Restless Legs Syndrome

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Disclosures

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Restless Legs Syndrome (RLS)

Overview

- Clinical features
- Epidemiology and Genetics
- Early (primary) versus late-onset (secondary) RLS
- Pathophysiology
  - Brain iron dyshomeostasis
  - Link between iron deficiency & dysfunction in the dopamine and other neurotransmitter systems
- Treatment

Restless Legs Syndrome (RLS)

Definition

A sensorimotor disorder characterized by:

an irresistible urge to move the legs,

often accompanied by uncomfortable sensations,

that typically occurs in the evening or when at rest,

and which may be temporarily relieved with movement

Allen et al. *Sleep Med*. 2003;4:101-119.

RLS - Historical Aspects
[Descriptive]

- Thomas Willis (1685)
  - *"Instructions for Curing the Watching Evil"*

"Wherefor to some, when being in bed they betake themselves to sleep, presently in the arms and legs, leapings and contractions of the tendons and so great a restlessness and tossing of their members ensue that the diseased are no more able to sleep, than if they were in the place of greatest torture."

RLS - Historical Aspects
[Conceptual]

- 1861: Theodor Wittmaack - “anxietas tibiarum” (form of hysteria)

- 1923: Herman Oppenheim - “Restlessness in the legs is a special kind of subjective paralgesia. It can become an agonizing torture, lasting for years or decades, and can be passed on and occur in other members of the family”

- 1944: Karl Ekbom - “Restless legs syndrome”

  - clinical symptoms and 8 cases published (1945)

Diagnostic Criteria for RLS

(International Classification of Sleep Disorders, 3rd Edition, 2014)

Criteria	Specifications
A. An urge to move the legs, usually accompanied by uncomfortable and unpleasant sensations in the legs.	These symptoms must 1. Begin or worsen during rest or inactivity (eg, lying down or sitting); 2. Be partially or totally relieved by movement, such as walking or stretching; and 3. Occur exclusively or predominantly in the evening or night rather than during the day.
B. These features are not solely accounted for as symptoms of another medical or a behavioral condition.	Examples: habitual foot tapping, leg cramps or positional discomfort, myalgia, venous stasis, leg edema, arthritis.
C. The symptoms of RLS cause dysfunction.	Levels of dysfunction: concern; distress; sleep disturbance; or impairment in mental, physical, social, occupational, educational, behavioral, or other important functional areas.

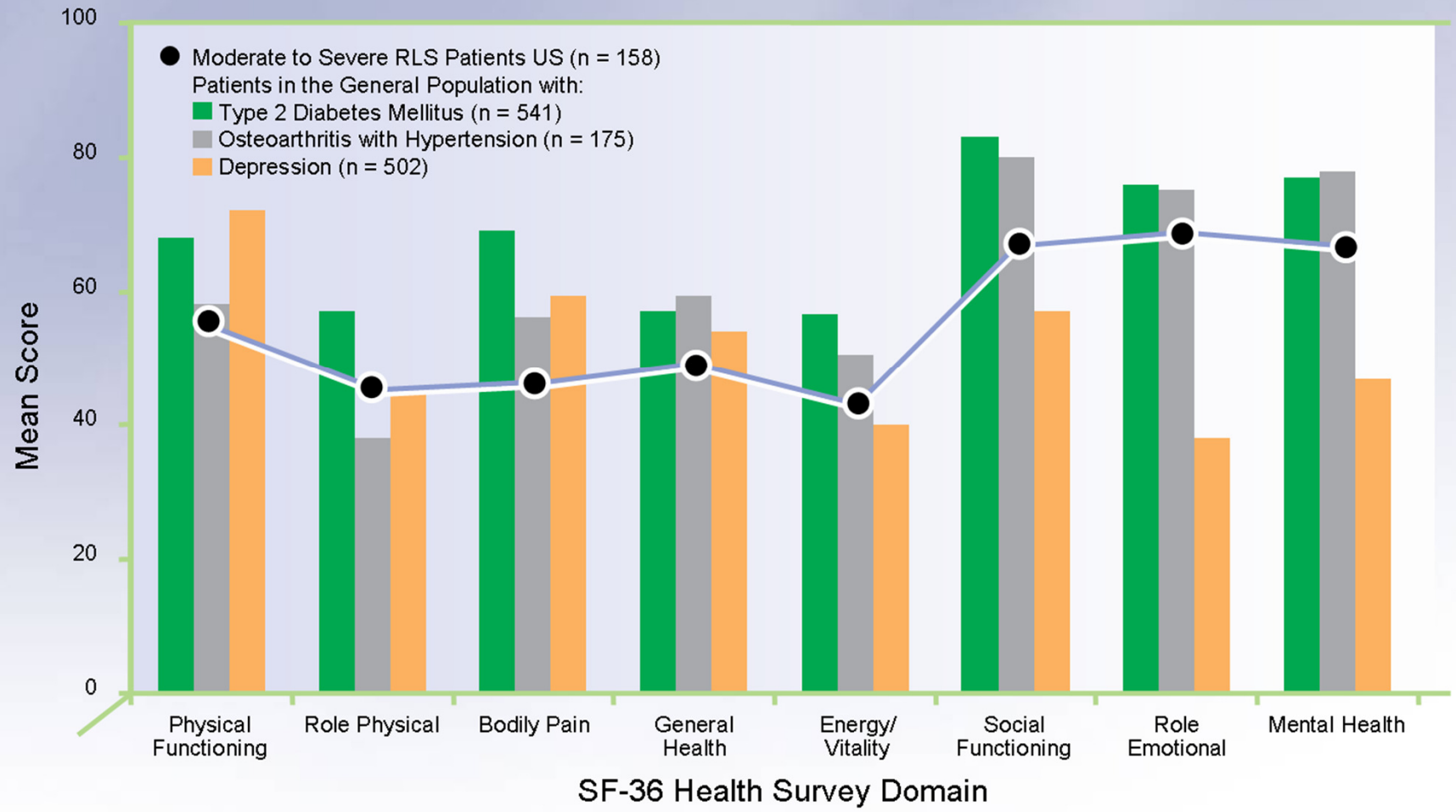
Chronic Versus Intermittent RLS (IRLSSG)

