



RLS
WEBINAR
SERIES
2017



Restless Legs Syndrome

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Disclaimer

- Grant Support: Lundbeck, Luitpold, PSG, HSG, TRG, RLSF
- Speaking/Consulting fees: TEVA, UCB Pharma, Xenoport, ACADIA



Clinical Definition

- Urge to move the legs with or without paresthesias
- Symptoms worse during inactivity
- Symptoms improve with activity
- Worsening of symptoms in evening and night

Supportive Criteria

- Sleep disturbances
- Normal neurologic examination
- Chronic progressive course
- Periodic limb movements of sleep (PLMS)
- Family history
- Dopamine response

Clinical Description (Paresthesias)

- Need to move
- Crawling
- Tingling
- Cramping
- Creeping
- Pulling
- Painful
- Electric
- Tension
- Discomfort
- Itching
- Heebie Jeebies
- Wriggling maggots
- Fidgets
- Elvis legs

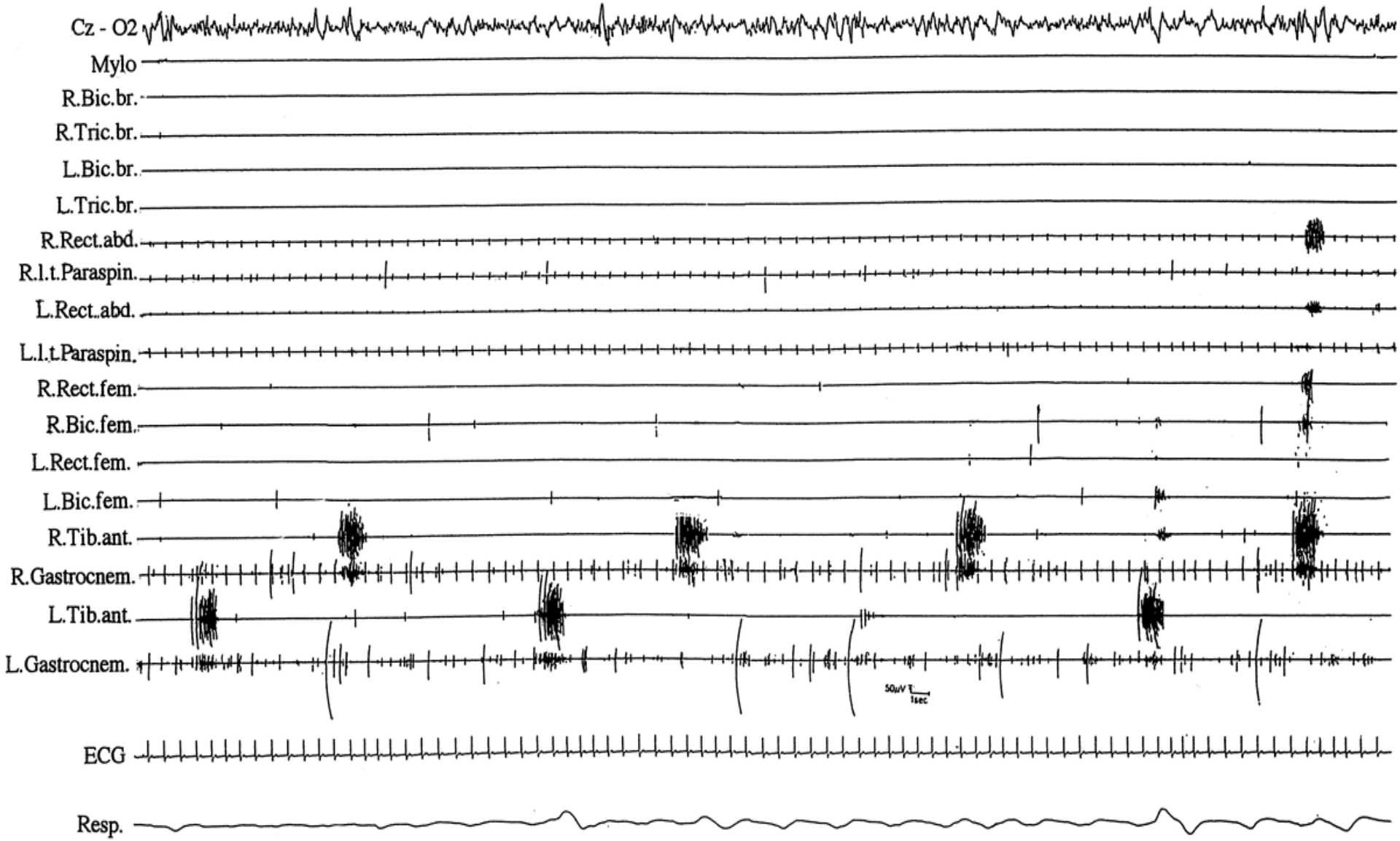
Ondo W. 1996

Clinical Descriptions

- Usually between knees and feet
- Deep sensation (90%)
- Bilateral, unilateral or alternating
- Arms may be involved (22%-57%)
- Periodic Limb Movements of Sleep (PLMS)



PLMS



Differential Diagnosis

- Akathisia
- Painful legs and moving toes
- Nocturnal leg cramps
- Growing pains
- Attention deficit hyperactivity disorder
- Vesper's curse
- Orthostatic hypotension
- Orthostatic tremor
- PLMS without RLS
- Psychogenic



RLS in Children

- No definitive epidemiology (1-2%)
- Many children do not meet criteria for adult RLS

May present with:

- “growing pains”
- Associated with low ferritin and PLMS
- Attention deficit hyperactivity disorder

Picchietti D, 2013

RLS and ADHD

ADHD Children have:

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

Picchiatti 1998, Picchiatti 1999, Cherven 2002



Epidemiology of RLS

- REST = 9.6 % (U.S. Europe)
- Hogl = 10.2% (Austria)
- Berger = 10.6 % (Germany)
- Rothdach = 9.8 % (Germany)
- Phillips = 10.0 % (Kentucky)
- Stepansky = 7.9 % (Austria)
- Lavigne* = 10-15 % (Canada)
- Ulfberg = 5.8% m 11.4% w (Sweden)
- Tan = <1% (Singapore)
- Kageyama = 1.5 % (Japan)

Epidemiology (REST Study)

Country	N	Any	Weekly
UK	2114	14.2	11.3
USA	3655	13.3	11.3
Germany	6723	11.4	7.9
France	4804	7.4	5.0
Spain	5752	5.5	3.6
Total	23052	9.6	7.1



Epidemiology

- Highest in Caucasion, esp Scandanavian
- Women > men 2:1
- Onset any age
 - 45 often cut-off between young and old onset



RLS Pathophysiology

What causes RLS?

