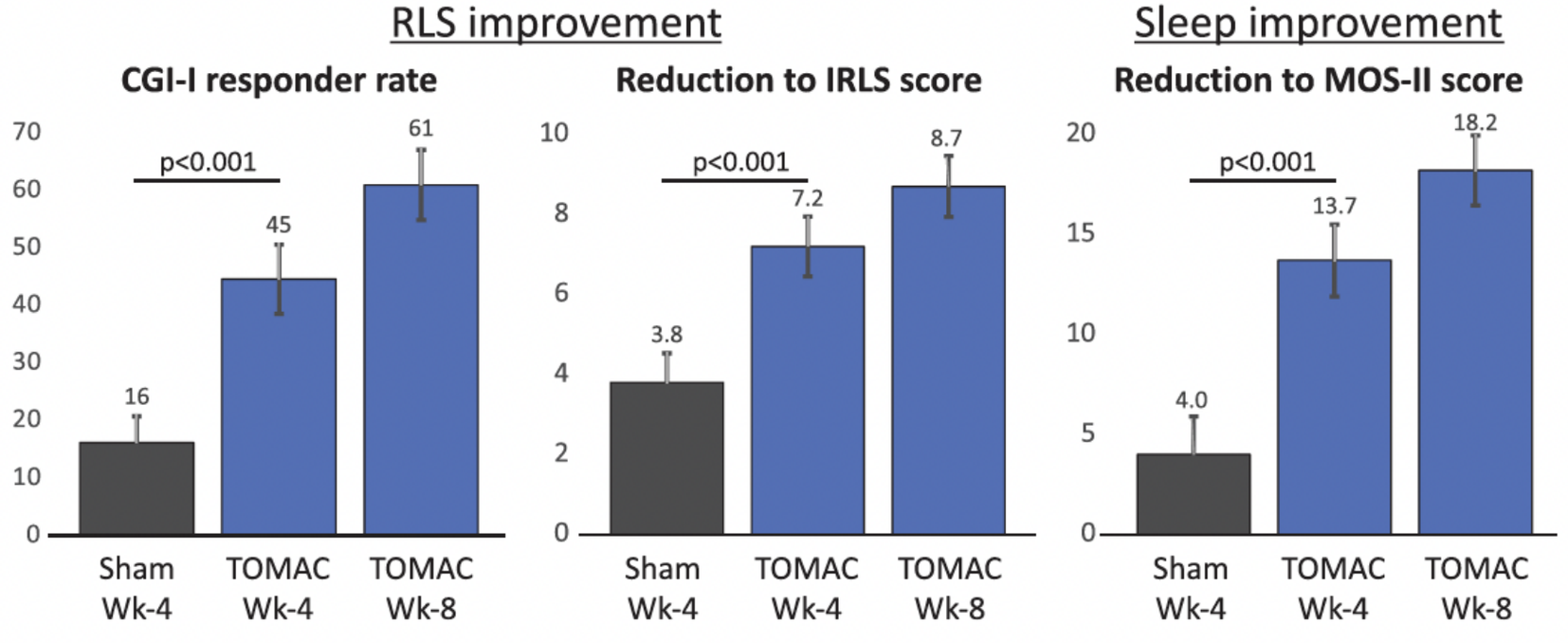
2023

Original Article

Efficacy and safety of tonic motor activation (TOMAC) for medication-refractory restless legs syndrome: a randomized clinical trial

Richard K. Bogan[1], Asim Roy[2], Jerrold Kram[3], Joseph Ojile[4], Russell Rosenberg[5], J. Douglas Hudson[6], H. Samuel Scheuller[7], John W. Winkelman[8] and Jonathan D. Charlesworth[9,*]





Augmentation

- Worsening of symptoms after initial therapeutic benefit not accounted for by other factors
- Earlier onset of symptoms (<4 hours) OR,
- Earlier onset of symptoms (>2 hours) AND one
  - Shorter latency to symptoms when at rest
  - Extension to other body parts
  - Greater intensity
  - Less relief from treatment

Ondo, 2024



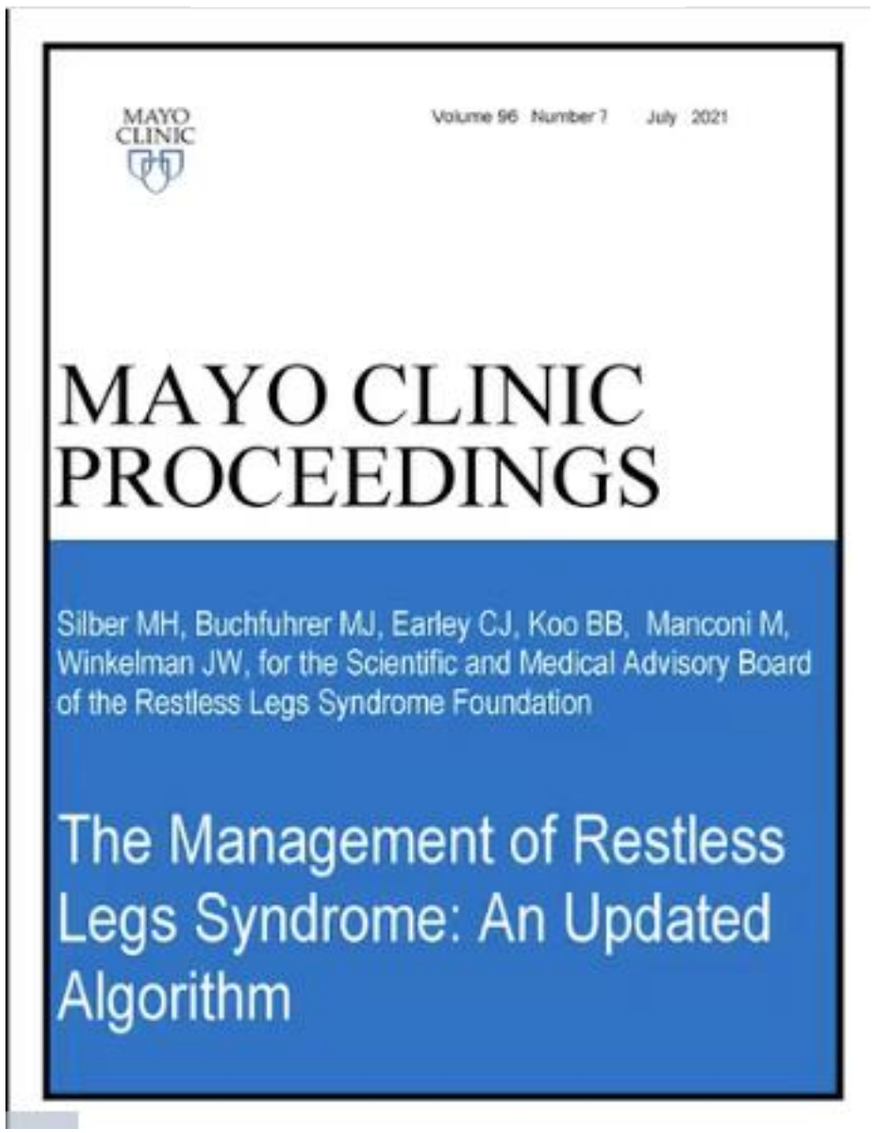
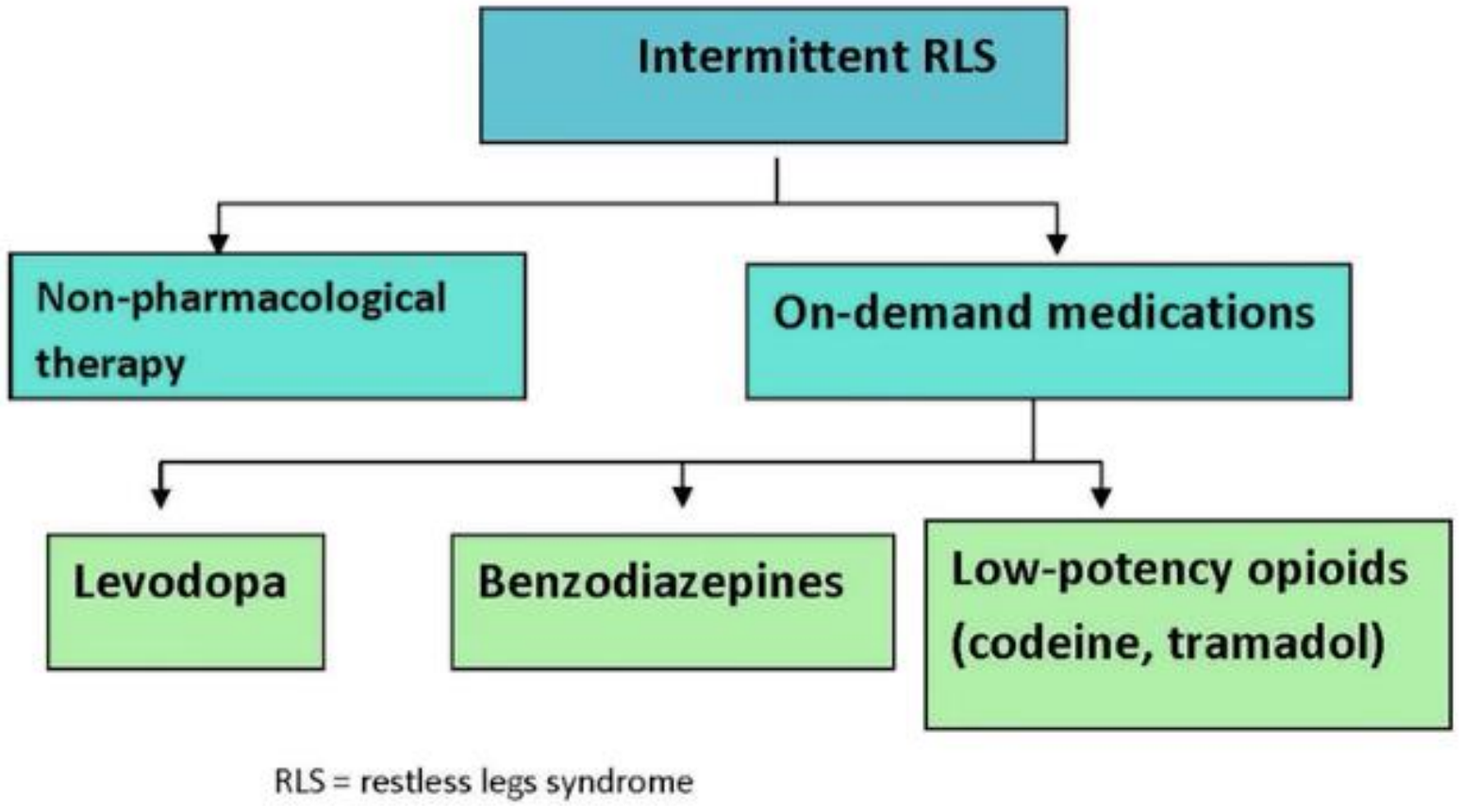


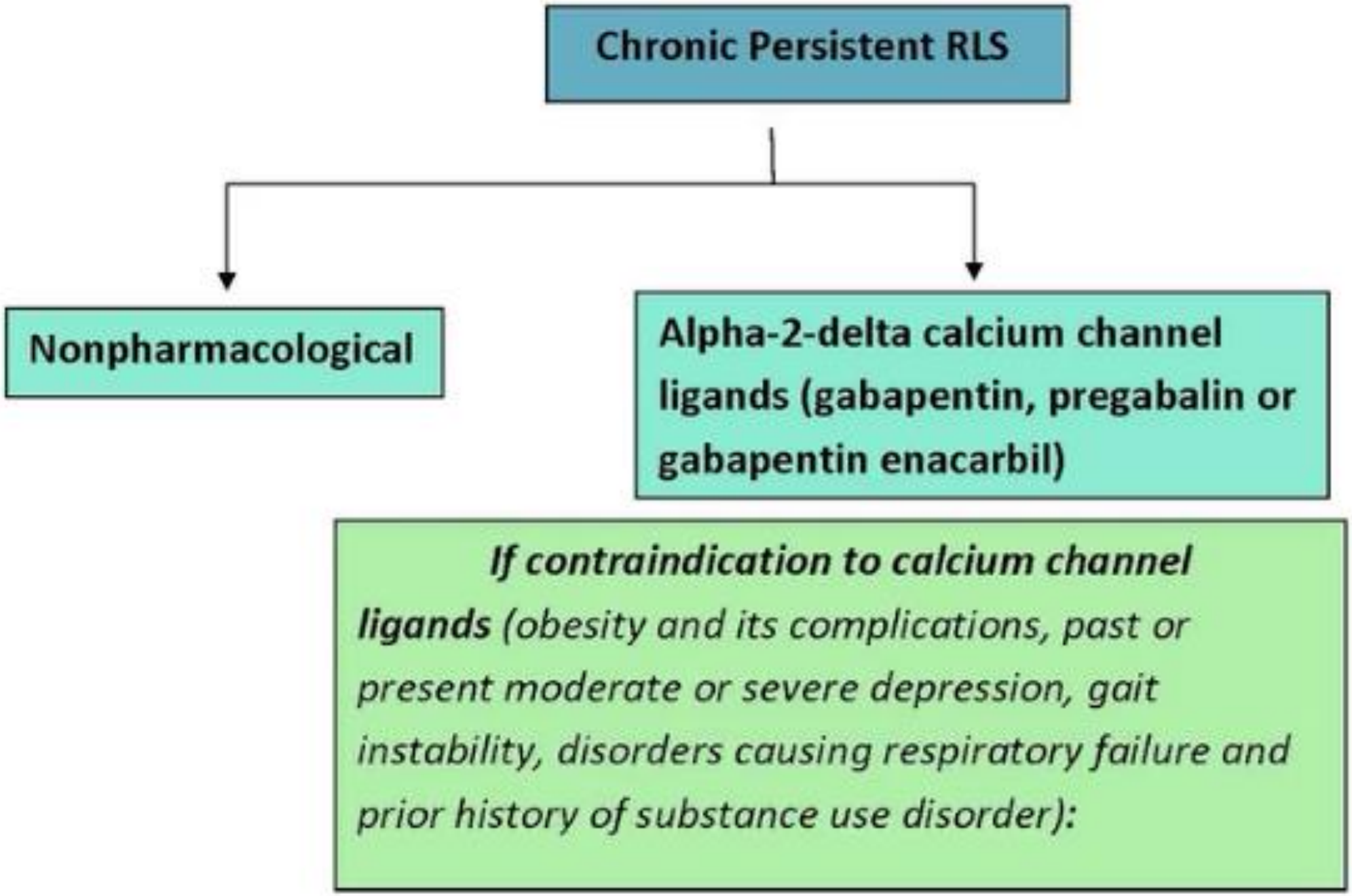
Figure 1 Approach to the Management of Intermittent RLS



RLS = restless legs syndrome

Silbur, 2024

Figure 2 Approach to the Management of Chronic Persistent RLS

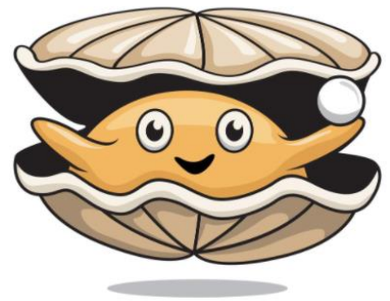


RLS = restless legs syndrome

Silbur, 2024

Peripheral Movement Disorders

Hemifacial spasm in one slide



- Intermittent twitching of muscles innervated by the facial nerve
- Synkinesis
- Twitching occurs in flurries and contraction can become tonic
- Twitching is spontaneous and is made worse by voluntary movement, stress, fatigue, anxiety
- In chronic cases, there may be some muscle weakness
- Women more commonly affected than men (3:2)
- Onset between 2nd and 8th decades, mean 45-50 years
- Begins around the eye in 90% of cases
- Rarely bilateral, and then not synchronous on the two sides
- Treat with carbamazepine, botulinum toxin, surgery