- Chronic-persistent RLS:
  - ≥ x2/week for past year (average, untreated)
- Intermittent RLS:
  - < x2/week for past year, with ≥5 lifetime events

RLS: DSM-5 Criteria

- Consistent with IRLSSG criteria, with additional specifications:
  - Sx occur ≥3x/week, persistent for ≥ 3 months
  - Sx cause significant distress or impairment of social, occupational, educational, academic or behavioral functioning
  - Can't be explained by effects of a drug or abuse of medication
  - Supportive clinical features (NIH workshop): positive family history, positive response to dopaminergic therapy, presence of periodic limb movements in sleep (PLMs)

RLS Impact on QOL Resembles the Impact of Major Diseases



Adapted from Allen RP, et al. *Arch Intern Med*. 2005;165:1286-1292.

RLS Prevalence

REST Study

(RLS Epidemiology, Symptoms, and Treatment)

Multinational survey (182 primary care practices)

23,052 patients completed RLS diagnostic symptoms questionnaire

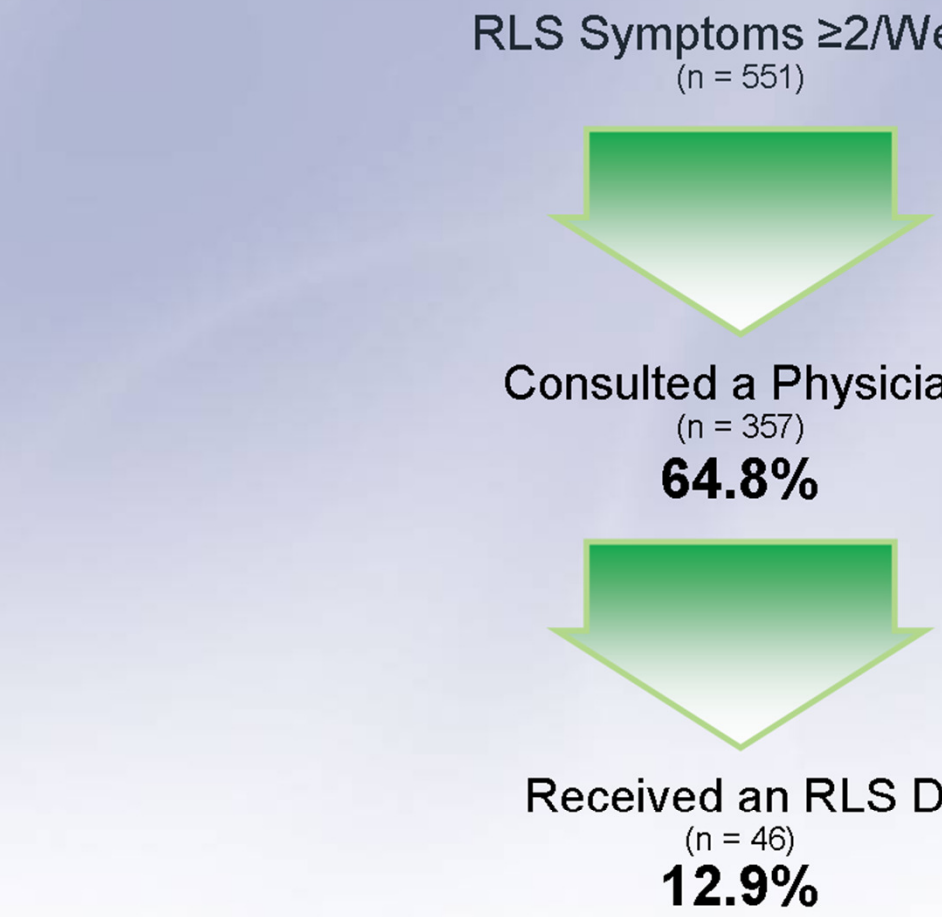
- Prevalance of RLS
  - 11.1% - RLS symptoms occurring at any frequency
  - 9.6% - RLS symptoms occurring at least once a week
  - 3.9% - RLS symptoms occurring at least twice a week

Hening et al, 2004

Epidemiology of Restless Legs Syndrome

- Prevalence[1,2]
  - Affects approximately 10% of US adults; 12 million individuals in US have moderate to severe RLS; 1.6-2.0% prevalence in Asia and South America
- Mean age of onset 3rd-4th decade (varies widely); onset before age 45 indicates an increased risk of the disorder among 1st and 2nd degree relatives
- 2% prevalence in children; prevalence increases with age
- F:M prevalence = 2:1 if > 35 yrs old

RLS is Often Undiagnosed



Hening W, et al. *Sleep Med*. 2004;5:237-246.