RLS Pathophysiology

- Genetic Evaluation
- Pharmacologic Response
- Animal Models
- Imaging
- Functional Studies
- Pathology



Genome Wide Associations

Chrom	Gene	O.R.	Distribution	
6p21.2	BTBD9	1.47	Diffuse	Zinc Finger
2p	MEIS1	1.68	Diffuse	homobox gene
9	PTPRD	1.29	Spinal cord	mitogen-activated protein kinase
15q23	MAP2K5/ SKOR1	1.41	Diffuse	Atypical protein kinase
2p14	Intergenic Near MEIS1	1.23		
16q12.1	TOX3	1.33		Non-histone chromatin



Multiple RLS Genetic Loci



Chr 12q – RLS1



Chr 14q – RLS2



Chr 9p – RLS3



Chr 2q

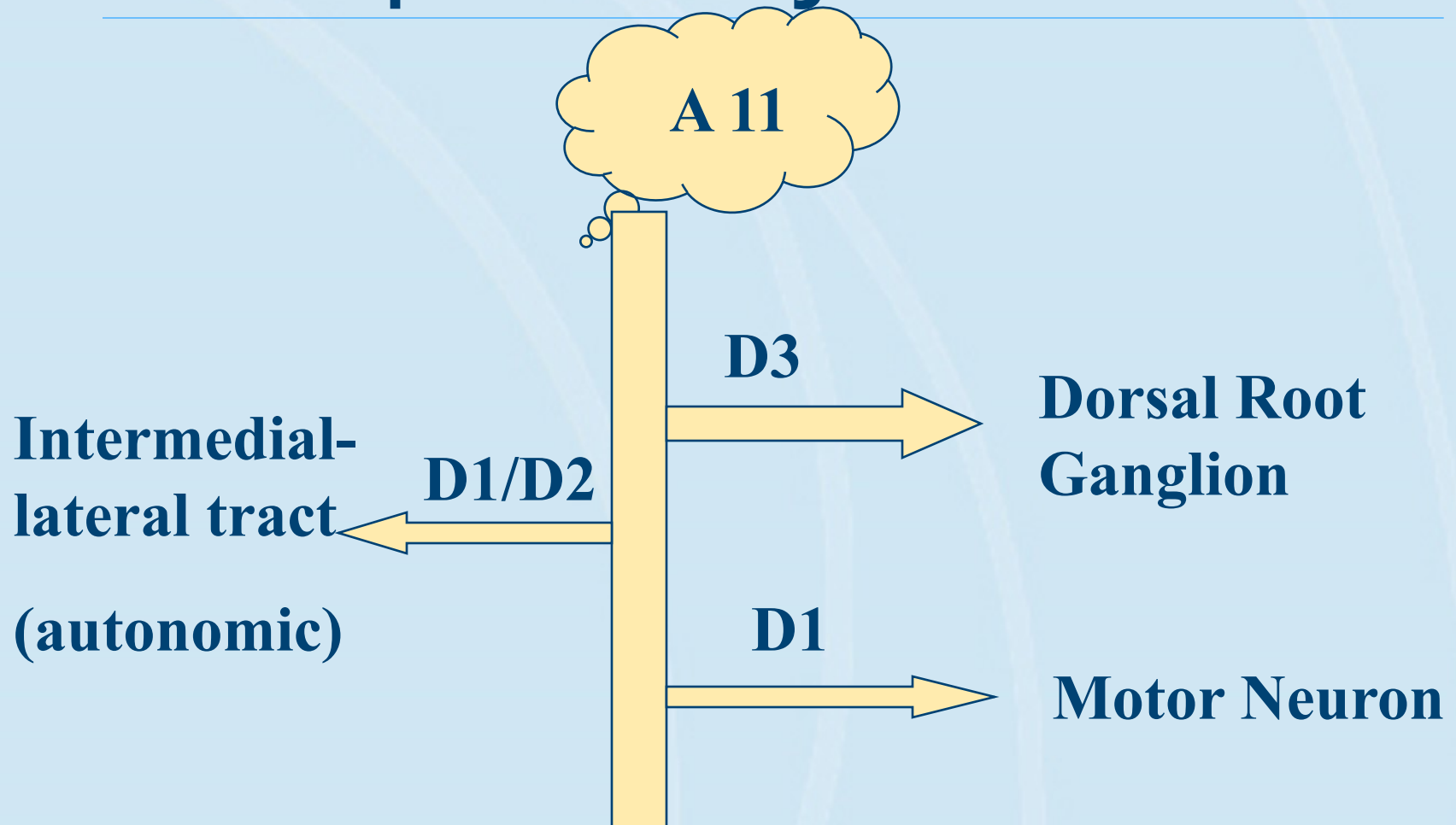


Chr 20p

Animal Models of RLS ?



A11 Spinal Projections



Human Neurologic Studies

- Normal gross MRI
- No Bereitschaftspotential (BP) preceding DWA
- No cortical back-averaged potentials in PLMS
- Near normal electrical blink reflex
- Normal BAER and SSEP
- Normal H reflex, H/M ratio



Dopamine PET / SPECT Studies (generally unremarkable)

- 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
 $\frac{1}{2}$ studies: mild reduced striatal D_2 binding



MRI (mixed data)

- Mildly increased pulvinar grey volumes ¹
- Decreased bihemispheric primary somatosensory cortex grey matter ²
- No volumetric changes ³
- No volumetric changes ⁴
- Increased fractional anisotropy in diffuse white matter ⁵