Left hemifacial spasm

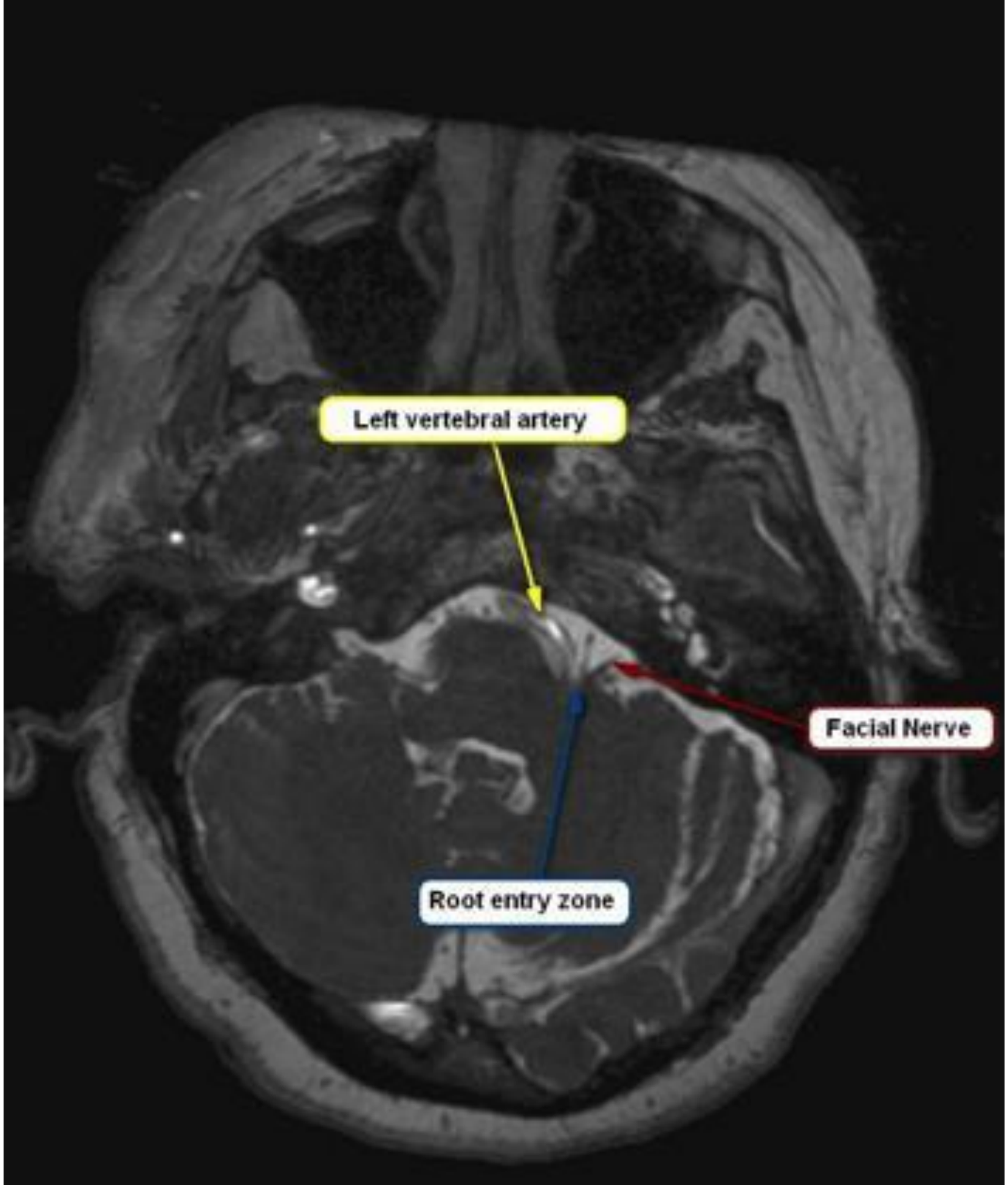
Paradoxical raising of the eyebrow as the eye closes

The “other” Babinski sign.

Devoize, JNNP 2001;70:516



Patient from Jankovic


Left vertebral artery
Facial Nerve
Root entry zone

The New York Times

January 15, 2010



Doug Mills/The New York Times

TWITTER

SIGN IN TO RECOMMEND

President Obama, sitting next to Speaker Nancy Pelosi on Capitol Hill, gave a wink to a House member before his remarks.

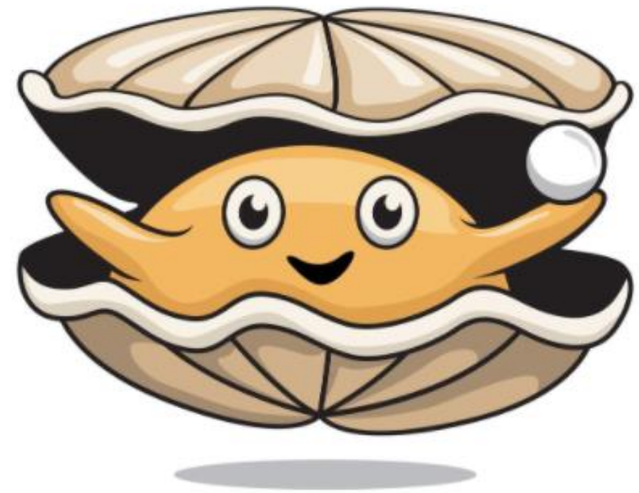
The Many Faces of Hemifacial Spasm: Differential Diagnosis of Unilateral Facial Spasms

Movement Disorders, Vol. 26, No. 9, 2011

Toby C. Yaltho, MD[1] and Joseph Jankovic, MD*

Classification	n	Sex (M/F)	Age at onset (y)
1. Idiopathic	133 (62%)	48/85	55.4 ± 15.0
2. Familial	4 (1.9%)	2/2	49.5 ± 32.0
3. Bell's palsy	23 (11%)	5/18	53.7 ± 17.7
4. Facial nerve injury	13 (6%)	2/11	46.8 ± 16.0
5. Brain vascular insult	2 (1%)	1/1	72 and 72
6. Demyelinating	2 (1%)	1/1	55 and 64
7. Psychogenic	16 (7.4%)	1/15	37.4 ± 19.5
8. Facial tics	14 (6.5%)	10/4	33.9 ± 22.2
9. Facial dystonia	5 (2.3%)	2/3	52.8 ± 8.1
10. Facial myoclonus	2 (1%)	0/2	20 and 5
11. Hemimasticatory spasm	1	F	59

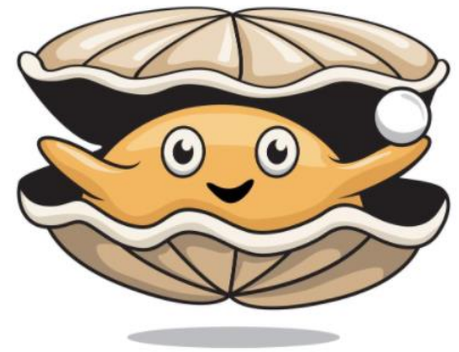
Pearl: Get an MRI



- Vascular compression 94%
- Tumor 4%
- Bony lesion or structural abnormality
- Secondary, e.g., Bell's palsy, stroke, infection

Jumpy stumps (jactitation)

- Painful, jumpy stump
  - Spontaneous or action induced
- Participating in tardive dyskinesia
- Phantom dyskinesia
  - Metoclopramide induced





Morgan et al, 2017
MDCP

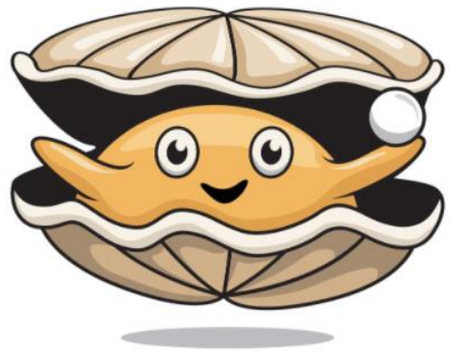




Jacques et Stine

1.34K subscribers

Painful Legs and Moving Toes



- Severe pain: aching, burning, crushing, throbbing, searing, surging, bursting
- Paresthesias: occasional
- Hyperpathia and allodynia may occur
- Moving toes: sinuous, athetoid-like dystonic movements, various combinations of directions at 1-2 Hz
- Look for cauda equina lesions, neuropathy, trauma



Supplement to *Arch Neurol.* doi:10.1001/archneurol.2012.161. © AMA.

Hassan JAMA Neurology 2012

Treatment

- Sympathetic blockade
- Epidural block
- TENS
- Spinal cord stimulation
- Carbamazepine, phenytoin, amitriptyline, phenothiazines, adenosine, gabapentin, pregabalin
- Botulinum toxin

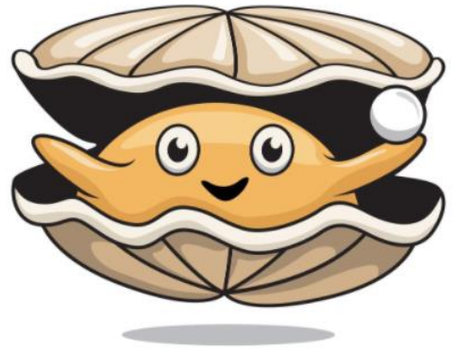
Peripheral Dystonia

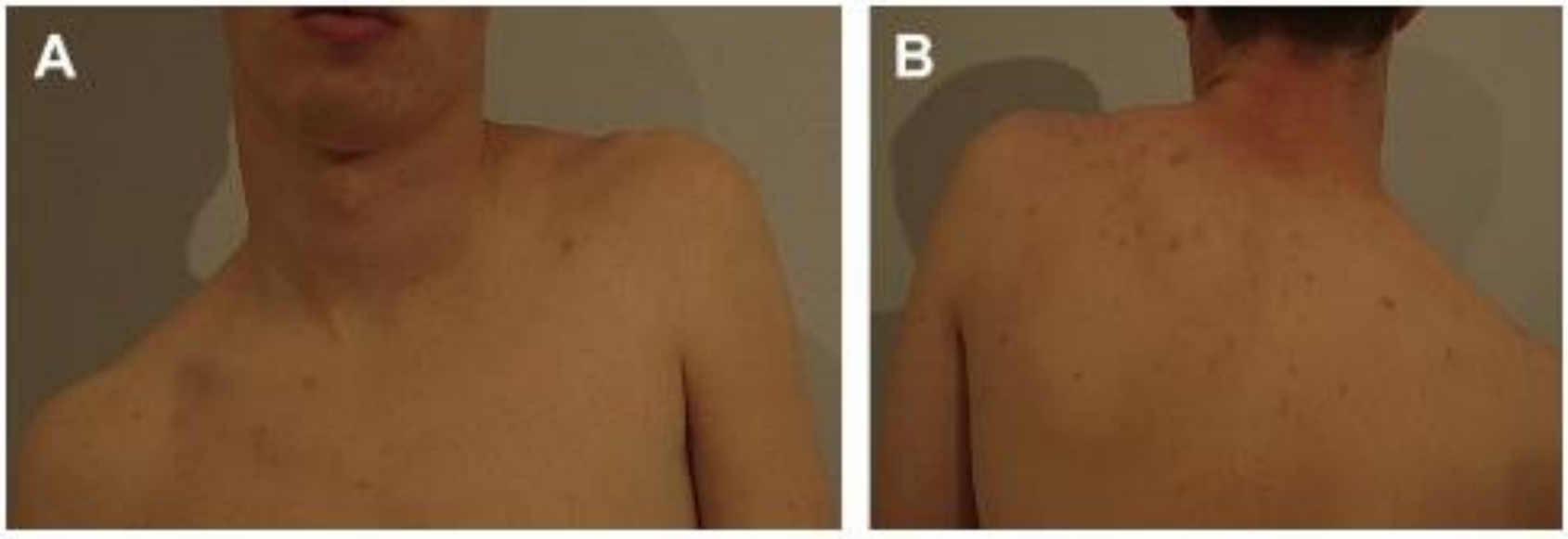
Barbara Scherokman, MD; Farhat Husain, MD; Albert Cuetter, MD; Bahman Jabbari, MD; Elvira Maniglia, MD

● **We studied four patients with distal, action-induced involuntary postures of the hand that could be considered focal dystonia. All four patients had electrophysiologic findings consistent with peripheral nervous system lesions (pronator teres syndrome, radial nerve palsy, lower brachial plexus lesion, or median nerve lesion). With varying success, patients were treated with carbamazepine, trihexyphenidyl, methocarbamol, and wrist splinting. We wish to emphasize that peripheral entrapment and brachial plexopathy should be added to the causes of secondary dystonias.**

(*Arch Neurol* 1986;43:830-832)

Post-traumatic dystonia









Peripherally Induced Movement Disorders

Neurol Clin 27 (2009) 821–832

Joseph Jankovic, MD

Peripherally induced dystonia



Patient of J. Jankovic

Complex regional pain syndrome (CRPS)

- **Reflex sympathetic dystrophy** (RSD) = CRPS I
  - Trauma without (overt) nerve injury
- **Causalgia** = CRPS II
  - Trauma with nerve injury

THE CAUSALGIA-DYSTONIA SYNDROME

18 cases, aged 12-51 years, 16 women and 2 men

15 followed peripheral injury (often minor); 3 spontaneous

None had a family history of this disorder

All had reflex sympathetic dystrophy

Painful fixed dystonia presented at or following onset of RSD, initially in the injured limb

Lower limb in 12; upper limb in 6

Contractures developed

Dystonia spread in 10 cases to other limbs, as did causalgia in 7 cases.

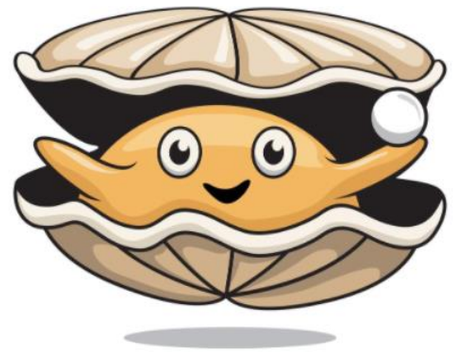
Brain and spinal cord imaging normal

No response to treatment

Two spontaneous recoveries (4 and 9 years after onset)

(Bhatia et al. 1993)

CRPS & Movement Disorders



- 58 patients with CRPS I & II and a movement disorder were studied prospectively
  - Verdugo & Ochoa *Muscle Nerve* 2000;23:198
- All cases had CRPS I
- Many had FND (psychogenic) features
- Some were malingering as documented by secret surveillance

DOI: 10.1093/brain/awh262 *Brain* (2004), **127**, 2360–2372

The syndrome of fixed dystonia: an evaluation of 103 patients

Anette Schrag,[1,2] Michael Trimble,[2] Niall Quinn[2] and Kailash Bhatia[2]

[1]*University Department of Clinical Neurosciences, Royal Free and University College Medical School and* [2]*Institute of Neurology, University College London, London, UK*

Correspondence to: Dr Anette Schrag, University Department of Clinical Neurosciences, Royal Free and University College Medical School, London NW3 2PF, UK
E-mail: a.schrag@medsch.ucl.ac.uk

Summary

We describe the clinical features of 103 patients presenting with fixed dystonia and report the prospective assessment and investigation of 41 of them. Most patients were female (84%) and had a young age of onset [mean 29.7 (SD 13.1) years]. A peripheral injury preceded onset in 63% and spread of dystonia to other body regions occurred in 56%. After an average follow-up of 3.3 years (overall disease duration 8.6 years), partial (19%) or complete (8%) remission had occurred in a minority of patients. The fixed postures affected predominantly the limbs (90%), and rarely the neck/shoulder region (6%) or jaw (4%). In the prospectively studied group, pain was present in most patients and was a major complaint in 41%. Twenty percent of patients fulfilled criteria for Complex Regional Pain Syndrome (CRPS). No consistent investigational abnormalities were found and no patient tested ($n = 25$) had a mutation in the *DYT1* gene. Thirty-seven percent of patients fulfilled classification criteria for documented or clinically established psychogenic dystonia; 29% fulfilled DSM-IV (*Diagnostic and statistical manual of mental disorders*, 4th edition) criteria for somatization disorder, which was diagnosed only after examination of the primary care records in many cases; and 24% fulfilled both sets of criteria. Ten percent of the prospectively studied and 45% of the retrospectively studied patients did not have any evidence of psychogenic dystonia, and detailed investigation failed to reveal an alternative explanation for their clinical presentation. Detailed, semi-structured neuropsychiatric assessments in a subgroup of 26 patients with fixed dystonia and in a control group of 20 patients with classical dystonia revealed dissociative (42 versus 0%, $P = 0.001$) and affective disorders (85 versus 50%, $P = 0.01$) significantly more commonly in the fixed dystonia group. Medical and surgical treatment was largely unsuccessful. However, seven patients who underwent multidisciplinary treatment, including physiotherapy and psychotherapy, experienced partial or complete remission. We conclude that fixed dystonia usually, but not always, occurs after a peripheral injury and overlaps with CRPS. Investigations are typically normal, but many patients fulfil strict criteria for a somatoform disorder/psychogenic dystonia. In a proportion of patients, however, no conclusive features of somatoform disorder or psychogenic disorder can be found and, in these patients, whether this disorder is primarily neurological or psychiatric remains an open question. Whilst the prognosis is overall poor, remissions do occur, particularly in those patients who are willing and able to undergo multidisciplinary treatment including physiotherapy and psychotherapy, suggesting that this type of treatment should be recommended to these patients.