Missing the RLS Diagnosis – Look for Sleep Complaints

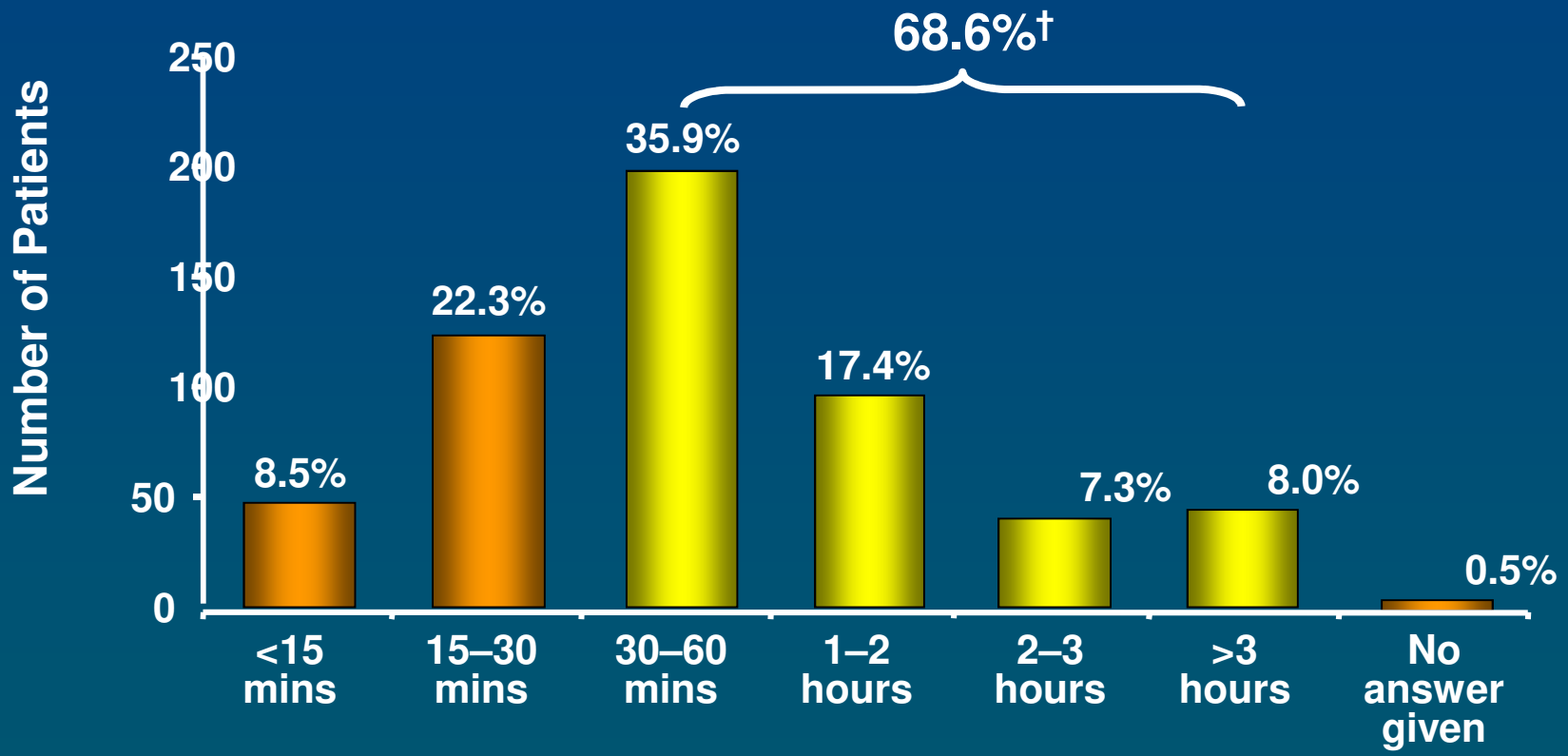
- A large cohort study of 62 primary-care practices in 6 Western European countries found that 91% of patients with RLS had not been previously diagnosed [1]

- Patients may initially report sleep complaints rather than leg symptoms, especially difficulty falling asleep [2]

[1] Allen et al, 2010 **[2]Earley, 2003**

REST Study

Time Required for Patients to Fall Asleep*



Difficulty falling asleep may frequently be associated with moderate-to-severe RLS.

* n=551, time self-reported by patients.

† Indicates the range of values considered abnormal and representing insomnia.

Hening et al. Reprinted from *Sleep Med.* 2004;5:237-246.

Periodic Leg Movements
A Supportive Feature of RLS

- Periodic Leg Movements (PLMs) occur in at least 80% of people with RLS[1]
  - x1 /20-40 secs, last for 0.5- 5 secs.
  - Rhythmic extension of big toe and ankle dorsiflexion, ± knee and hip flexion, but may be variable
  - Strongly supportive when PLMS > 7/hr; rate correlates well with subjective RLS severity scales
  - Can be accompanied by nighttime awakenings or transient arousals, disrupting sleep, but can also be an epiphenonmenon, not recognized by the patient but reported by the bed partner