1. Etgen T 2005, 2. Unrath A, 2007, 3. Hornyak 2007, 4. Celle S, 2009, 5. Unrath A 2008,



Brain Iron Content in RLS

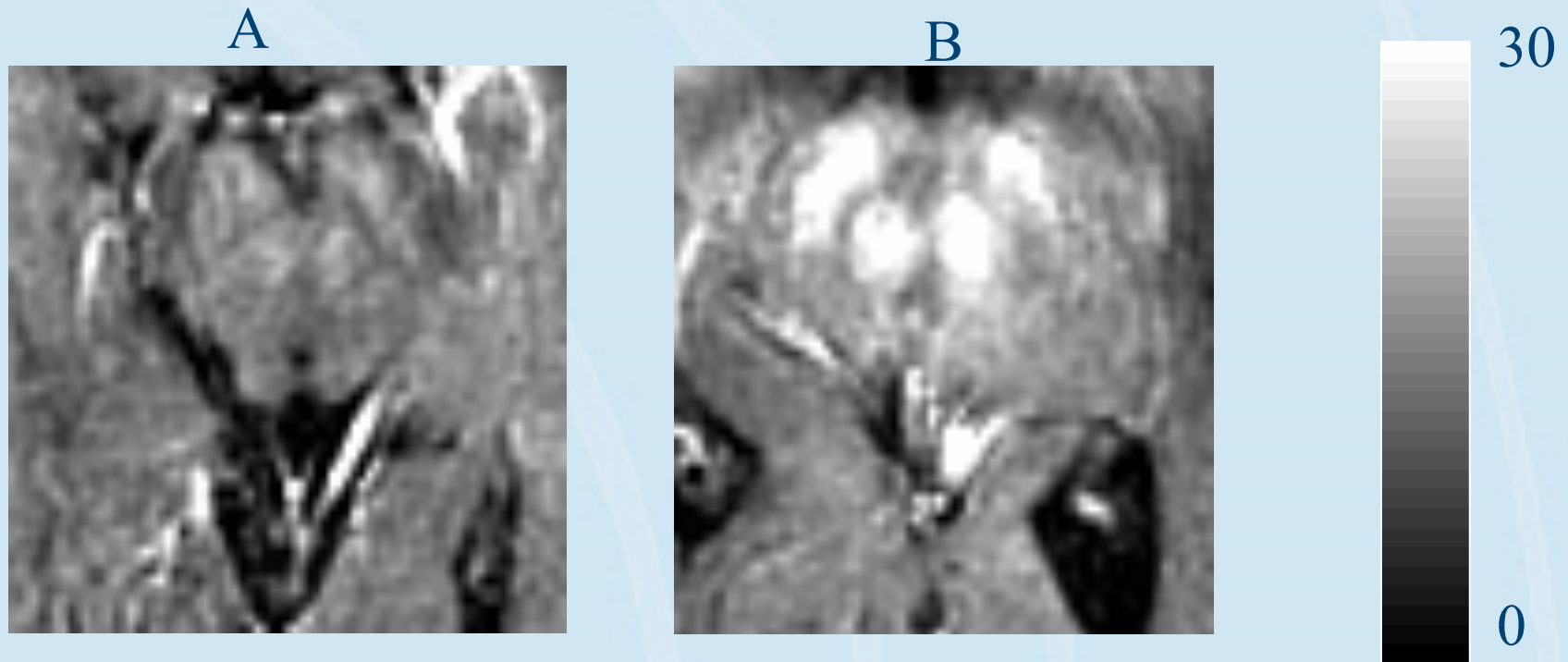


Figure 2. R2* images in (A) a 70 year old RLS patient and (B) a 71 year old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both red nucleus and substantia nigra.

(Allen RP, Earley CJ and Barker P Johns Hopkins Univ.)

Ultrasound showing decreased echogenicity in the midbrain area of the nigra for RLS compared to control

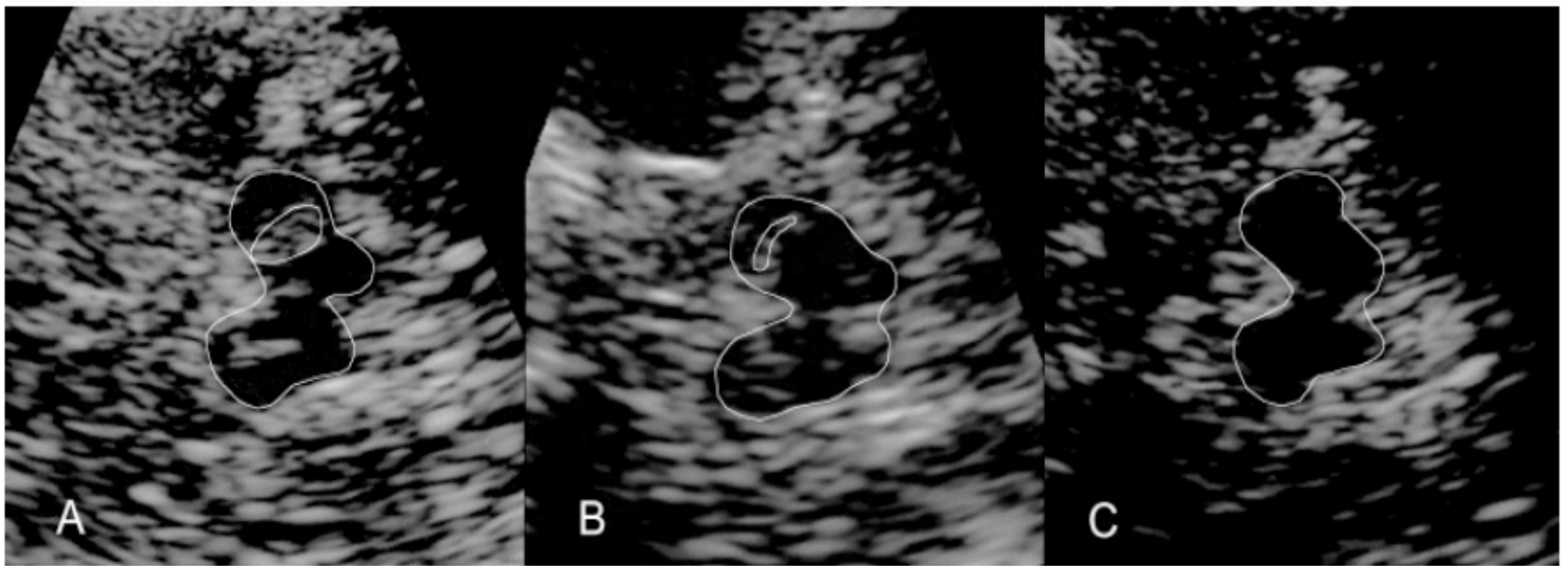


Fig 2. Typical examples of transcranial ultrasound appearances (axial scanning plane) in three patients. (A) Patient with Parkinson's disease (PD). (B) Normal control subject (CO). (C) Patient with restless legs syndrome (RLS). Midbrain and areas of hyperechogenicity encircled in (A) and (B) on the side of insonation.

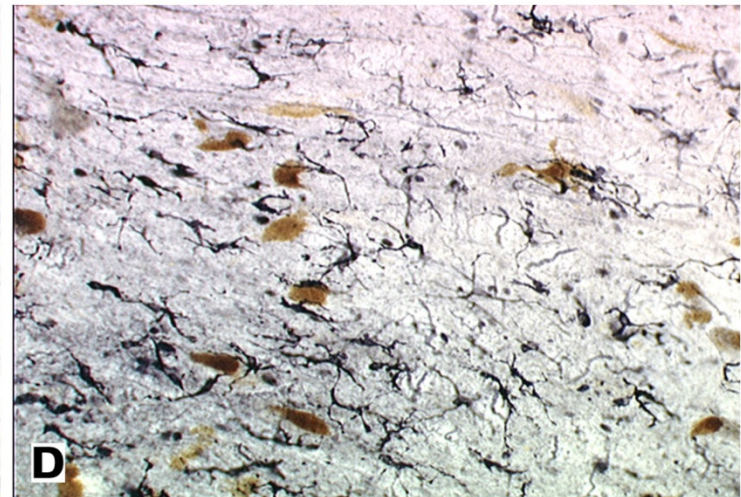
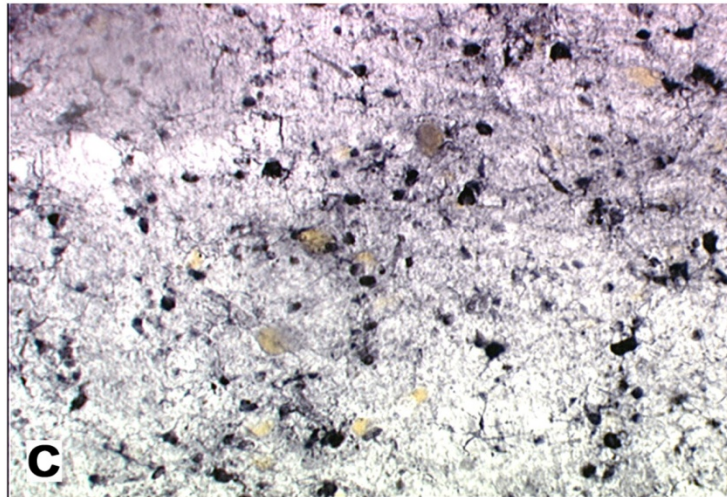
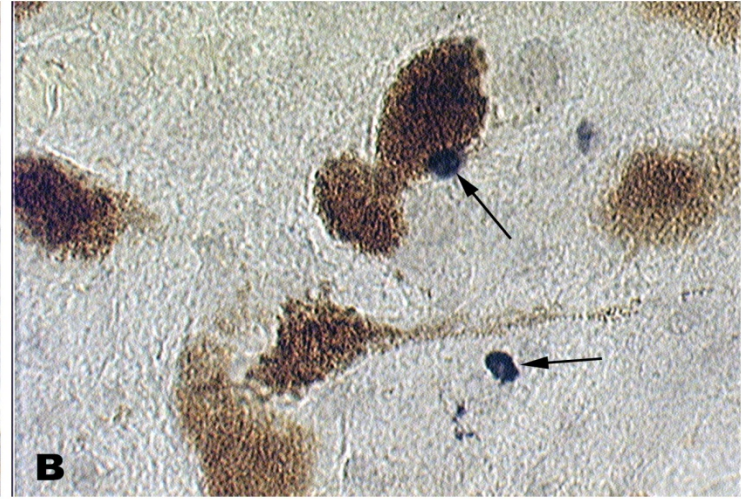
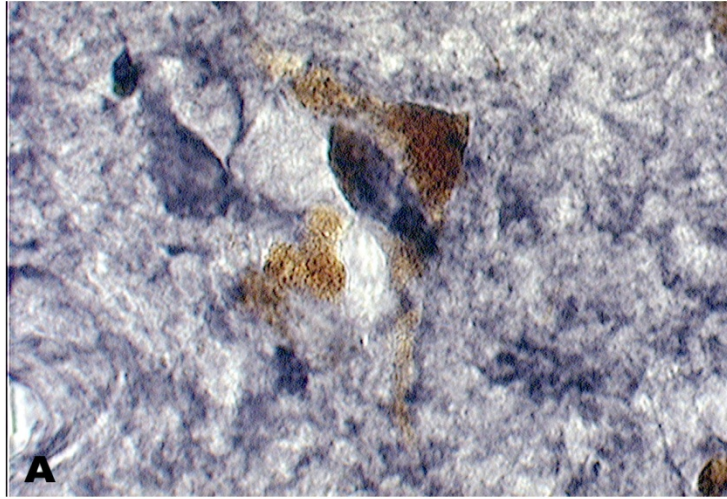
(Schmidauer, et al, Ann Neurol 58:630-634, 2005)