Psychogenic dystonia and peripheral trauma

Jason S. Hawley and William J. Weiner

Neurology 2011;77;496

Table 2 Clinical features of trauma-induced dystonia compared to idiopathic, CRPS dystonia, and psychogenic dystonia

Clinical feature	Idiopathic focal or genetic dystonia	Trauma-induced "dystonia"	CRPS dystonia	Psychogenic dystonia
Associated pain	Occasional	Common	Severe	Common
Fixed postures	Rare	Common	Common	Common
Muscle hypertrophy	Not uncommon, particularly cervical	Uncommon	Uncommon	Uncommon
Sensory tricks	Common	Rare	Rare	Rare
Onset of symptoms	Slow	Abrupt	Abrupt to subacute	Abrupt to subacute
Response to treatment	Good for focal dystonia[a,c]; moderate for genetic dystonia[b,c]	Poor[a]	Poor[a]	Poor[c]

Abbreviation: CRPS = complex region pain syndrome.

[a] Treatment with botulinum toxin.

[b] Treatment with anticholinergics, dopaminergic therapy, deep brain stimulation.

[c] Psychological treatment and rehabilitation.

Thank You

Twitter, Instagram, Threads:
@MichaelOkun
Blog: www.pdplan.org



Contact Information:
okun@neurology.ufl.edu

UFHealth
NORMAN FIXEL INSTITUTE FOR NEUROLOGICAL DISEASES

Parkinson's Foundation

Tourette Association of America
Awareness. Research. Support.

Tyler's Hope for a Dystonia Cure

NIH
National Institutes of Health

Extra Learning Slides on RLS and Peripheral Movement d/o's

Conclusions

- RLS is highly genetic
- Many genes contribute to it.
- To date no single gene strongly determines whether or not you have RLS
- There is no clinical reason to be genetically tested for RLS
- Understanding RLS gene functions greatly improves understanding of RLS and may aid treatments

Ondo 2023

Risks for Augmentation

- Duration of Treatment (linear)
- Dose / Initial Severity of Disease
- Family history of RLS
- Lack of Neuropathy
- Low ferritin (iron)
- Shorter acting dopaminergics ?

Borreguera D 2016, Ondo W 2004, Winkelmann J 2004, Frauscher B 2009, Trenkwalder C 2008

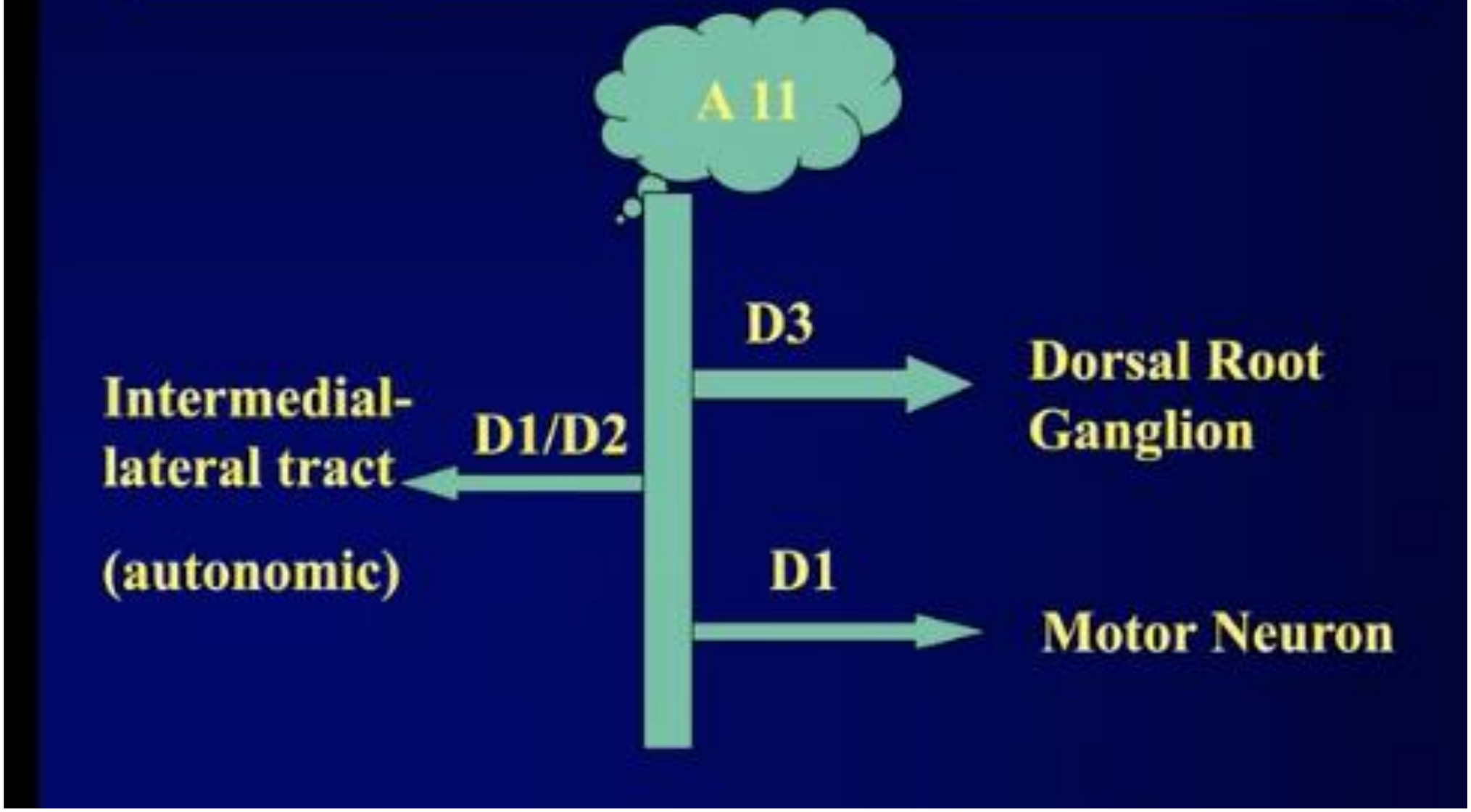
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Measuring Serum Iron is Difficult

- Ferritin:
  - Acute phase reactant can be elevated for 6 weeks
  - Increased with age (should be greater than age)
  - Increased with decreased GFR (renal function)
- Iron:
  - 50% higher in AM compared to night
  - Increased after meal
- Iron binding percentage:
  - Formula with iron, TIBC, transferrin

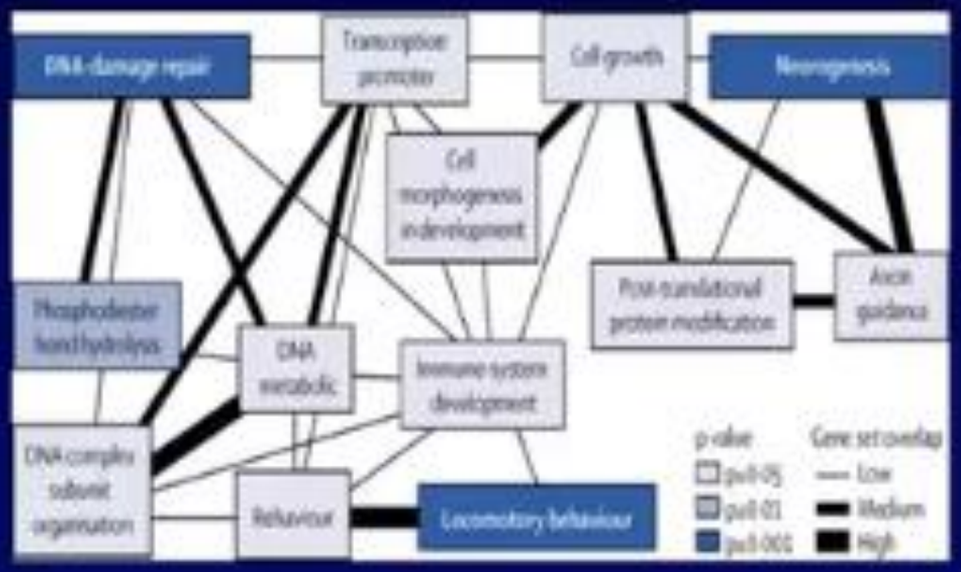
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A11 Spinal Projections



Ondo 2023

What Do These Genes Do?



- Mostly in CNS
- CNS development
- Synaptic and Axon Formation / Control/ Guidance
- DNA repair

MEIS1 Knock-out losses circadian pattern and hyperactive

Ondo 2023

RLS and ADHD

- ADHD Children have:
  - Greater PLMS
    - 26% have >5/hour
  - Worse sleep in general
  - 32% have a parent with RLS
  - Lower ferritin

Picchietti 1998, Picchietti 1999, Cherven 2002

Ondo 2023

Differential Diagnosis

- Akathisia
- Painful legs and moving toes
- Nocturnal leg cramps
- “Growing pains”
- Attention deficit hyperactivity disorder
- Vesper’s curse
- Positional dyscomfort
- Orthostatic tremor
- PLMS without RLS
- Psychogenic

Ondo 2023

Sleep Medicine Reviews 22 (2015) 64–77

Contents lists available at ScienceDirect

Sleep Medicine Reviews

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

CLINICAL REVIEW

Consensus 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, i], Arthur S. Walters [j], On behalf of the International Restless Legs Syndrome Study Group (IRLSSG)

RLS:
Potential relevance of iron

- **Iron deficiency reduces brain D2 receptors and dopaminergic function**
- **New evidence that MEIS1 abnormality influences iron metabolism**

RLS:
Alternate Theory

- **Symptoms are caused by peripheral hypoxia**
- **Dopaminergic agents can also act by vasodilation and reduce the hypoxia**
- **It is possible that iron metabolism in the periphery can lead to the hypoxia**

Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease)

Aaro V. Salminen, Ville Rimpilä and Olli Polo

Neurology 2014;82;1856-1861 Published Online before print April 30, 2014

RLS Genetics

- **Genes are elusive!**
- **Some linkages have been identified**
  - **But no genes with strong mendelian influence have been found so far**
- **GWAS findings**
  - **BTBD9, MEIS1, MAP2K5/SKOR1, PTPRD, TOX3, BC034767**

PLMS: Etiology

- **Reduction of supraspinal inhibition of the spinal cord**
- **Release of spinal reflexes**
- **Similar appearance to flexor reflex**
  - **Possible relevance of dorsal reticulospinal tract**
  - **Possible relevance of loss of descending inhibition from dopaminergic pathways**

RLS/PLMS: Etiology

- **There may be reduced D2 receptor binding in the striatum (with normal presynaptic dopamine function)**

What is the story with Iron (Fe)?

- **Low CSF ferritin and iron**
- **Normal serum ferritin and iron**
- **Increased CSF transferrin**
- **Low brain iron concentration caused by the dysfunction of iron transportation from serum to CNS in patients with idiopathic RLS**

Mizuno et al. 2005

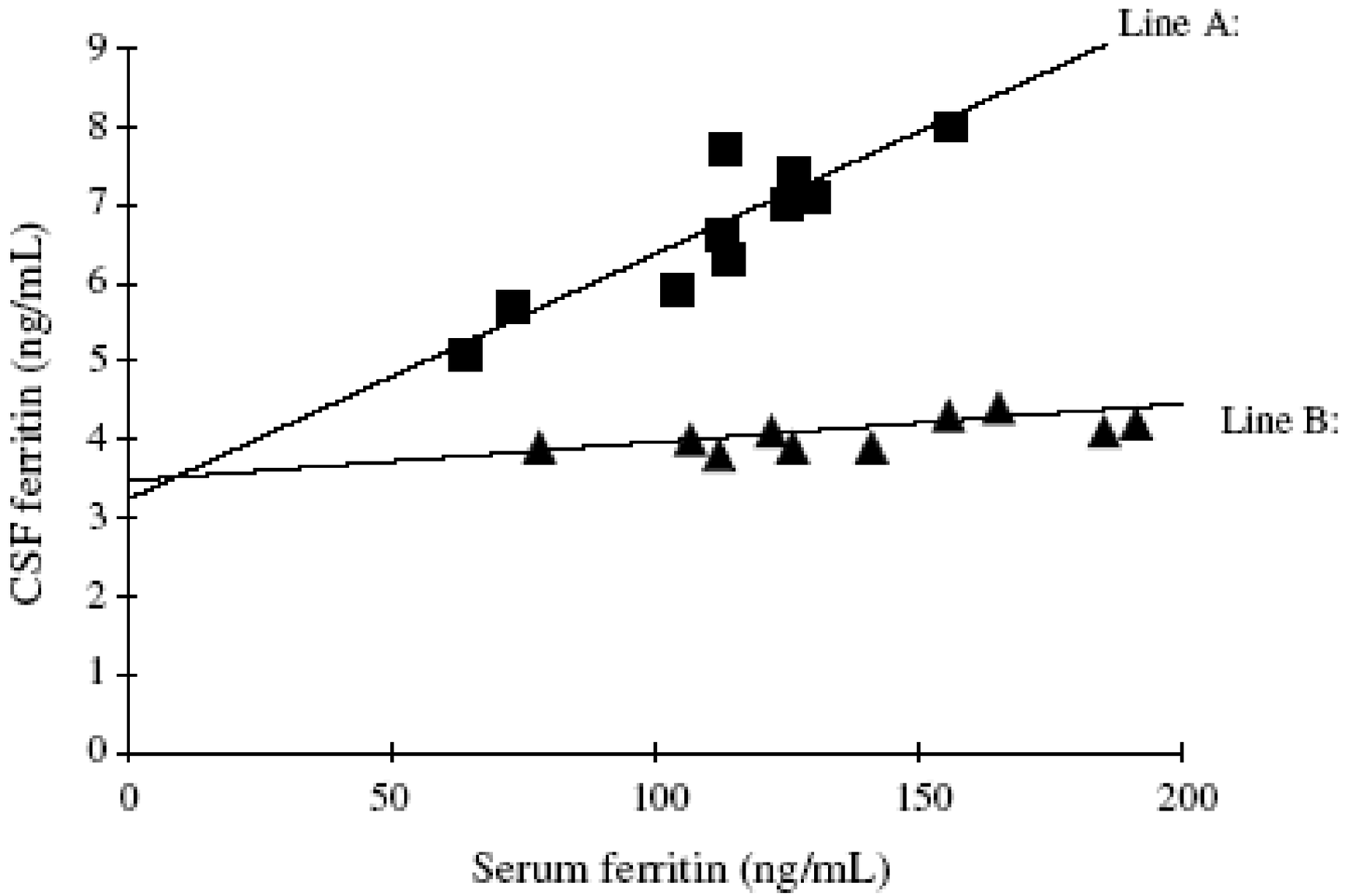
Iron and RLS

- Systemic iron deficiency associated with RLS
  - Anemia
  - Pregnancy
  - Blood donors
- Prevalence of RLS is 32% in anemia (6X greater than normal)
- Severity of RLS correlates with degree of ferritin reduction
- Replacement of iron improves symptoms of RLS

Earley et al. Sleep Med 2014
Allen et al Am J Hematol 2013

CSF Iron and Ferritin

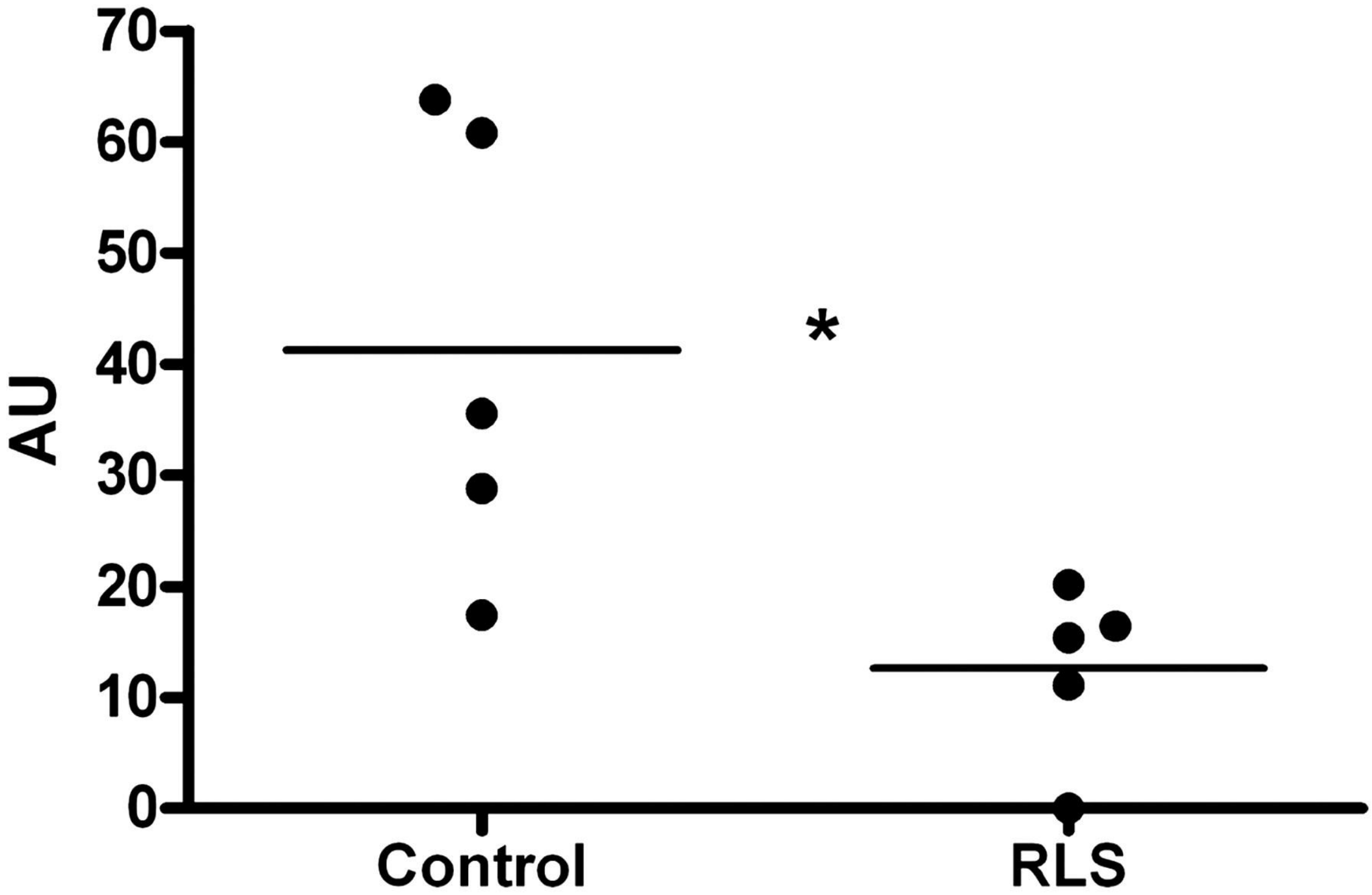
RLS (▲) compared to controls (■)