Periodic Limb Movements During Sleep

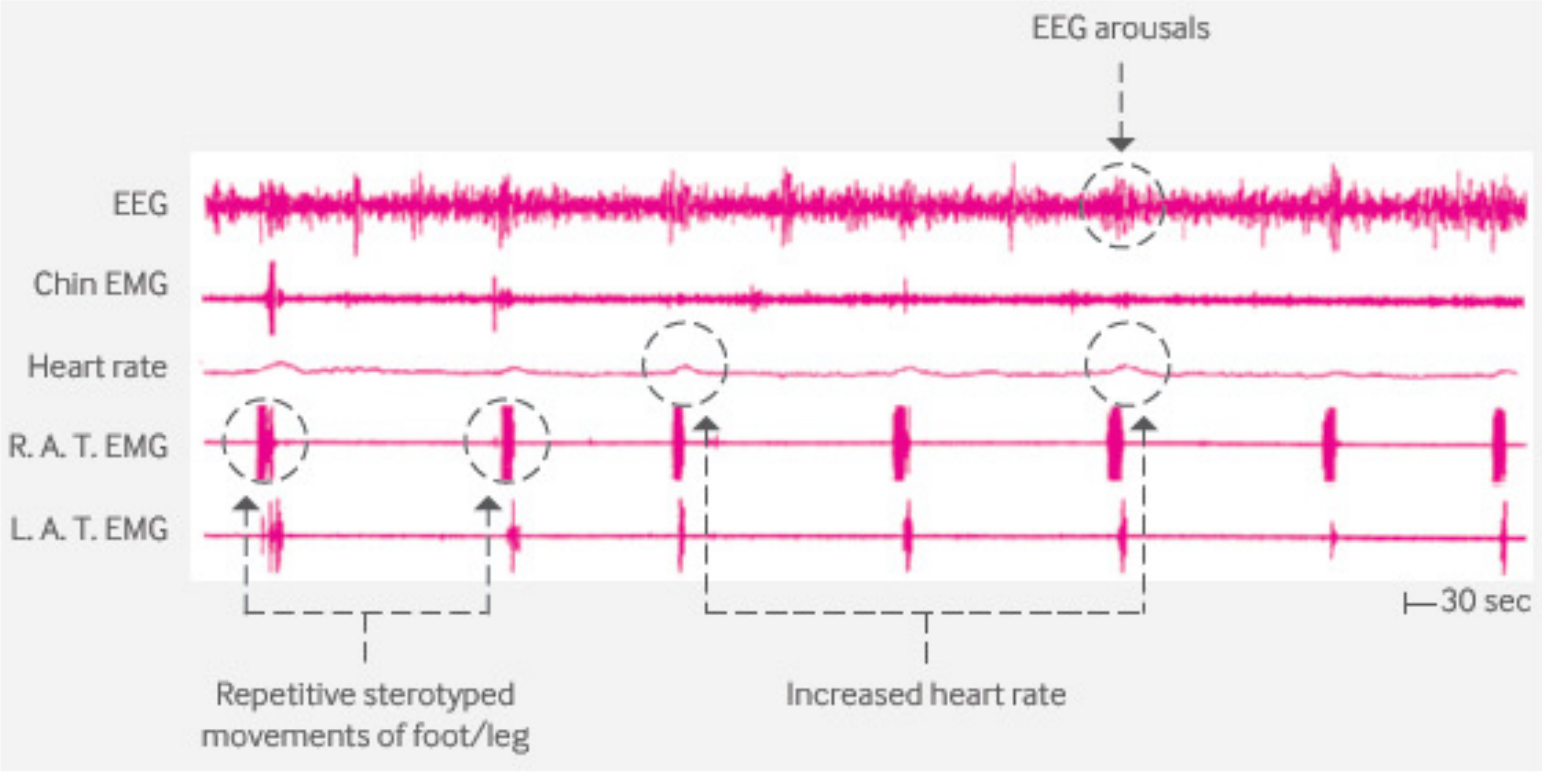


Fig 1 | Periodic leg movements (PLMs) during sleep. The presence of repetitive PLMs causes arousals seen on electroencephalography, which contribute to sleep fragmentation. In addition, repetitive sympathetic arousals are caused, which might lead in the long term to systemic hypertension and increased cardiovascular risk

Early versus Late-Onset RLS

- **Early-Onset/Primary RLS**
  - Peak incidence: 20-40 years
  - Accounts for most cases of RLS and involves CNS dysfunction
  - Likely familial: +ve FH in 50% - 60% of cases
  - Slow disease evolution