RLS Human Pathology

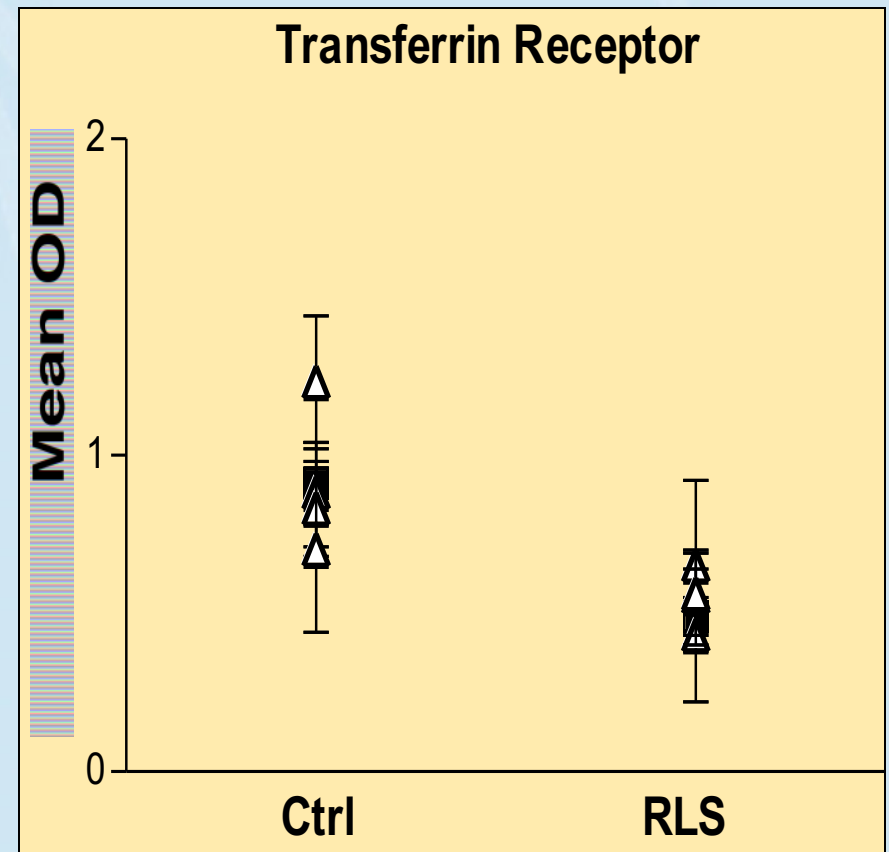
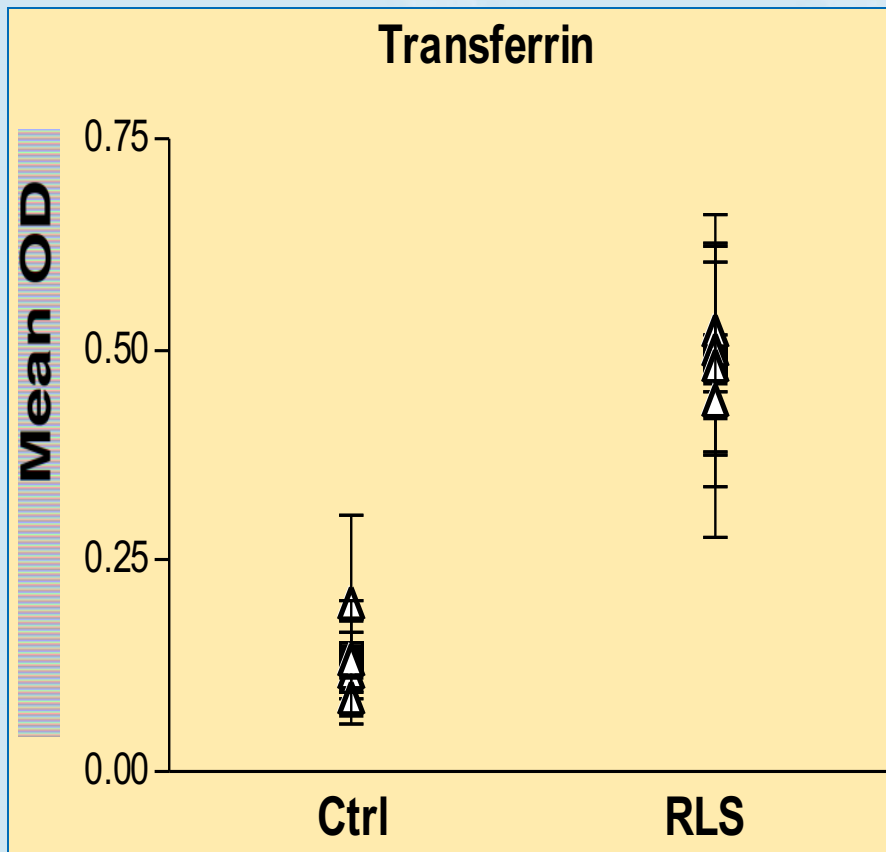