RLS also with increased CSF transferrin c/w central iron deficiency

Mizuno et al. J Sleep Res 2005;14:43-47; similar findings Earley Sleep 2005

Total iron regulatory protein binding activity in the RLS and control brain microvasculature



Connor J R et al. Brain 2011;134:959-968

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BRAIN A JOURNAL OF NEUROLOGY

Treatment of RLS
Non-pharmacologic

- Exercise
- Cognitive behavioral therapies
- Massage, compression stockings
- Acupuncture
- Counter-stimulation
- Vibratory devices (Relaxis®)
  - FDA approved (2014) device for RLS



Comella C. Neurotherapeutics 2014

Table 3: Drug therapies			
	Half-life (hours)	**Initial dose**	**Maximum**
Dopaminergic agents			
Levodopa	1-2	50/12.5mg	400/100mg
Pramipexole	8-12	0.125mg	1.5mg
Pramipexole extended release	20	0.375mg	2.25mg
Ropinirole	6	0.5mg	4mg
Rotigotine	5 — constant	2mg/24 hrs	4g/24 hrs
Anticonvulsants			
Gabapentin	5-7	300mg	1200mg
Gabapentin enacarbil*	6	600mg	2700mg
Pregabalin	10	25mg	300mg
Opioids			
Oxycodone	6.5	5mg	25mg
Tramadol	5-7	50mg	150mg
Others			
Clonazepam	39	0.25mg	2mg
Clonidine	12	0.05mg	0.4mg

Australian Doctor 2013

RLS and PD Surgery

- **Pallidotomy improved RLS**
  - Rye et al. 1999
- **GPi DBS improved RLS**
  - Ondo et al. 2012
- **STN DBS worsened RLS**
  - **This might be due to lowering of dopaminergic medications --** Kedia et al. 2004
  - **Medications less reduced in those with RLS –** Marques et al. 2015
- **STN DBS can improve RLS**
  - Driver-Dunckley et al. 2006

Voon et al. BMC Neurology 2011, 11:117
http://www.biomedcentral.com/1471-2377/11/117

BMC Neurology

RESEARCH ARTICLE Open Access

Frequency of impulse control behaviours associated with dopaminergic therapy in restless legs syndrome

Valerie Voon[1], Andrea Schoerling[2], Sascha Wenzel[2], Vindhya Ekanayake[3], Julia Reiff[4], Claudia Trenkwalder[2*] and Friederike Sixel-Döring[2]

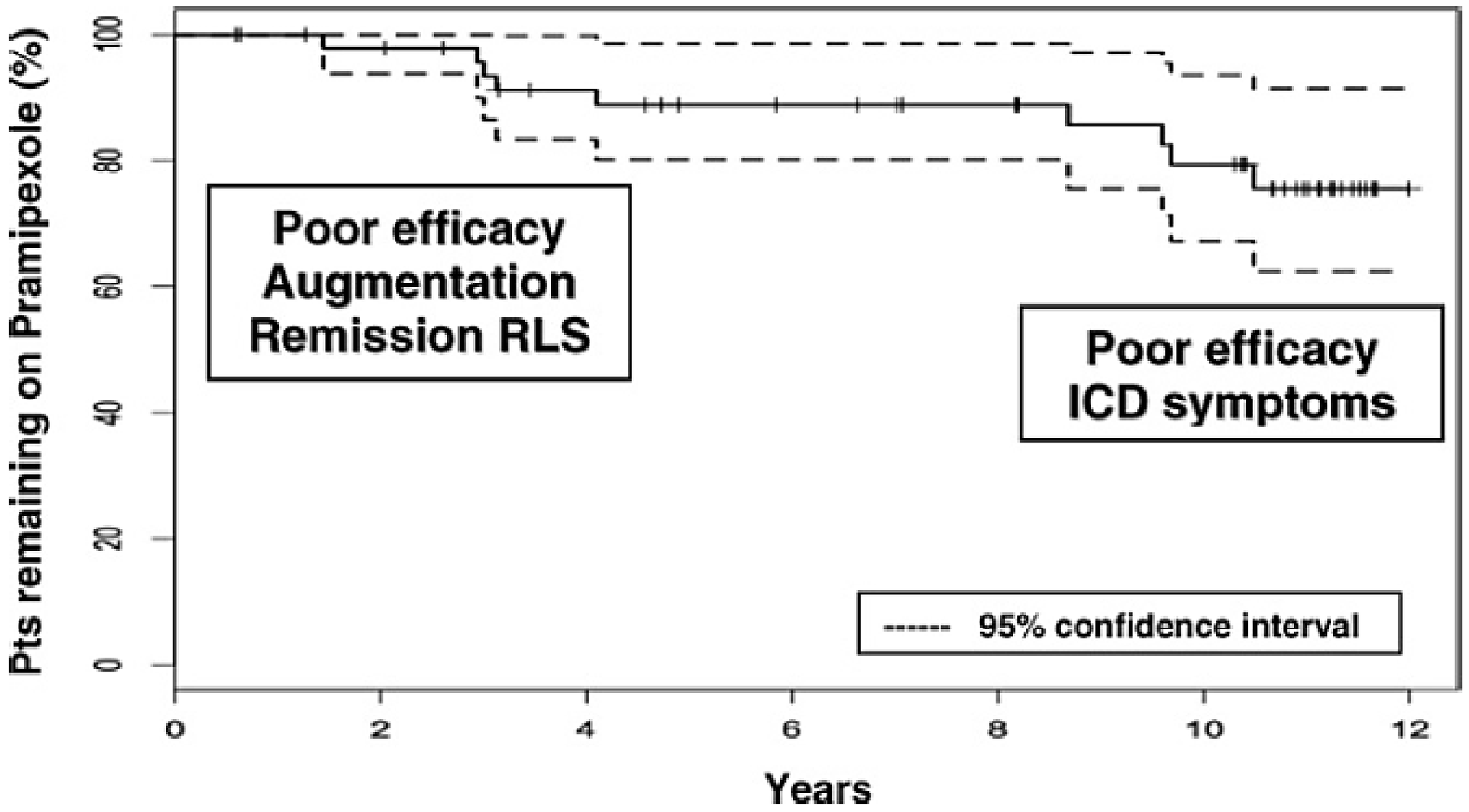
10 of 140 patients:

Table 1 Impulse control and compulsive behaviours diagnoses and medication data in patients with restless legs syndrome

Patient	ICB diagnosis	DA type/dose	L-dopa dose
1	Compulsive shopping, binge eating	Ropinirole/2mg	100 mg
2	Computer gambling, hypersexuality	Pramipexole/0.72 mg	–
3	Binge eating, punding	Pramipexole/1.4 mg	–
4	Gambling, binge eating	Ropinirole/4.5 mg	–
5	Compulsive shopping, binge eating	Ropinirole/2 mg	–
6	Computer gambling, hypersexuality, binge eating	Pramipexole/0.95 mg	–
7	Compulsive shopping, binge eating	Lisuride/2.5 mg	–
8	Punding	Cabergoline/3 mg	
9	Compulsive shopping	–	100 mg
10	Compulsive shopping, punding	–	500 mg

Long-term use of pramipexole in the management of restless legs syndrome

M.C. Lipford, M.H. Silber / Sleep Medicine 13 (2012) 1280–1285



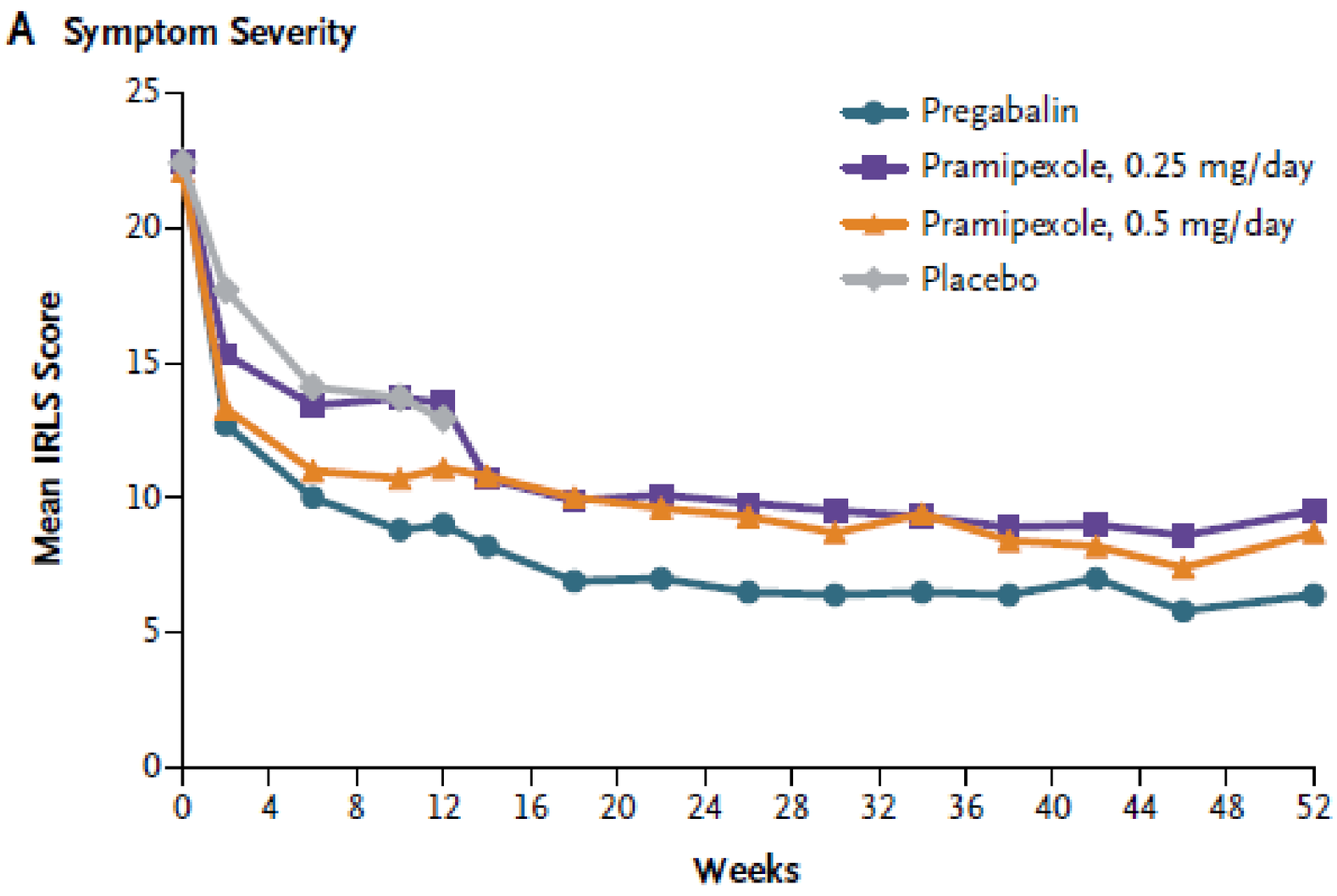
The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2014;370:621-31.

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.



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2014;370:621-31.

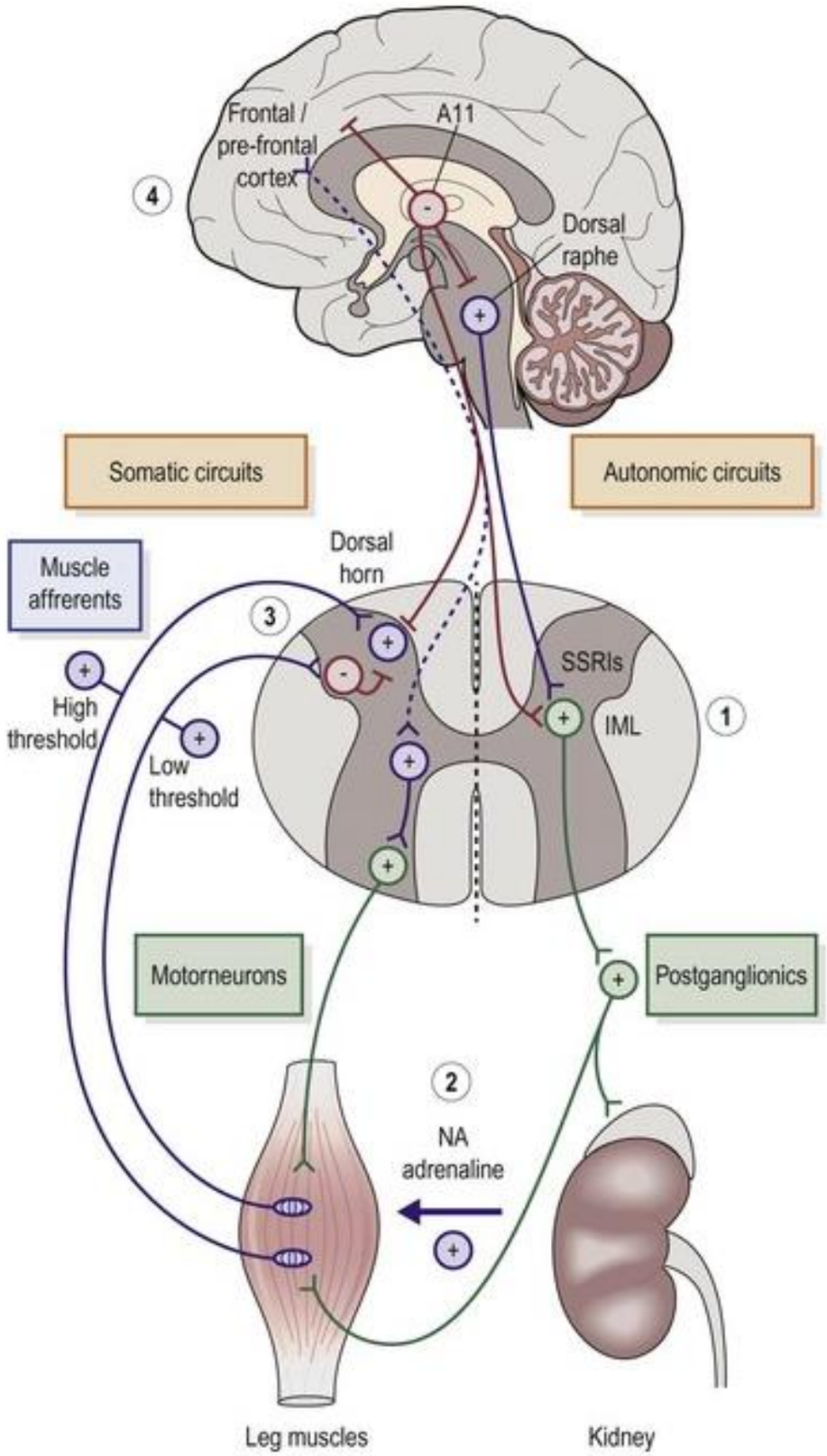
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Table 3. Rate of Augmentation after 40 and 52 Weeks of Treatment.*

Variable	Augmentation at 40 Wk	Augmentation at 52 Wk	Augmentation Overall	P Value
Pregabalin				
Patients assessed — no.	59	176	235	
Patients with augmentation — no. (%)	2 (3.4)	3 (1.7)	5 (2.1)	—
Pramipexole, 0.25 mg				
Patients assessed — no.	58	167	225	
Patients with augmentation — no. (%)	1 (1.7)	11 (6.6)	12 (5.3)	0.08
Pramipexole, 0.5 mg				
Patients assessed — no.	57	178	235	
Patients with augmentation — no. (%)	2 (3.5)	16 (9.0)	18 (7.7)	0.001



Jeff Durmer OBGYN Key

In patients with low ferritin, a double blind placebo controlled study showed benefit of oral ferrous sulfate 325 mg twice daily

Table 3
Results values at baseline to 12 weeks for patients randomized to iron and placebo groups.