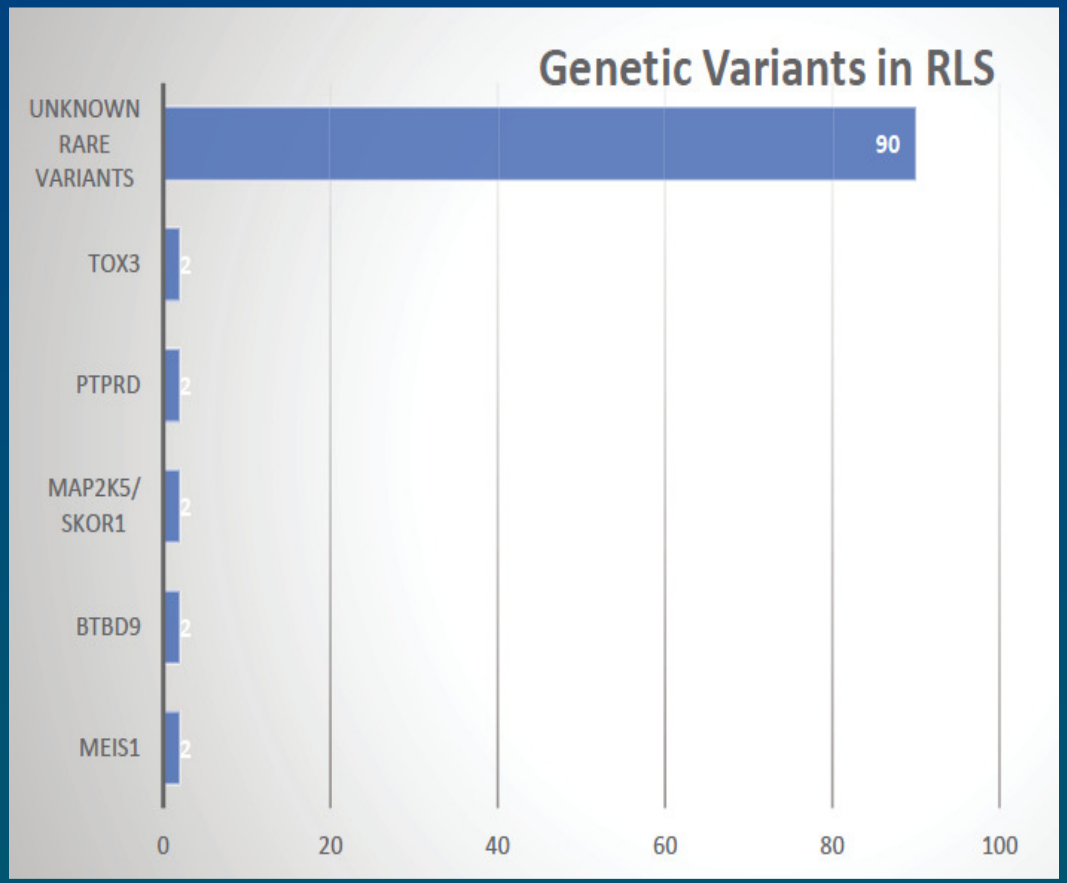
- **Late-Onset/Secondary RLS**
  - Onset after 45 years of age
  - May be a genetic contribution in some cases
  - Associated comorbidities are more common, especially iron deficiency
  - RLS may improve if underlying condition resolves or is treated

Genetics of RLS

- Initially considered a Mendelian disease, with autosomal dominant inheritance, it is now considered as a complex multifactorial disorder with both genetic and non-genetic factors contributing to susceptibility

- Genome-wide association studies have identified 6 different genes (BTBD9, MEIS1, MAP2K5/LBXCOR1, PTPRD, TOX3) with allelic variants (single nucleotide polymorphisms) which convey RLS risk. These loci suggest new concepts such as neurodevelopmental processes and links to known pathways such as iron metabolism

Genetic Variants in RLS



BTBD9 (chromosome 6p) – RLS with PLMS (70%-80% raised risk), and reduced serum ferritin levels

MEIS1 (chromosome 2p) - active in limb development, part of a gene network involved in spinal neuron identity and connectivity;important role in brain iron metabolism

MAP2K5/LBXCOR1 (chromosome 15q) - both part of a signalling cascade that targets the development of sensory pathways in the spinal cord

PTPRD – encodes gene of the receptor type protein tyrosine phosphatase D, a presynpatic cell adhesion molecule that plays an important role in synaptogenesis, particularly of excitatory synapses

TOX3 – encodes transcription factors which function to modify chromatin structure

Secondary RLS

- Low serum ferritin levels or iron deficiency
- Pregnancy
- Renal failure
- Peripheral neuropathy
- Spinal cord conditions
- Parkinson’s disease; TS/ADHD
- Rheumatologic disorders
- Medications (iatrogenic RLS)

Neuropathy and RLS

- In patients with RLS, numerous forms of neuropathy, including diabetic, alcoholic, amyloid, occur at higher than expected frequency

- In contrast, in populations presenting with neuropathy, RLS prevalence is similar to the general population (5% - 10%). In one large neuropathy cohort, 18% of patients endorsed RLS on screen questionnaires (vs 6% of controls), but this narrowed to 12% versus 8% (controls) upon interview [1].

- Specific forms of neuropathy may incur different risks for RLS. In one study, 37% of patients with CMT II (an axonal neuropathy) had RLS, versus 0% (of 17 patients) with CMT I (a demyelinating neuropathy) [2].

[1] Hattan et al, 2009; [2] Gemignani et al, 2006

RLS with Underlying Neurological Disorders: Spinal Conditions, PD, ADHD/TS

- Transient or permanent spinal cord lesions - traumatic, neoplastic, postinfectious/demyelinating, syringomyelia, spinal cord blocks for anesthesia [1]
- Hereditary spastic paraparesis - 20.5% of 132 patients [2]
- Spinocerebellar ataxia, types 1, 2 and 3 - up to 30%
- Multiple sclerosis - 37.5% of 200 French-Canadian patients [3]
- Parkinson's disease - 20.8% [4]; associated with lower serum ferritin, less frequent FH, higher age of onset; often mild with lower PLM index
- ADHD and (?)Tourette Syndrome

[1] Ondo, 2oo5; [2] Sperfeld et al, 2006,[3] Auger et al, 2005; [4] Ondo et al, 2002

RLS in Uremia

- 20-57% prevalence of RLS in renal dialysis patients; Sx often severe
- Compared to idiopathic RLS: increased PLMS, increased wakeful leg movements, and a more rapid progression
- Both RLS and PLMS have been associated with increased mortality in the dialysis population
- Dialysis does not improve RLS. (One study suggested that RLS correlated with greater dialysis frequency)
- Patients with a successful kidney transplant usually experience dramatic improvement in RLS in days to weeks. The degree of symptom alleviation correlates with improved kidney function.