H-ferritin

L-ferritin



Transferrin and Transferrin Receptor Expression in Neuromelanin cells isolated from Substantia Nigra



Iron and Dopamine

Co-factor for tyrosine-hydroxylase

- Rate limiting step for dopamine synthesis

Component of the D2 receptor

- Down-regulates D2 receptors
- Changes behavior

Thy-1 reduced

- Involved in dopamine release



Restless Legs Syndrome Associated Conditions

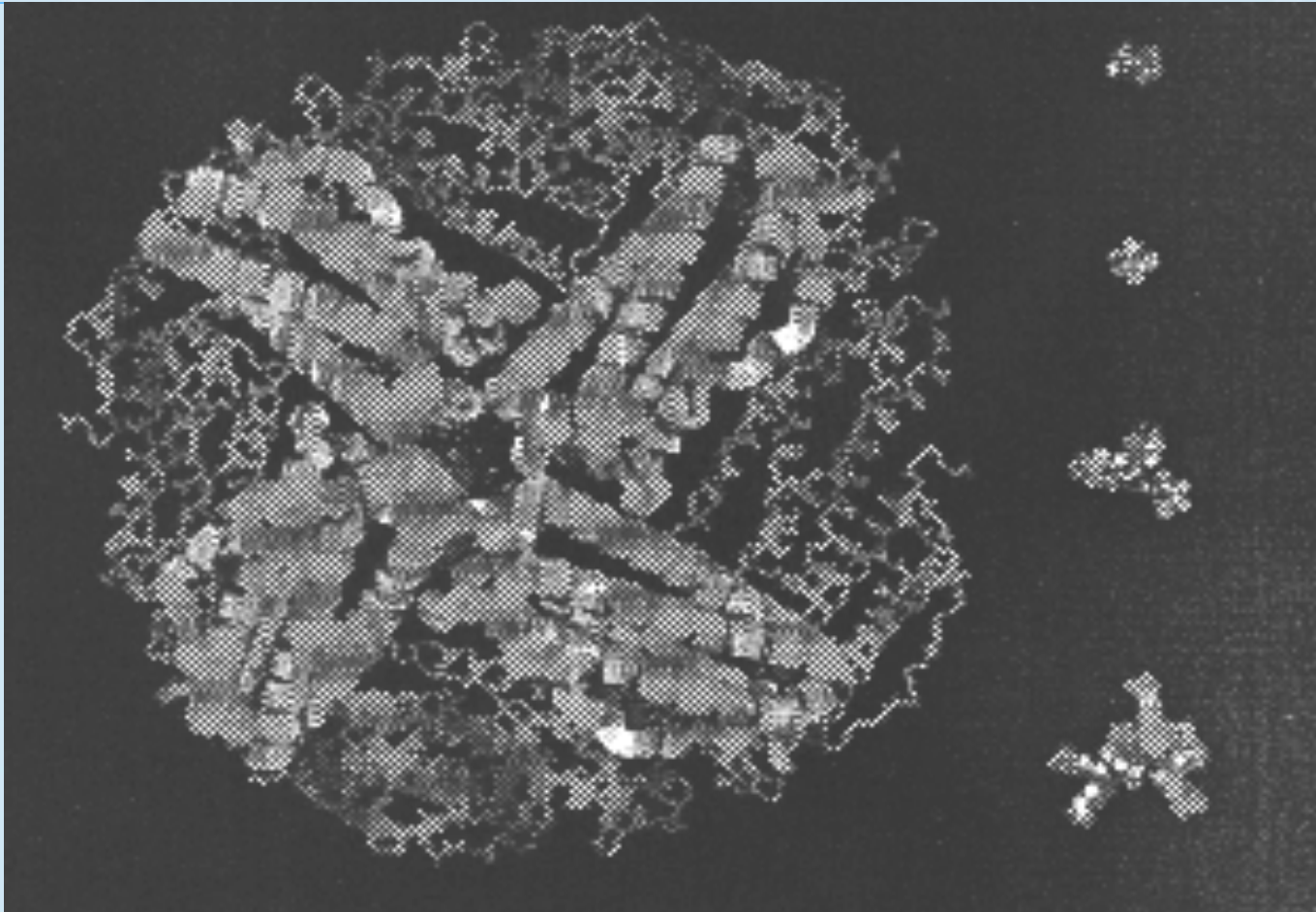


Secondary Causes of RLS

- Iron deficiency*
- Renal failure*
- Neuropathy*
- Pregnancy*
- Multiple sclerosis*
- Essential Tremor
- Parkinson's Disease
- SCA – 3 (Machado-Joseph)
- MANY OTHERS



Ferritin Model with other FE species



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



Serum Ferritin and RLS

Late Onset of RLS (Non-familial)

- Lower serum ferritin
- Severity correlated with serum ferritin levels

Early onset of RLS (Familial)

- Normal serum ferritin
- Severity not correlated with ferritin levels

Uremic (Kidney failure) RLS

- Can very very severe
 - Increased PLMS
- Correlates with mortality
- Does not improve with dialysis
- Does improve with successful transplant
- Same treatments but may need higher doses