	Iron group	Placebo group	*p*-Value*
IRLS baseline score (mean ± SD)	24.8 ± 5.72	23.0 ± 5.03	0.49
IRLS score change at 12 weeks (mean ± SD)	−10.3 ± 7.40	−1.14 ± 5.64	*0.01*
Ferritin baseline (mean ± SD)	40.6 ± 15.3 (ng/ml)	36.7 ± 20.8 (ng/ml)	0.68
Ferritin change at 12 weeks (mean ± SD)	+25.1 ± 20.3 (ng/ml)	+7.5 ± 13.7 (ng/ml)	*0.04*
Overall quality of life[a]			
Improved	7	1	0.07
Stayed the same or worsened	4	6	

[a] Dichotomous variable of improvement.
* Two-tailed *p*-value, 95% confidence interval.

Wang et al. 2009

Treatment of RLS: non pharmacologic

- Correction of iron deficiency
  - Serum ferritin < 75 µg/l ; transferin saturation < 20-75%
  - *Assess for cause of iron deficiency*
- Iron replacement
  - Strongest evidence ferric carboxymaltose infusion 500 mg X2
    - Low incidence of anaphylaxis
  - Oral ferrous gluconate, ferrous sucrose
  - Follow ferritin level to avoid iron overload
- Assess medications that trigger or enhance symptoms
  - Serotonergic antidepressants, DRBA, antihistamines

Hogl and Comella, Mov Disordr 2015
Avini et al, Eur J Intern Med. 2019
Allen et al. Sleep Med 2018
Garcia-Malo et al. Sleep Med 2020

Lower molecular weight intravenous iron dextran for restless legs syndrome

Yong Won Cho [a,*], Richard P. Allen [b], Christopher J. Earley [b]

Sleep Medicine 14 (2013) 274–277

Table 2
Changes in variables before and three weeks after intravenous dextran therapy ($n = 23$).

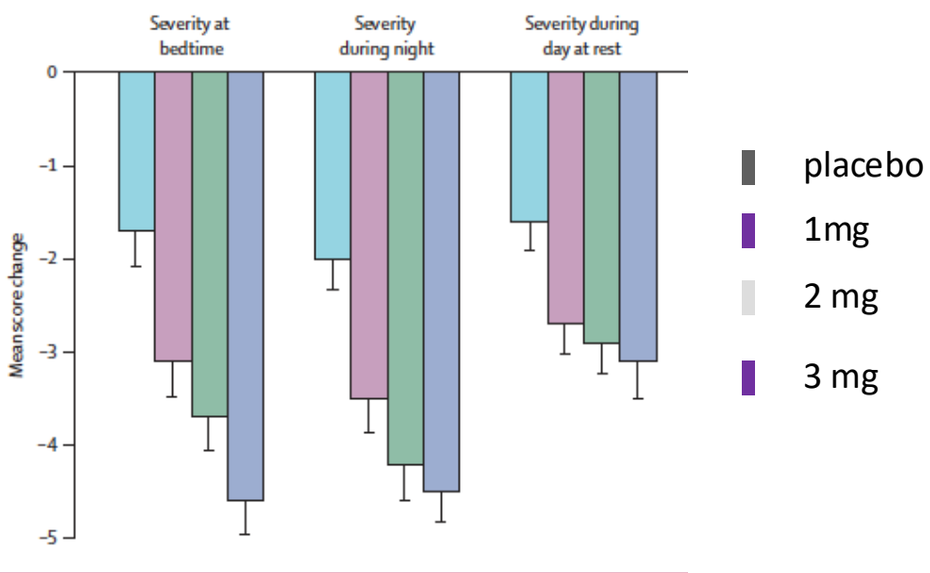
	Before treatment	Three weeks after treatment	*p*-Value
Hemoglobin	12.7 ± 2.4	13.5 ± 1.3	0.019
Serum ferritin	41.0 ± 37.0	274.4 ± 142.2	<0.001
CSF ferritin	7.2 ± 2.4	8.8 ± 2.4	0.001
K-IRLS	23.5 ± 6.6	16.7 ± 9.5	0.001
Visual analog scale	7.8 ± 1.1	4.2 ± 2.3	<0.001
PAM_RL ($n = 12$)	31.0 ± 15.6	11.2 ± 9.6 ($n = 12$)	0.001

K-IRLS; the Korean version of the International RLS Severity scale.

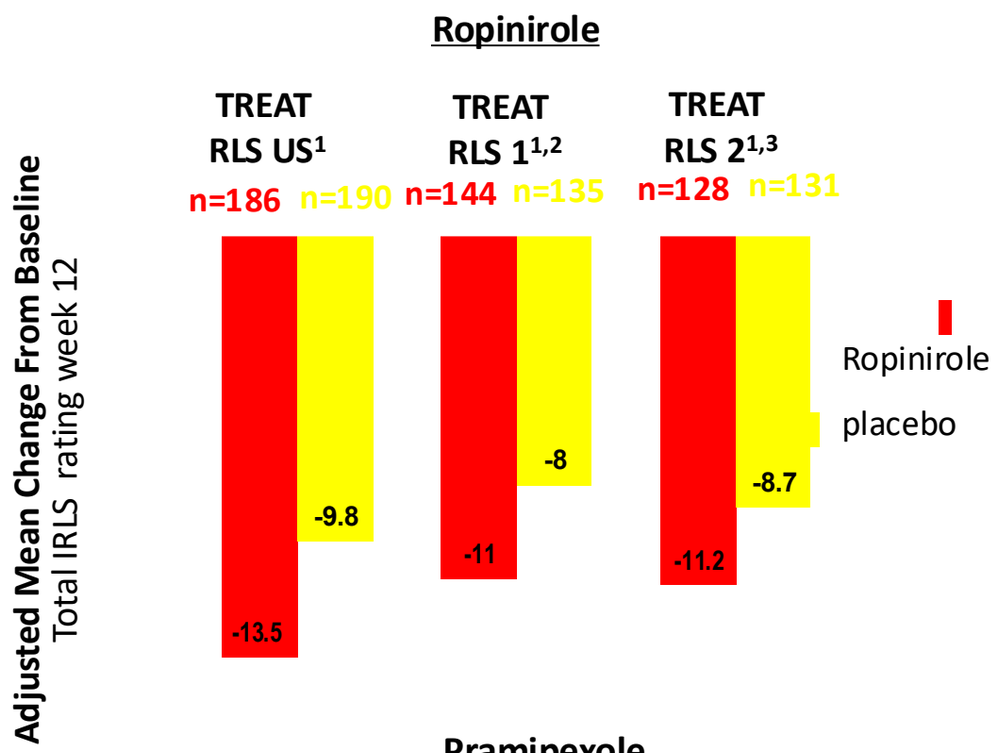
Dopamine agonists for RLS

- Improved RLS severity
- Improved PLMS
- FDA approved
  - Ropinirole:
  - Pramipexole:
  - Rotigotine patch

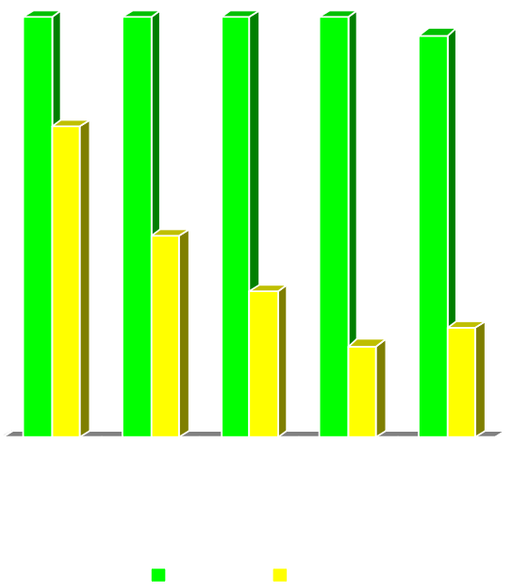
Rotigotine patch



Ropinirole



Pramipexole



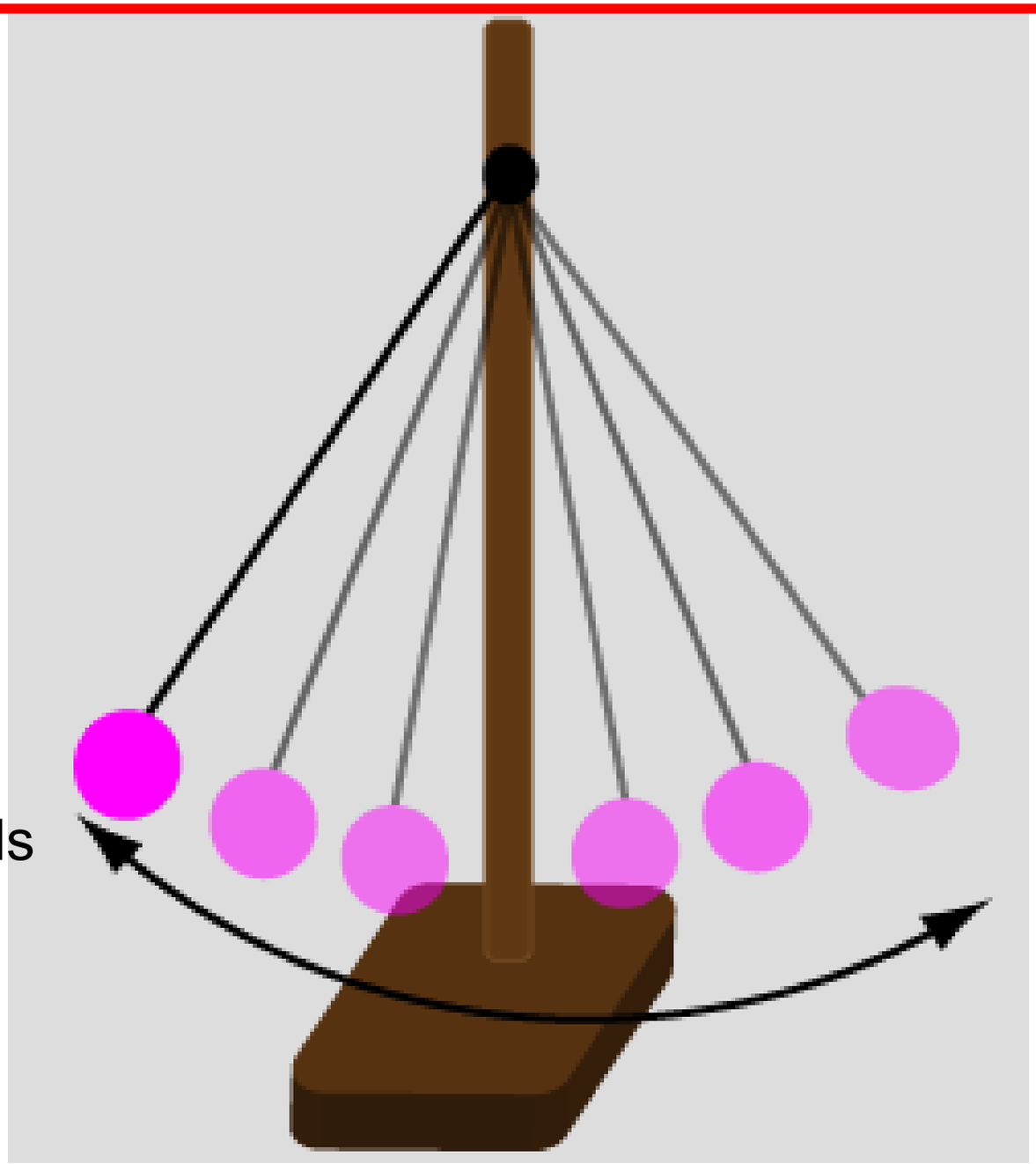
Trenkwalder et al. *J Neurol Neurosurg Psychiatry.* 2004;75:92-97
Walters et al. *Mov Disord.* 2004;19:1414-1423.
Partinen et al. Sleep Med 2006;7:407-417
Trenkwalder et al. Lancet Neurology 2008

Dopaminergic Agonists
Adverse Effects

- Nausea, dizziness, somnolence, headache
- Orthostatic hypotension
- Rebound (occurs during the night)
- Impulse control disorders (5-17%)
- Augmentation (30-80%)
  - More frequent with short acting DA
  - Associated with higher doses

De Biase et al. Expert Opinion 2014
Silber et al. Mayo Clin Proc 2013

Shifting treatment paradigm for RLS



Alpha-2 Delta
Calcium Channel Ligands

Dopamine agonists

Romero-Peralta et al, Chest 2020
De Biase et al. Expert Opin Pharmacother 2019
Wanner et al. Adv Pharmacol 2019

Gabapentin Enacarbil

- Prodrug of gabapentin
- Better, more consistent absorption
- 3 double blind, placebo controlled studies
- GBE 600-2400mg

- Reduced IRLS
  - GBE : -13.6
  - Placebo: - 9.3
- Responders
  - GBE: 70.2%
  - Placebo: 42.2%
- No difference in effect among doses
- AE's somnolence, dizziness increased with increasing doses

Yaltho TC, Ondo WG. Ther Adv Neurol Disord
Lal et al. Clin Neuropharm 2012
VanMeter. CNS Drugs 2012