Iatrogenic RLS

- SSRIs
- SNRIs
- TCAs
- Neuroleptics
- Dopamine-blocking antiemetics
- Sedating antihistamines
- Lithium

Role of Iron in RLS

- Some of the established causes of secondary RLS involve compromise of iron sufficiency [1,2]
  - Correction of iron insufficiency alleviates symptoms
- There is evidence for central iron deficiency in primary RLS [3,4]

[1]Allen, 2004; [2]Allen & Earley, 2001; [3]Sun et al, 1998; [4]O' Keeffe et al, 1994

Pathophysiology of RLS
Evidence for Central Iron Deficiency

- Transcranial ultrasound:
  Nigral hypo-echogenicity [1]

- MRI: Reduced iron stores in substantia nigra, red nucleus, thalamus and striatum [2]

- Pathology: Reduced H-ferritin and iron [3]

[1]Schidauer et al, 2005; [2]Allen et al, 2001; [3]Connor et al, 2003

Nigral Hypoechogenicity on Transcranial Utrasound in RLS

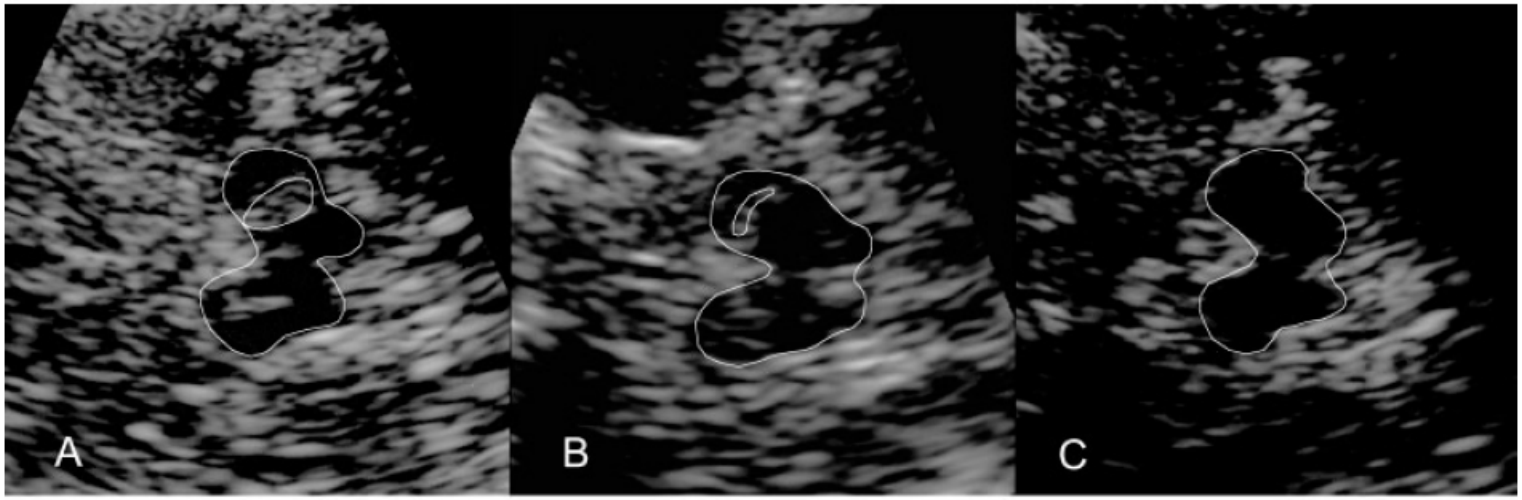
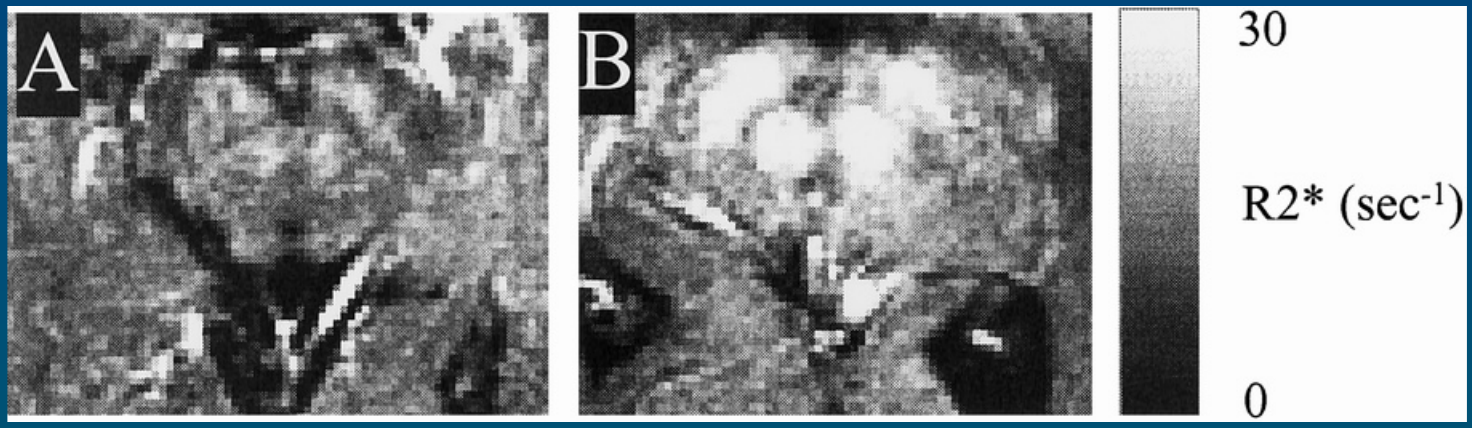