Neuropathy in RLS Patients OR RLS in Neuropathy Patients



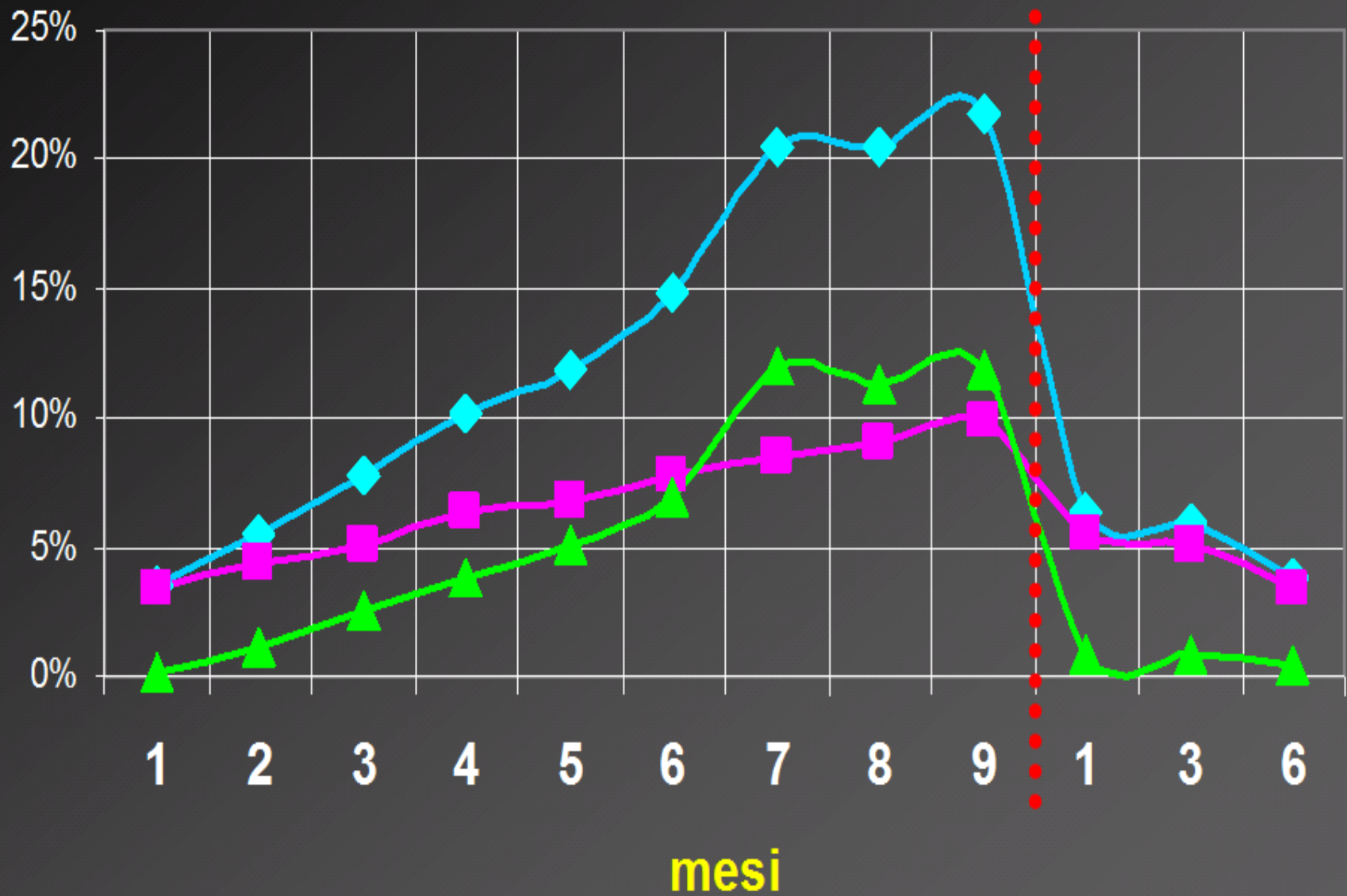
Multiple Sclerosis

- 20-40% of cases have RLS
- More common if spinal chord is involved
- More common in Progressive MS

Pregnancy

- Incidence = 11% - 27 %
 - Associated with low folate, Hgb, low iron
 - estradiol
- Usually third trimester
- Symptoms resolve with delivery
- Rate of later life recurrence unknown
- Multiple pregnancies may be risk for RLS





—◆— tot RLS —■— pre RLS —▲— new RLS

Pregnancy RLS Risk Factors

- Low folate
- Low iron
- Increased estradiol

Boetz M NEJM 1976, Lee K. J Wom Health Gen Med 2001, Fulda S J Sleep Res 2004

Medications

- Anti-histamines
- Dopamine blockers
- Anti-depressants



Treatment of Restless Legs Syndrome



Caveat

- No two people are alike
- Everything I say may be wrong for you



RLS Treatments

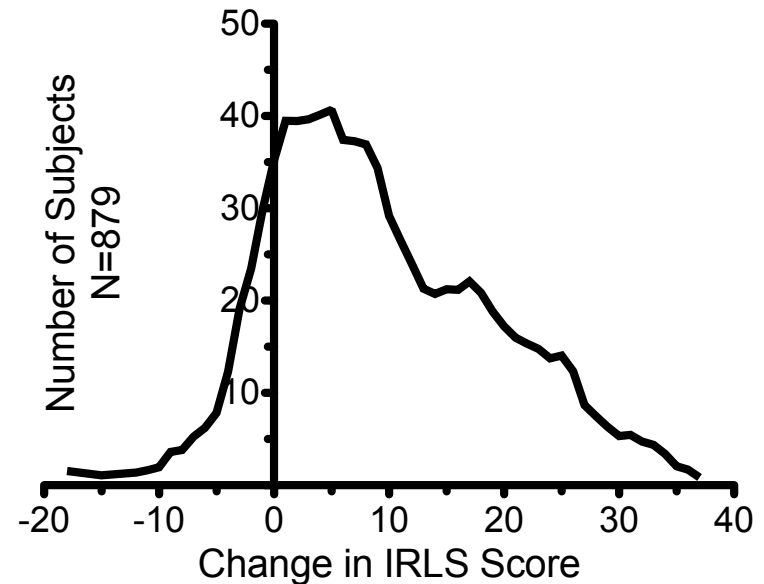
- Dopamine Agonists
- Gabapentin (Enacarbil)
- Pregabalin
- L-dopa
- Opioids
- Benzodiazepines
- Tramadol
- Carbamazepine
- Clonidine
- amantadine
- Iron (oral, IV)
- Mg⁺⁺
- Sclerotherapy
- TENS unit
- Thermal therapy
- Any sensory therapy
- Cognitive Activation



IRLS Placebo Response

Belgium	3	22.33 (4.61)
Finland	65	12.10 (9.19)
Ireland	24	11.88 (10.92)
Slovakia	5	11.20 (8.58)
Spain	20	10.75 (10.25)
USA	214	10.44 (9.08)
United King	79	10.27 (8.74)
Netherlands	46	10.04 (8.29)
South Kor	27	9.89 (8.63)
Italy	52	9.42 (11.59)
Norway	36	8.64 (9.51)
Sweden	119	8.26 (9.37)
Germany	149	7.31 (10.76)
Denmark	14	7.21 (11.17)
Austria	11	6.91 (11.40)
France	15	5.07 (8.02)
MEAN	879	9.51 (9.78)

Figure 1. Distribution of Placebo IRLS Scores



Predictors: greater IRLS score ($p < 0.001$), absence of previous dopaminergics ($p < 0.001$), female sex ($p = 0.05$), randomized drug: placebo ratio of $> 1:1$ ($p < 0.001$), and trials in America ($p < 0.001$)