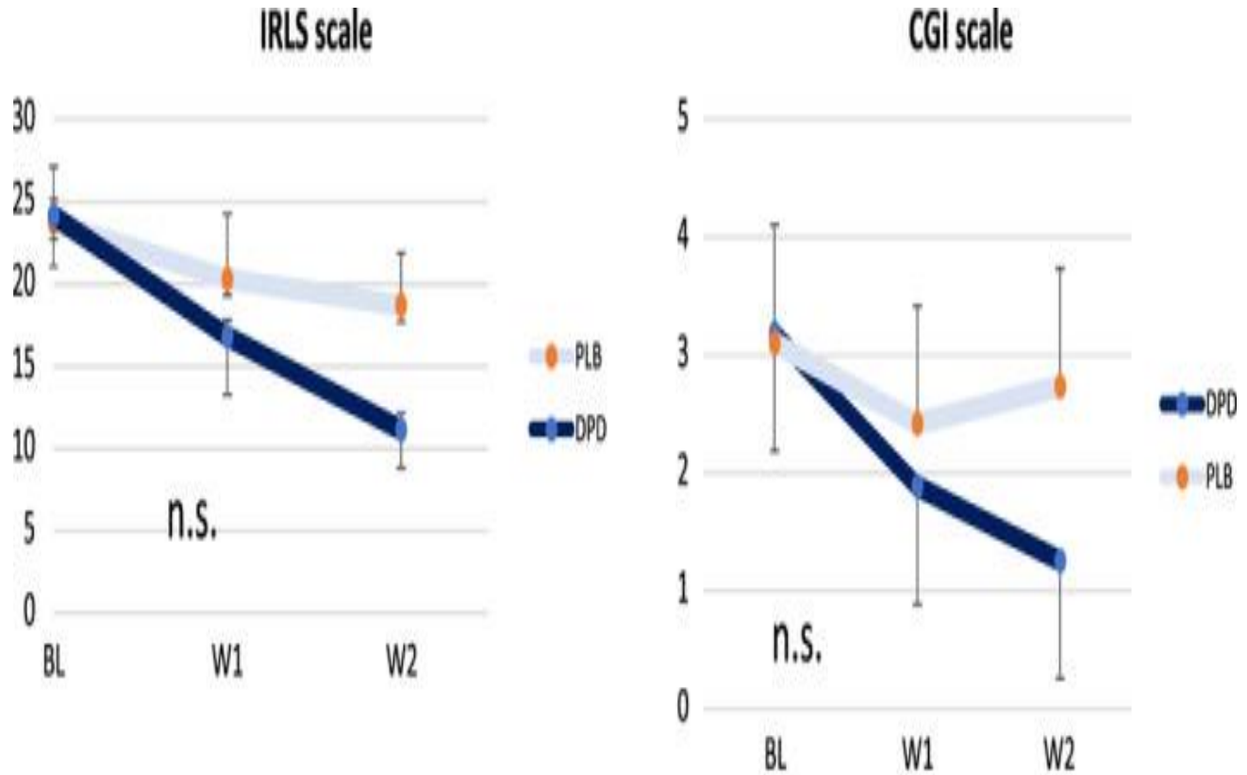
Pregabalin vs Pramipexole in RLS

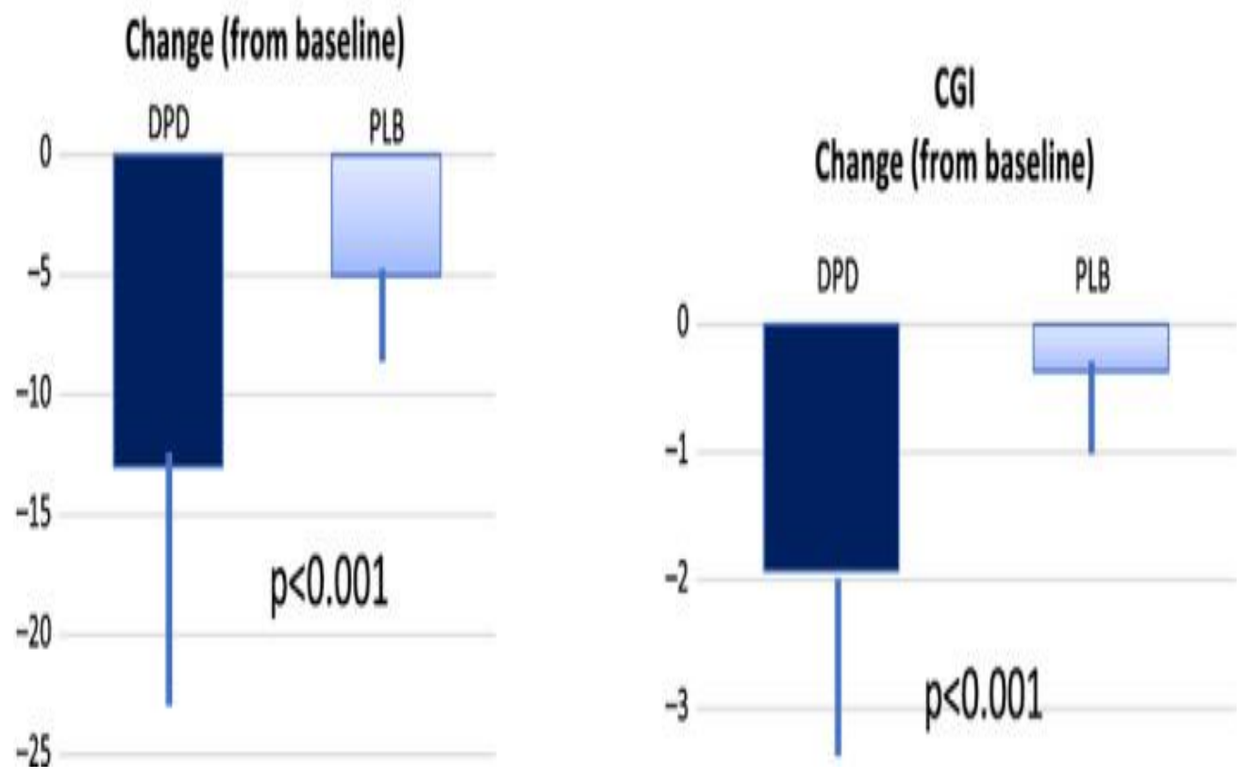
- 719 RLS patients
- 52 week study
  - Placebo vs Pregab vs Prami (12 weeks)
  - Pregab vs Prami (40 weeks)

- Pregab with greater improvement

- Discontinuation for AE
  - Pregabalin 27.5%
  - Prami 0.5 mg 24%
  - Prami 0.25 mg 18.5%

- Augmentation at 52 weeks
  - 2.1% pregabalin
  - 5.3% prami 0.25mg
  - 7.7% prami 0.5mg

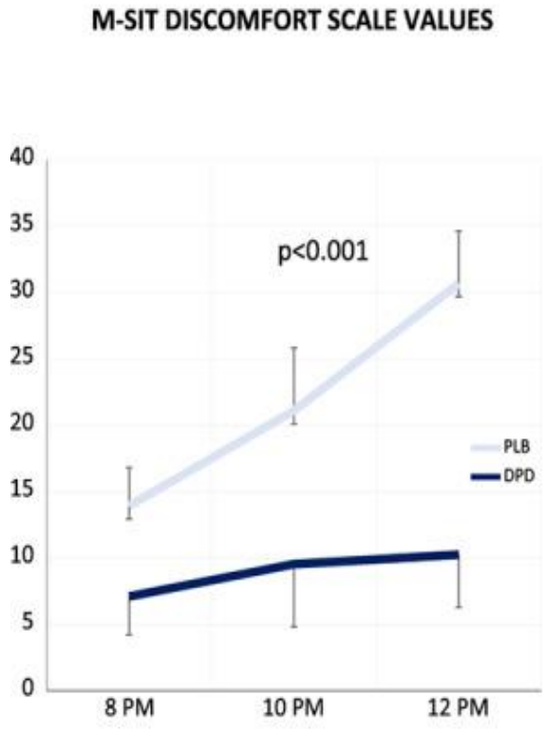


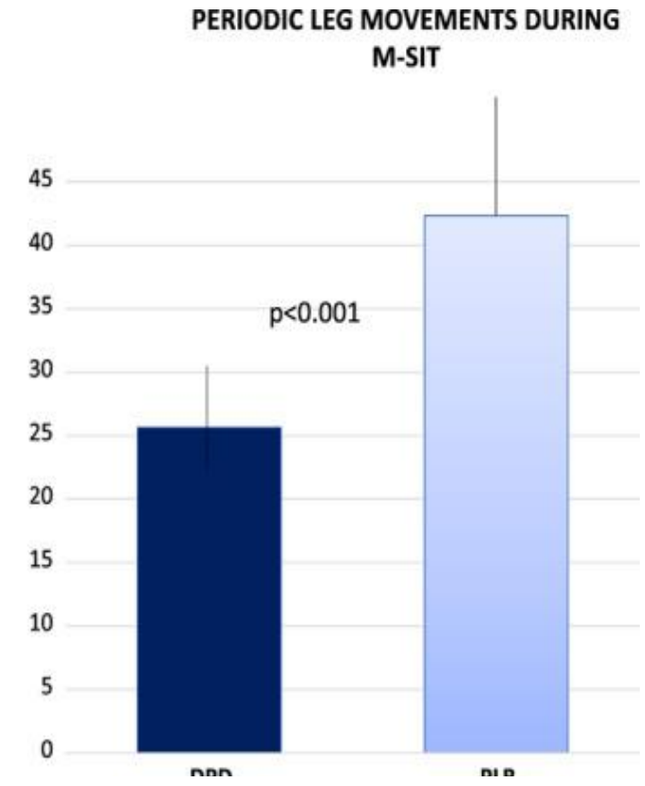


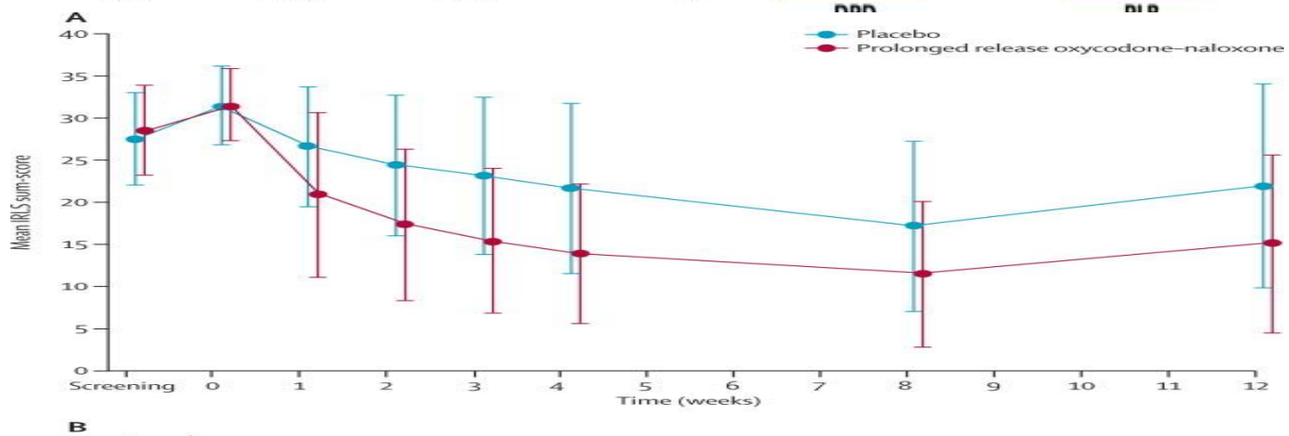
Allen RP et al. N Engl J Med 2014;370:621-631.
Garcia-Borreguero et al. Sleep 2014

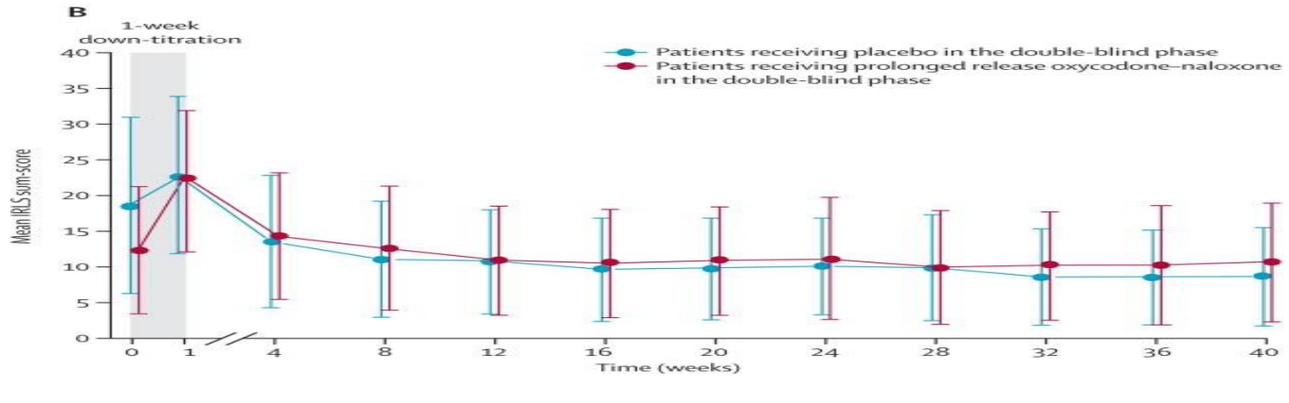
Dipyridamole
(vasodilator and antiplatelet agent) for RLS

- DBPC crossover study
- Dipyridamole in (100-300 mg) in 28 RLS over 2 weeks
- SE:
  - Abdominal distension, dizziness, diarrhea









Garcia-Borreguero D et al. Mov Disord 2021

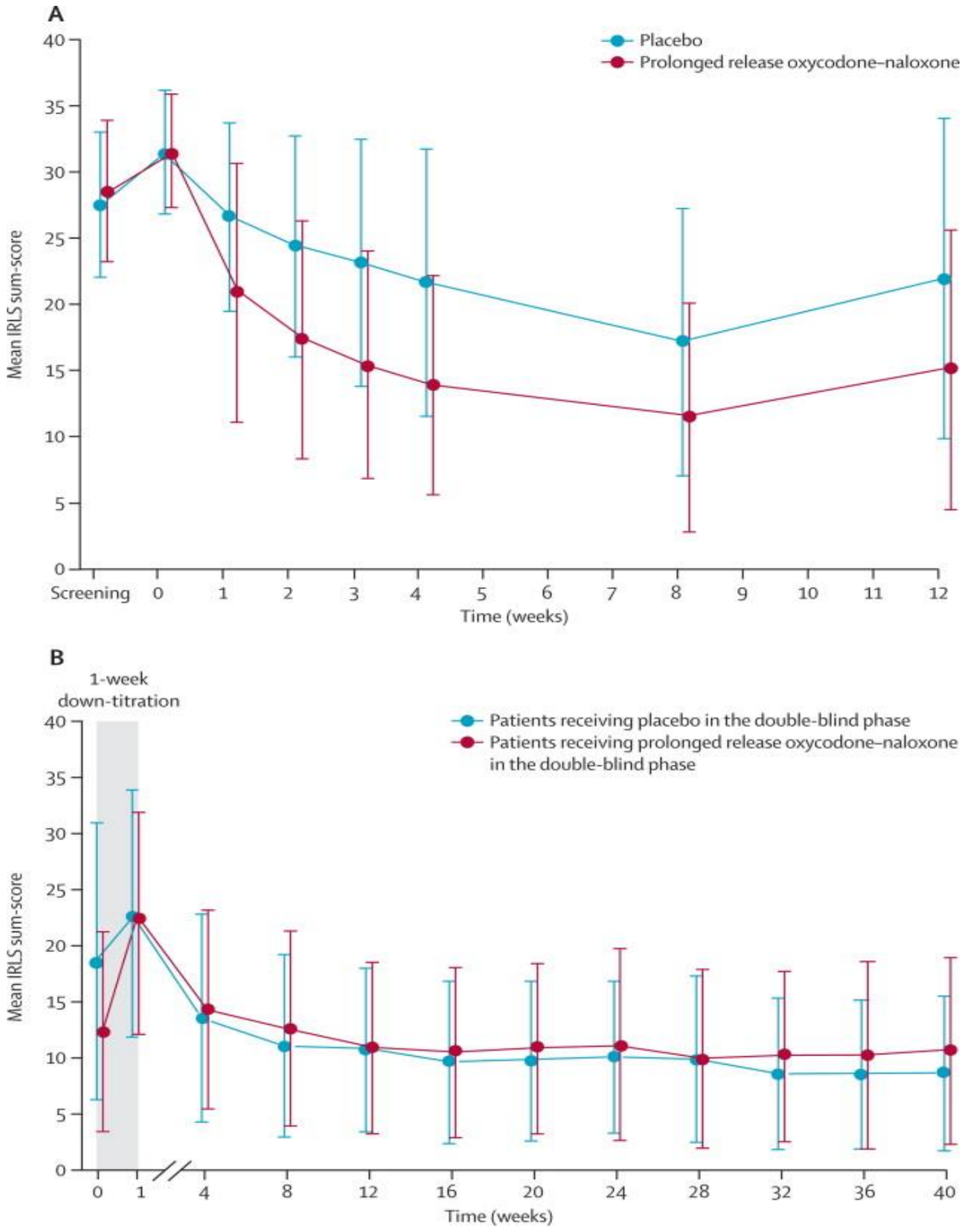
Other Treatments for RLS

- Opioids and opiates (most with renal clearance)
  - Codeine
  - Tramadol
  - Oxycodone
  - Methadone (5-15 mg) in refractory RLS or augmentation
- Benzodiazepine agonists
  - Temazepam
  - Eszopiclone
  - Clonazepam

Winkelmann et al. Mov Disord 2018

Prolonged Release Oxycodone-Naloxone For Severe RLSo

- 306 severe RLS failing prior treatment
  - Placebo vs oxy (22 mg)-nal (11 mg) for 12 weeks (Fig A)
  - OLE 40 weeks (Fig B)
- DB Drug AE's causing withdrawal
  - PL 7%; Oxy-nal 15%
- OLE dose oxy 18 mg (10.5)
  - 20% dropout: most AE
- Efficacy similar to that seen with DA
- No reports of augmentation



Trenkwalder et al. Lancet Neurol 2013

Long term use of Opioids for RLS

- National opioid registry: longitudinal registry study of opioid dose for refractory RLS
- 448 patients followed for 2 years
- Mean morphine milligram equivalent (MME) 38.4 (SD 43.5) baseline
  - No change in RLS severity over 2 years
  - Median change in daily dose was 0 MME
    - 41% increased by mean 10 MME
    - 59% remained stable or reduced the dose
- Side effects: constipation, fatigue, itching, wakefulness

MME:	
Methadone	4
Oxycodone	1.5
Hydrocodone	1

Winkelman JW et al. Neurology 2023

Risk of RLS associated with other disorders

- Increased risk of RLS:
  - Iron Deficiency anemia
  - Kidney disease

- Whether RLS increases risk of cardiovascular disease is controversial
  - Women with RLS: HR 1.43 (95% CI 1.02-2.00)
    - Longer duration associated with increased risk

Trenkwalder et al. Lancet Neurol 2018
Li et al Neurology 2018
Trenkwalder et al. Neurology 2016

RLS: A Heterogeneous Disorder

- Phenotype similar but varying underlying pathophysiology
  - Genetics
  - Reduced central iron
  - Abnormal brain dopaminergic activity
  - Receptor mediated?