Fig 2. Typical examples of transcranial ultrasound appearances (axial scanning plane) in three patients. (A) Patient with Parkinson's disease (PD). (B) Normal control subject (CO). (C) Patient with restless legs syndrome (RLS). Midbrain and areas of hyperechogenicity encircled in (A) and (B) on the side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

Schmidauer et al, Ann Neurol, 2005

MRI Measurement of Brain Iron in RLS



RLS Control

Reduced iron stores in the substantia nigra, red nucleus and putamen in RLS

Allen et al, Neurology, 2001

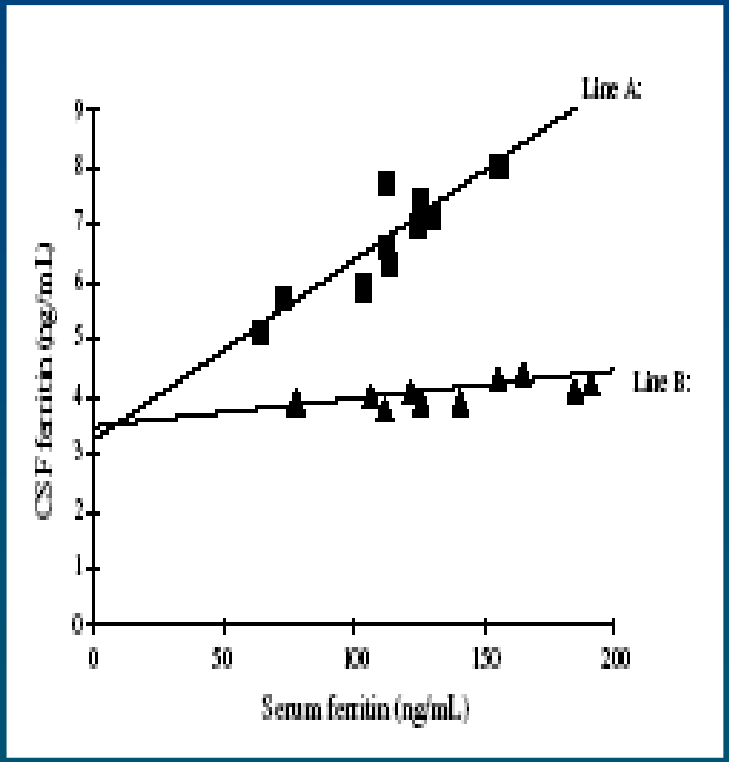
Serum and CSF Ferritin in RLS

- CSF ferritin, the major iron storage protein in the brain, is reduced in RLS [1]
- Strong correlation between serum ferritin levels and RLS symptom severity [2]

[1]Early et al, 2000; [2] O'Keeffe et al, 1994

Dysfunction of Iron Transportation from serum to CNS in RLS

Relationship between serum and CSF ferritin in RLS (line B) and non-RLS (line A) groups