Dopaminergics

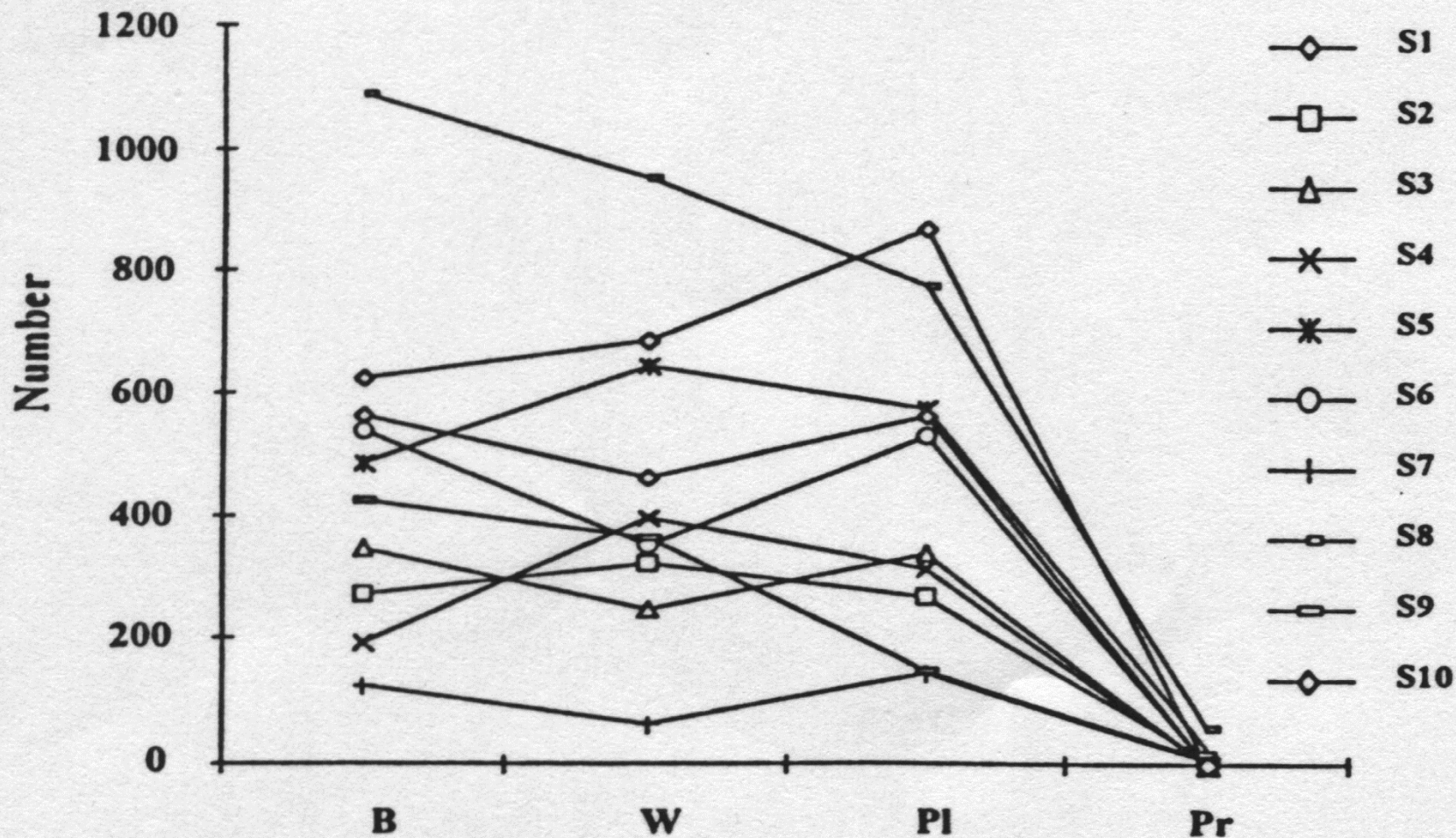
- Pramipexole* (Mirapex)
- Ropinirole* (Requip)
- Rotigotine* (Neupro)
- Pergolide (Permax)
- Bromocriptine (Parlodel)
- Cabergoline (Dostinex)
- Apomorphine
- Lisuride / Sumanriole
- Levodopa

Rotigotine / Pramipexole / Ropinirole (Comparisons)

- Overall results are similar
 - International RLS Rating Scale
 - Clinical Global Impressions
- All studies have large placebo response
- Rotigotine had a modestly higher percentage of complete responders
- Mirapex ER and Requip XR not tested in RLS



PLMS After Pramipexole



Dopaminergic Side Effects

- NO dyskinesia
- NO psychosis (hallucinations)
- Minimal orthostatic hypotension
- Mild impulse control disorders (gambling)
- Nausea, sedation, nasal congestion
- Augmentation



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



Risks for Augmentation

- Family history of RLS
- Lack of Neuropathy
- Dopamine dose
- Low ferritin (iron)
- Shorter acting dopaminergics



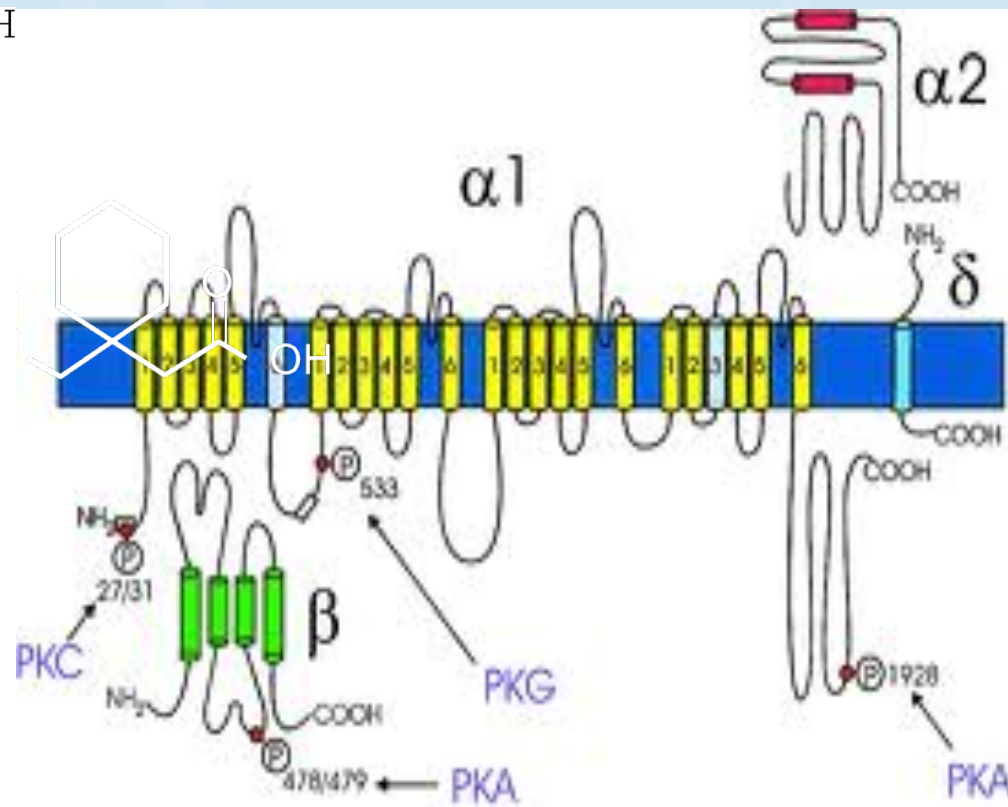
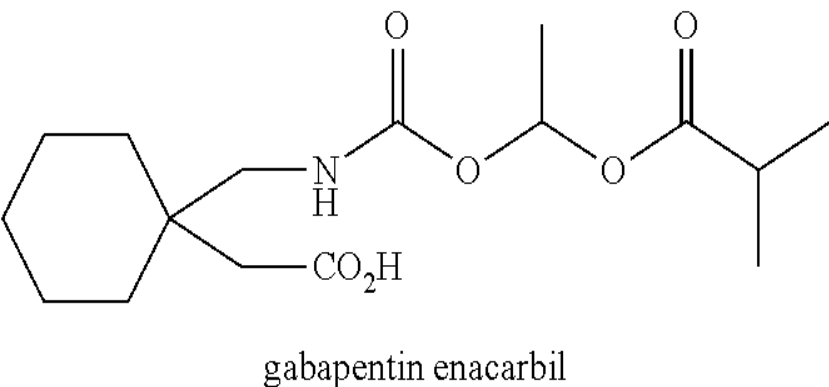
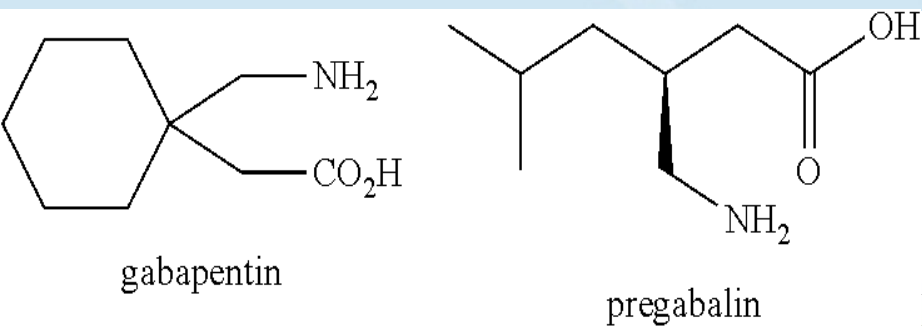
Dopamine Agonist Strategy