RLS :Complex genetic disorder

- Genome-wide Association studies
  - 6 single nucleotide polymorphisms account for a small percent (<10%) of genetic susceptibility
    - MEIS1 (2p) (strongest most consistent)
    - BTBD9 (6p)
    - MAP2K5/LBXCOR1 (15q)
    - PTPRD
    - TOX3
  - Meta-analysis of studies: 22-23 variants, 3 new variants found within the past year

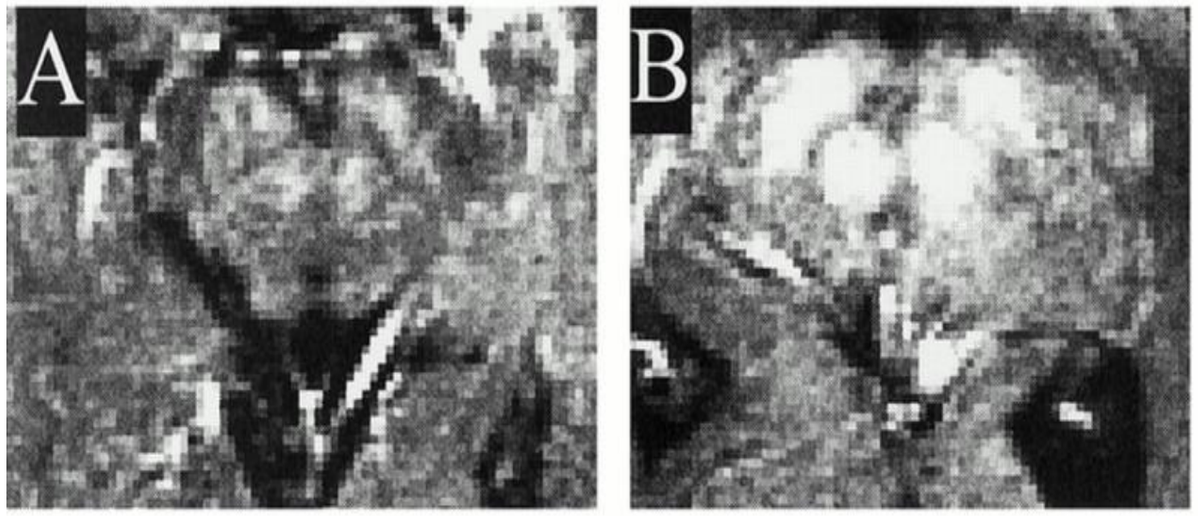
- GWAS in PLMD with 2 independent loci:
  - MEIS1
  - BTBD9
- Whole genome sequencing needed

Winkelmann et al. Sleep Med 2017
Scharmair et al. Lancet 2017
Didriksenetal et al, Comm Biol 2020
Edelson et al. Sleep Med 2022

Reduced Iron in the Midbrain

MRI R2* imaging

RLS



Control

R.P. Allen et al. Neurology 2001;56:263-265

Iron studies in RLS with and without anemia

- 196 RLS patients without anemia (IDNA), 26 anemia (IDA), and 63 controls were included.
  - serum ferritin, iron, transferrin, and total iron-binding capacity
- 42.3% of RLS patients **without anemia** had iron deficiency.
  - Women more susceptible for IDNA
    - relative risk of 5.51 ($p < 0.0001$)
    - younger age at RLS onset compared to women with RLS without iron deficiency anemia ($P < 0.01$).
- Non anemic RLS with tendency to higher risk of severe/very severe daytime sleepiness during the day
- Non-anemic RLS patients had longer duration of RLS younger age at onset

Xiao-Yung Zhu et al. Front Neurol 2020

Iron and circadian rhythms

- Despite normal blood iron levels, natural circadian variations in CNS iron may be at fault for producing circadian changes in symptoms.
- There is a nighttime rise in CNS iron levels to support an increased metabolic activity during sleep in normals
  - This may be inadequate in RLS
  - This decrease in the late night/early morning CSF ferritin in RLS relative to controls does not appear to exist in samples collected 12 h later

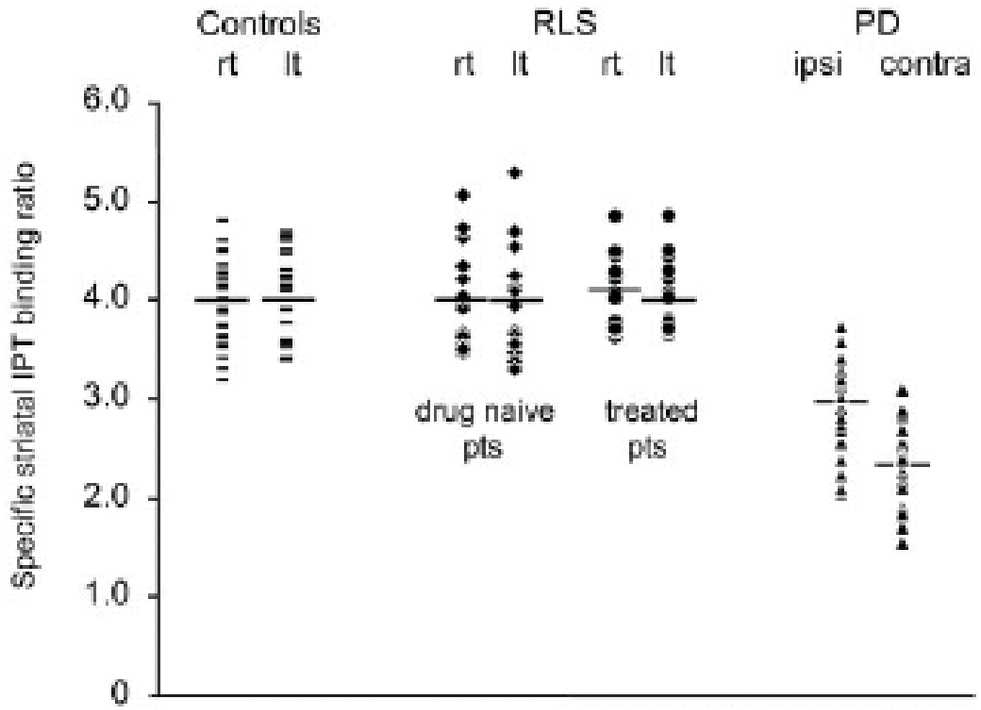
Early et al 2011
Vlasie A et al. 2022

Pathophysiology: Dopamine and RLS

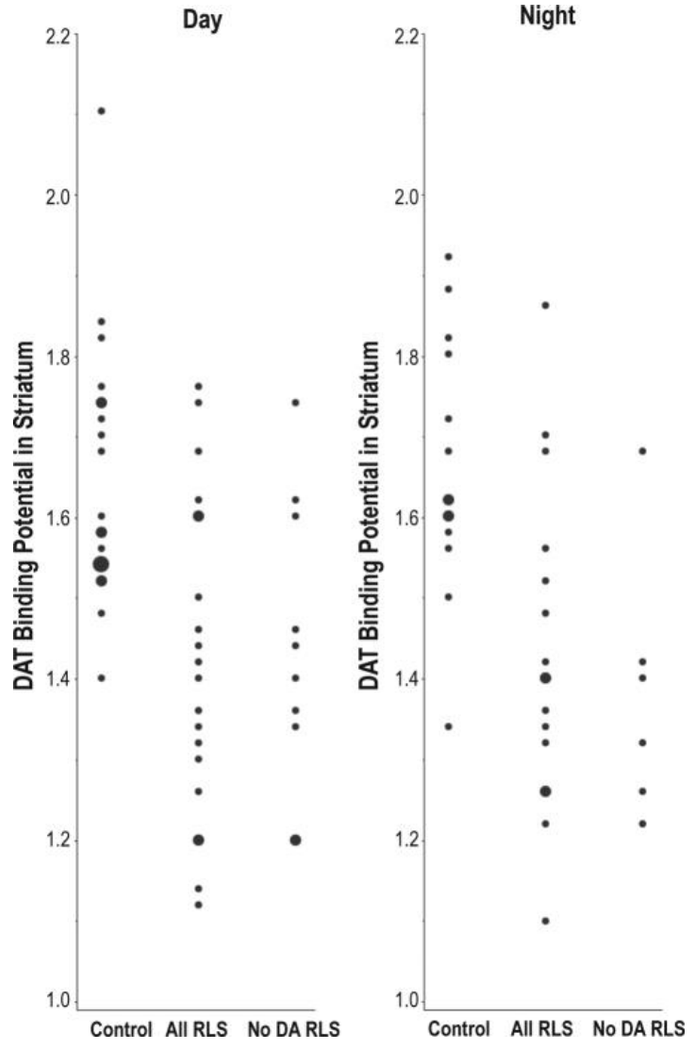
- Dramatic response to dopaminergic agents
  - Levodopa and dopamine agonists
  - Low doses
- Exacerbated by centrally active dopamine receptor antagonists
- Reduced D2 receptors described in RLS

Allen R. Sleep Med 2004;5:385-391
Earley et al. Sleep Med 2014

RLS and PD: DAT scan and MRI R2*
(iron)imaging



Linke et al. Mov Disord 2004;19:1158-62.
Li K,Int J Neurosci. 2019 Jun 17:1-9.



Earley et al. Sleep 2011

Circadian pattern in RLS

- Similar to iron, DA has circadian pattern being highest in the morning and 60% reduced between 8-10pm
- Iron is a cofactor for tyrosine hydroxylase involved in dopamine production

Functional MR studies:
Brain networks in RLS

- RLS vs Control:
  - Networks with **higher** intra-network connectivity:
    - salience, executive, cerebellar and lower cerebello-frontal cortex
  - Networks with **lower** connectivity:
    - cerebello-parietal connectivity in untreated patients, in regions associated with attention, response inhibitory control, and processing of sensory information
- Dopaminergic treated RLS:
  - Intact cerebello-parietal communication and increased thalamic connectivity to the prefrontal regions thalamus.

Tuovinen et al. Eur J Neurol 2021

Diffusion tensor imaging (DTI) of the brain in RLS

- Altered global structural connectivity of RLS patients (N= 69) using graph theory based on DTI
  - decreased segregation in the brain network compared to healthy controls (N= 51)
  - correlated with RLS severity
- Changes in local structural connectivity, especially in regions involved in sensorimotor function

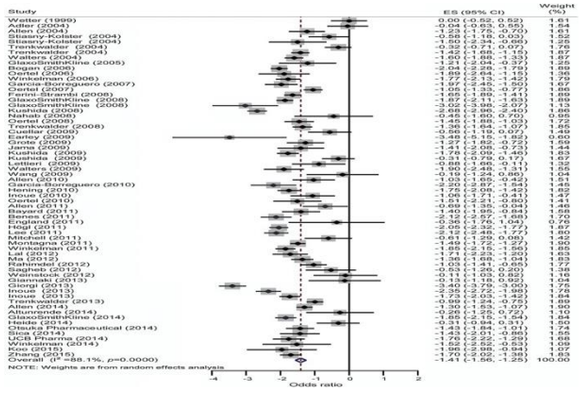
Park, KM et al. Sleep 2022

Summary
Pathophysiology of RLS

- MRI studies showed no structural brain lesions and confirmed a central iron deficiency
- Neurotransmission abnormalities : dopaminergic opiate, adenosine, glutaminergic systems.
- Structural and functional studies showed an involvement of the thalamus, sensorimotor cortical areas, and cerebellum in RLS
- Abnormal network connectivity

Provini and Chiari.Sleep Med Clin 2015
Tuovinen et al. Eur J Neurol 2021
Park et al. Sleep 2022

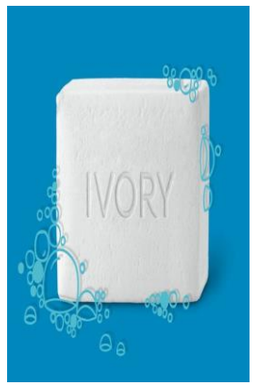
Therapeutic approach to RLS











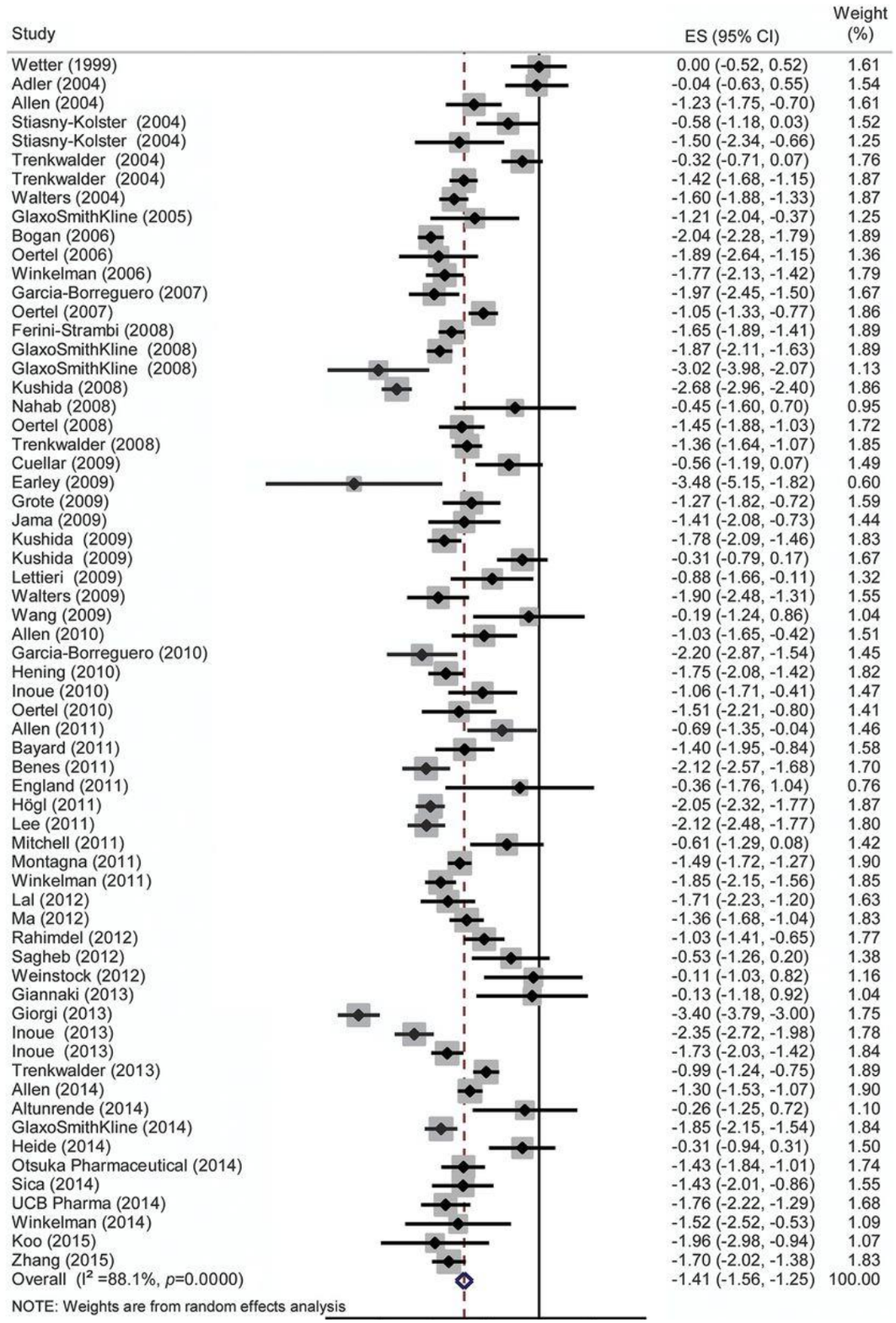






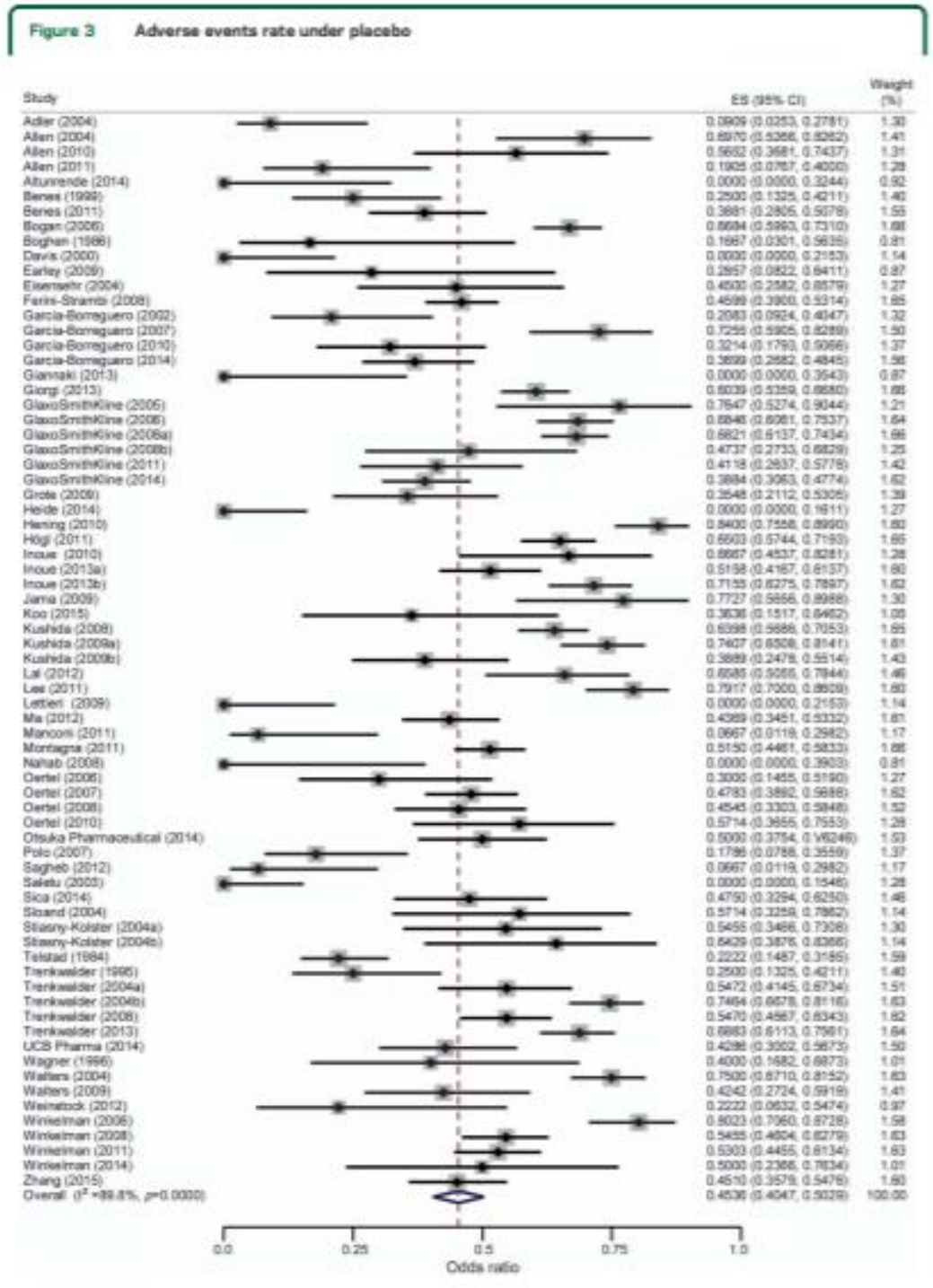
Placebo response: change from baseline in restless legs in RCT studies

- The placebo response greater:
  - trials with longer duration
  - evaluating pharmacologic interventions
  - idiopathic RLS
  - industry-funded



Maria A. Silva et al. Neurology 2017;88:2216-2224

Nocebo effects in RLS



CI – confidence interval; ES – effect size.