- Time dose according to symptoms
 - usually 1-3 doses
- Titrate to lowest dose that stops symptoms
- Avoid continuous dose augmentations after effective treatment initially achieved
- Consider rotating different dopamine agonists

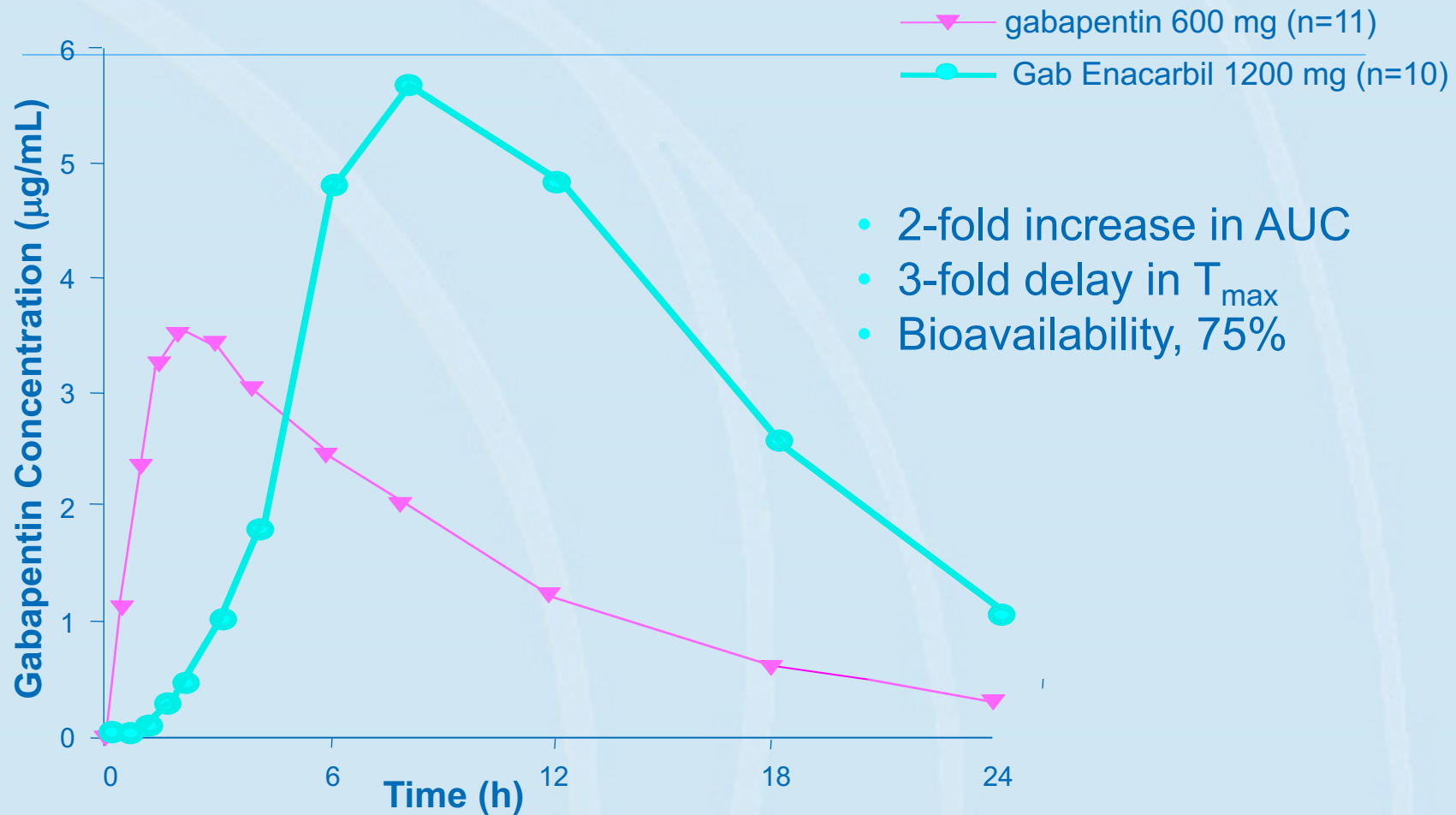


Alpha-2delta Subunit Voltage Gated Calcium Channel

Gabapentin, Gabapentin enacarbil, Pregabalin



Mean Concentrations of Serum Gabapentin After Oral Near-Equal Gabapentin Enacarbil or Gabapentin in Healthy Adults



2 mg of gabapentin enacarbil ~1 mg of gabapentin.

AUC indicates the area under the plasma concentration-time curve; T_{max}, time to maximum plasma concentration. XenoPort, Inc., Study XP022, data on file.

Alpha-2 Deltas vs. Dopaminergics

- Similar overall improvement in overall RLS

Dopaminergics:

- better PLMS reduction
- “urge to move” almost always improves

Alpha-2-Delta:

- Sleep architecture (SWS) improves
- Pain improves
- Less augmentation?

Opioids: A Long History

Used by Willis in his first description of RLS

- ...“ leapings and contractions of the tendons , and so great a restlessness and toppings of their members ensue that the diseased are no more able to sleep than if they were in a place of the greatest torture”
1685
- Tincture of opium

Willis T. Two discourses concerning the soul of brutes 1683



Opioid Overview

- May treat sensory more than motor symptoms
- Extended oxycodone-naloxone best studied
- Methadone most commonly used in U.S. ¹
- Usual adverse events:
 - Constipation, sedation, decreased testosterone
- Dose often very stable over many years
- Addiction and dependency relatively uncommon

Trenkwalder C, Lancet Neurol 2013



Iron

- Oral iron very poorly absorbed
 - Empty stomach
 - Avoid divalent cations including calcium, MVI
 - Organic preparations
- Intravenous iron
 - Markedly increases serum iron
 - Mixed data in studies, may depend on specific type



Iron Preparations

Intravenous:

- Iron dextran-low molecular weight (Infed)*
- Iron dextran-high molecular weight (Dexferrum)
- Iron Sucrose (Venofer)
- Ferric gluconate (Ferrlecit)
- Ferumoxytol (Feraheme)
- Ferric carboxymaltose (Ferinject)*

Oral

- Iron sulfate, iron sucrose, iron fumarate, iron gluconate, iron dextran, ferroglycine sulfate





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Question & Answer

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