Maria A. Silva et al. Neurology 2017;88:2216-2224

Concurrent sleep disorders that may exacerbate RLS

- sleep fragmentation
- insufficient sleep .
- obstructive sleep apnea (PSG)
- depression, anxiety
- behavioral (eg, excessive caffeine intake)

Silber et al. Mayo Clin Proc 2021

Peripheral movement disorders

- Hemifacial spasm
- Painful Legs, Moving Toes
- Belly Dancer’s dyskinesia
- Jumpy stump
- Focal myoclonus due to peripheral nerve injury
- Complex regional pain syndrome
- ? Dystonia due to peripheral injury

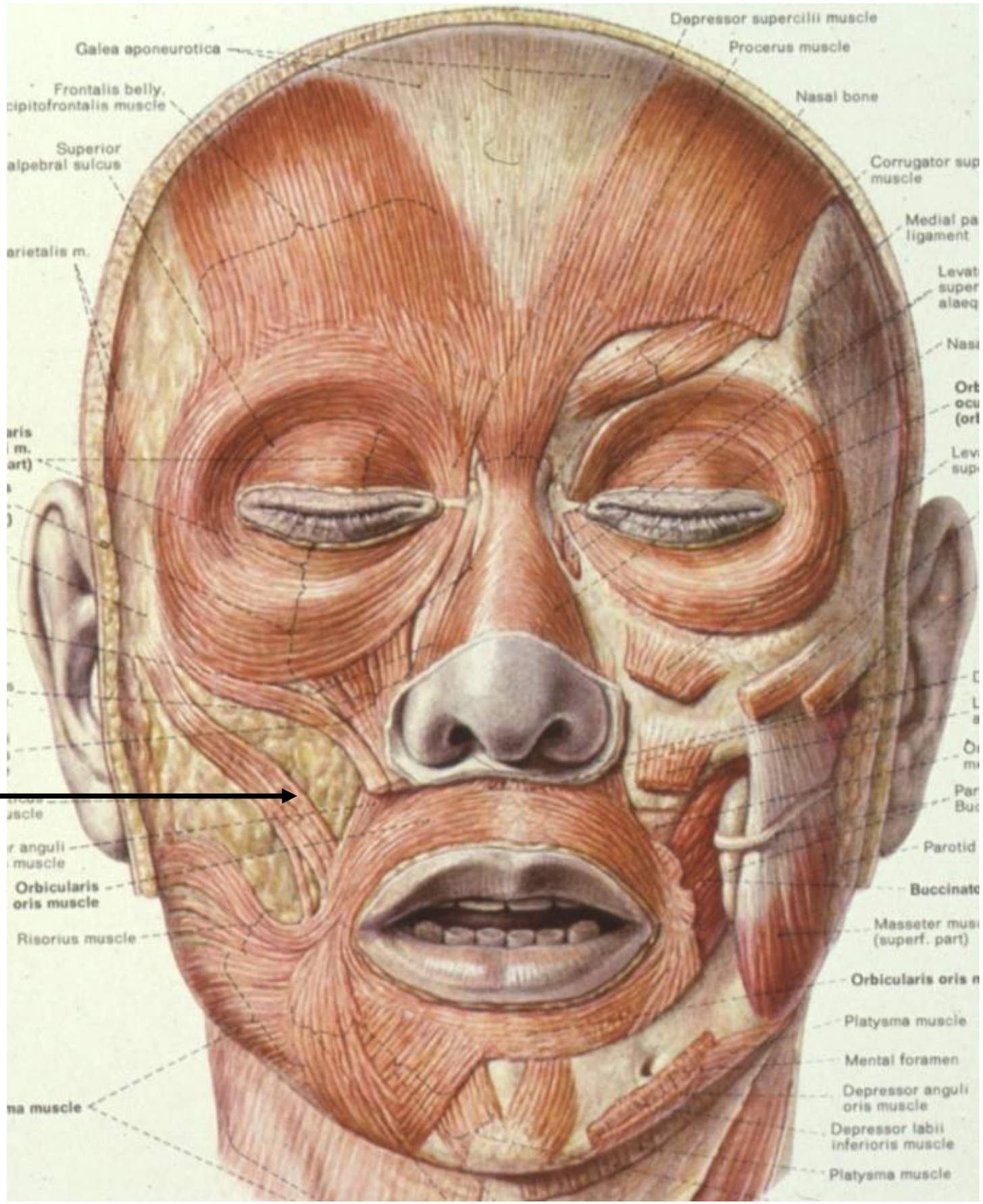
Hemifacial Spasm: Pathophysiology

- Peripheral nerve hypothesis
  - Ectopic discharges, ephaptic transmission*
- Nucleus hypothesis
- Both?
- *New variation on this idea
  - Ephaptic transmission occurs via sympathetic nerves in the compressing artery's wall (Zheng et al. *Neurosci Lett* 2012; Dou et al. *Neurol Res* 2015)

Hemifacial spasm: Treatment

- **Carbamazepine**
- **Microvascular decompression surgery**
- **Botulinum toxin**
  - **Average dose of Botox® is 7.5 to 30 units distributed to the different muscles**
    - **Other types of botulinum toxin might be used as well, but they do not have FDA approval**
  - **Can be used for 20 years or more**
  - **Avoid zygomaticus if possible**

Zygomaticus



British Journal of Neurosurgery, August 2012; 26(4): 438–444
© 2012 The Neurosurgical Foundation
ISSN: 0268-8697 print / ISSN 1360-046X online
DOI: 10.3109/02688697.2011.641613

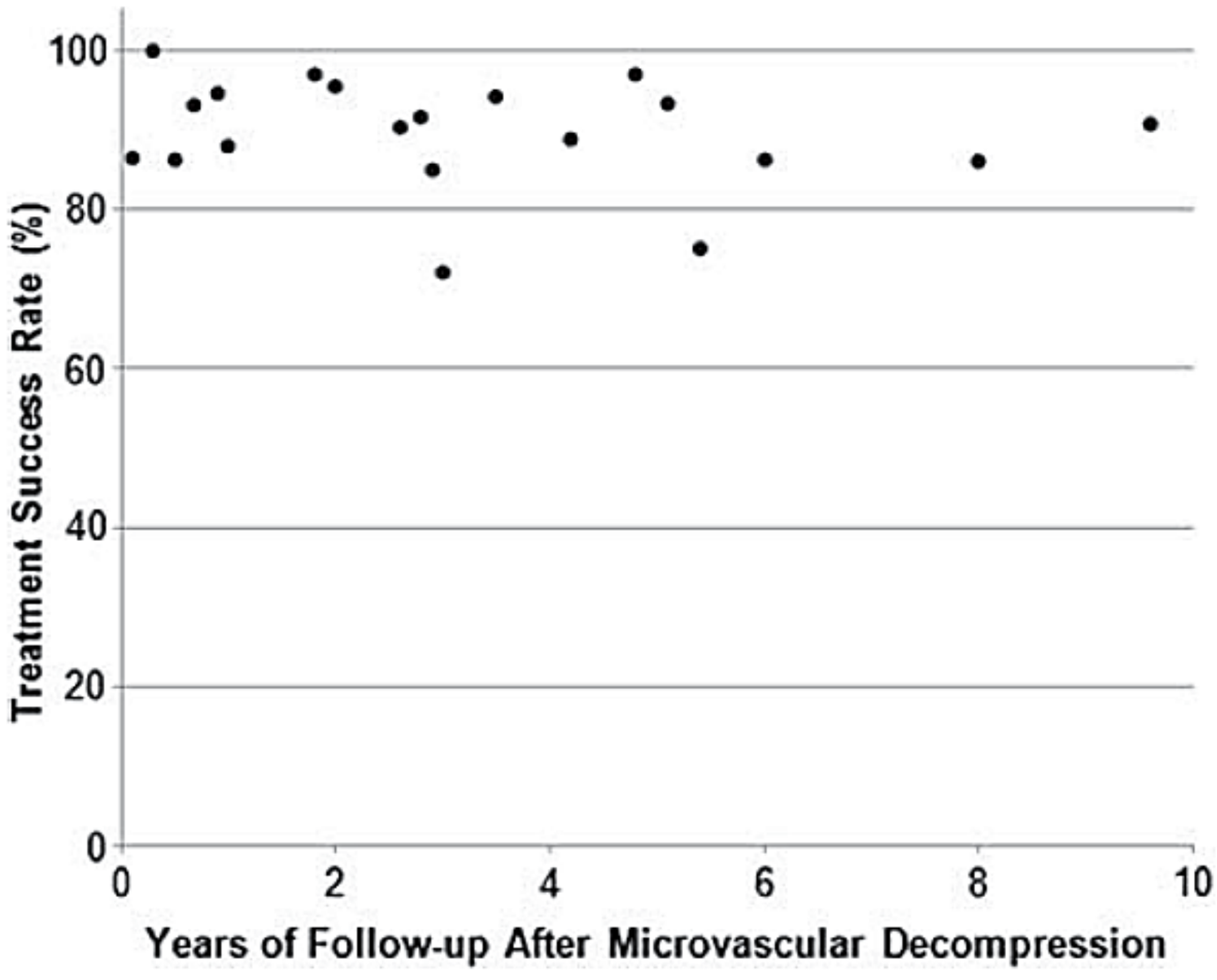
informa
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REVIEW ARTICLE

Safety and effectiveness of microvascular decompression for treatment of hemifacial spasm: a systematic review

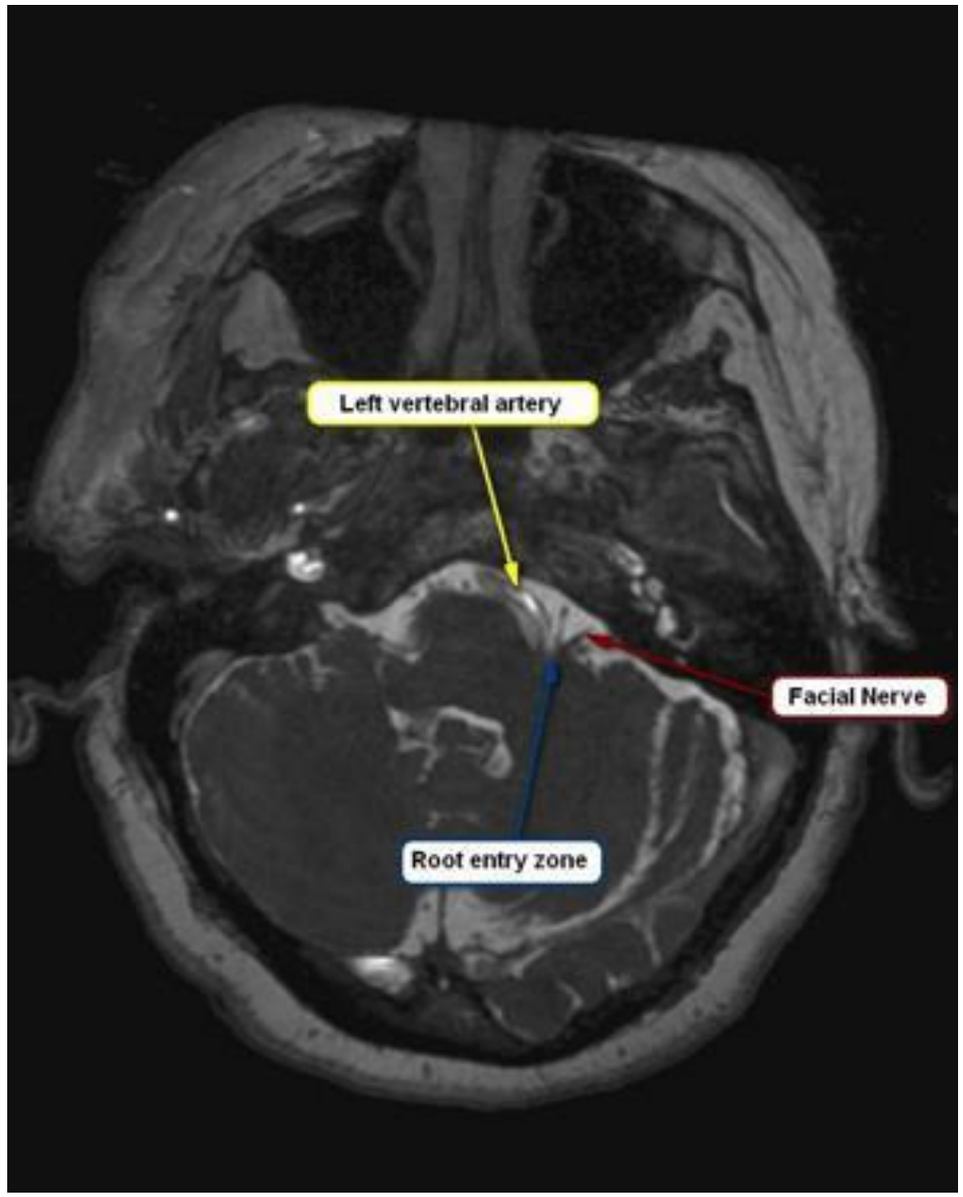
Larry E. Miller & Valerie M. Miller

Review of 22 papers with 5685 patients



Hemifacial spasm

- Unilateral
- Upper face first
  - Spreads to lower face, platysma
- Brief repetitive contractions
  - Tonic and clonic contractions
- Sudden eye closure with elevation eyebrow
- Persists in sleep
- Clicking in ear (stapedius)
- Chronic (remissions< 10%)
- 2:1 female
- Asians> Caucasians



- Aberrant blood vessel with local demyelination of facial nerve (PICA, AICA, VA)
- Ephaptic trasmission

Vascular decompression for HFS
Janetta procedure

- Posterior fossa microvascular decompression
  - PICA (most frequent)
  - AICA
  - Vertebral basilar
- Minimal evidence based reports
  - Up to 90% of patient with improvement,
- Adverse effects
  - Hearing loss in approximately 14%
  - Permanent facial nerve palsy

Kaufmann and Price J Neurosurg 2019
Bartindale et al. Otolaryngol Head Neck Surg 2018
Lee et al World Neurosurg 2019

Complex regional pain syndrome Criteria

The Harden/Bruehl Criteria, which became The Budapest Research[a] Criteria with minor modifications [20,439]:

1. Continuing pain which is disproportionate to any inciting event
2. Must report at least one symptom in each of the four following categories:
   Sensory: report of hyperesthesia
   Vasomotor: reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor/edema: reports of edema and/or sweating changes and/or sweating asymmetry
   Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign in two or more of the following categories:
   Sensory: evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch)
   Vasomotor: evidence of temperature asymmetry and/or skin color changes and/or asymmetry
   Sudomotor/edema: evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There must be no other diagnosis that better explains the signs and symptoms.

Borchers & Gershwin *Autoimmunity Reviews* 2014