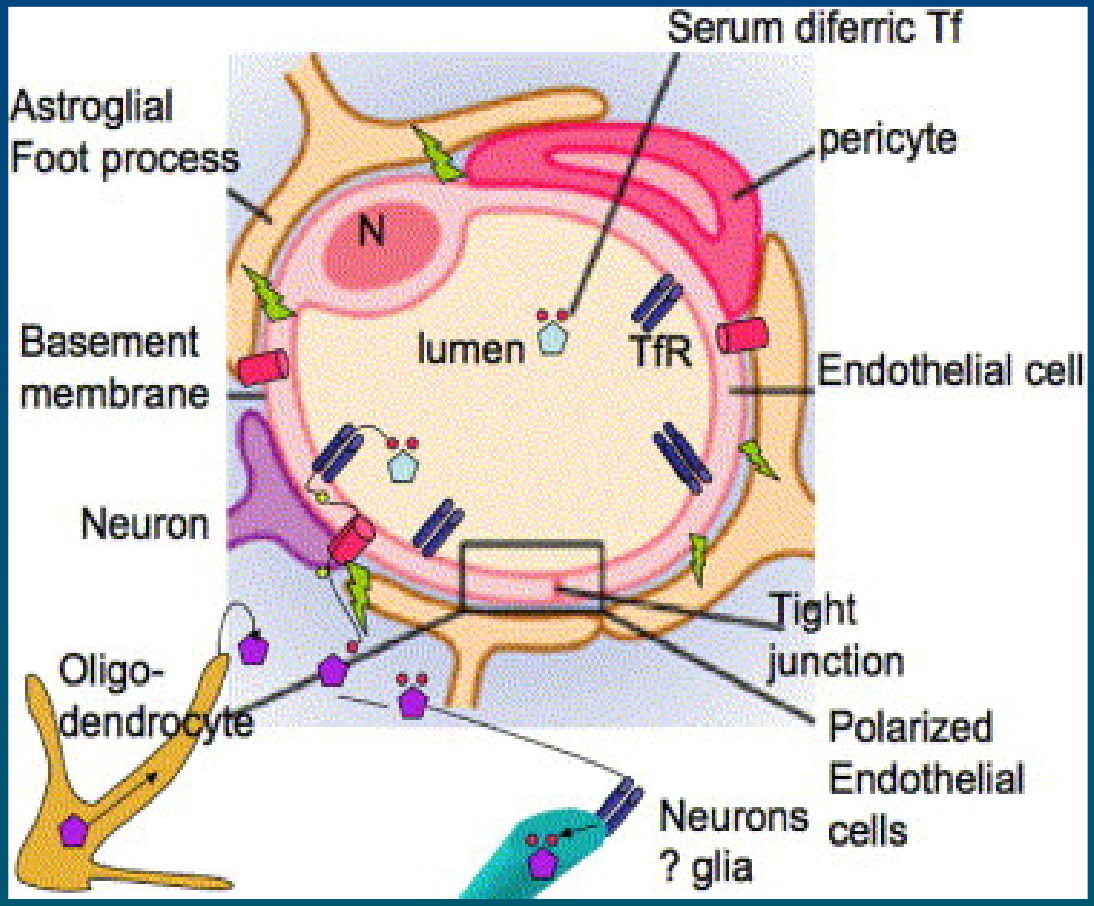


Mizuno et al, 2004

Line A: Non-RLS group

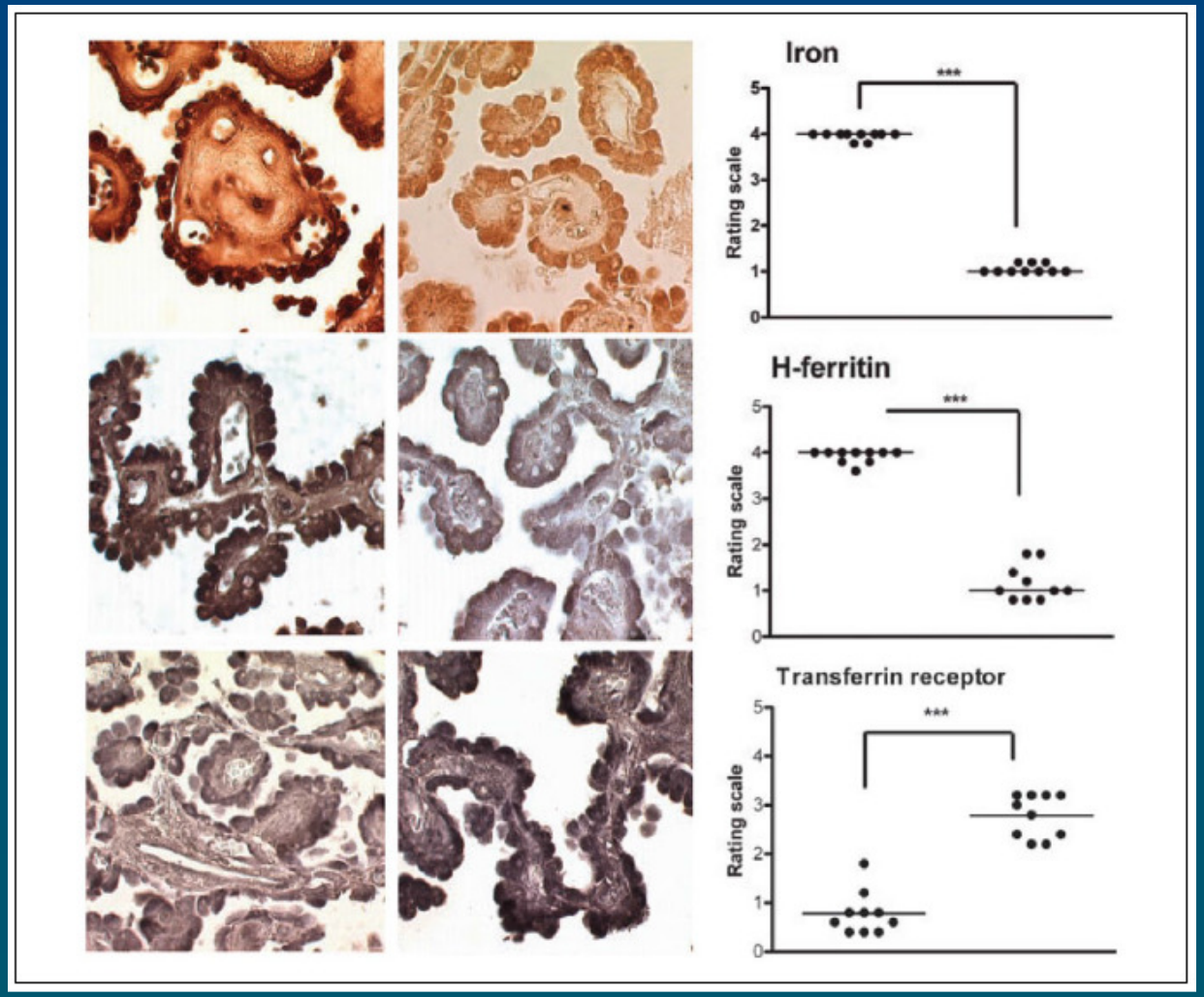
Line B: RLS group

Decreased Uptake and Storage of Iron Within the Cells of the Blood-Brain Barrier in RLS



- Transferrin and H-ferritin are decreased in the endothelial cells of the BBB
- This suggests decreased uptake and storage of iron within the cells of the BBB (choroid plexus) in RLS

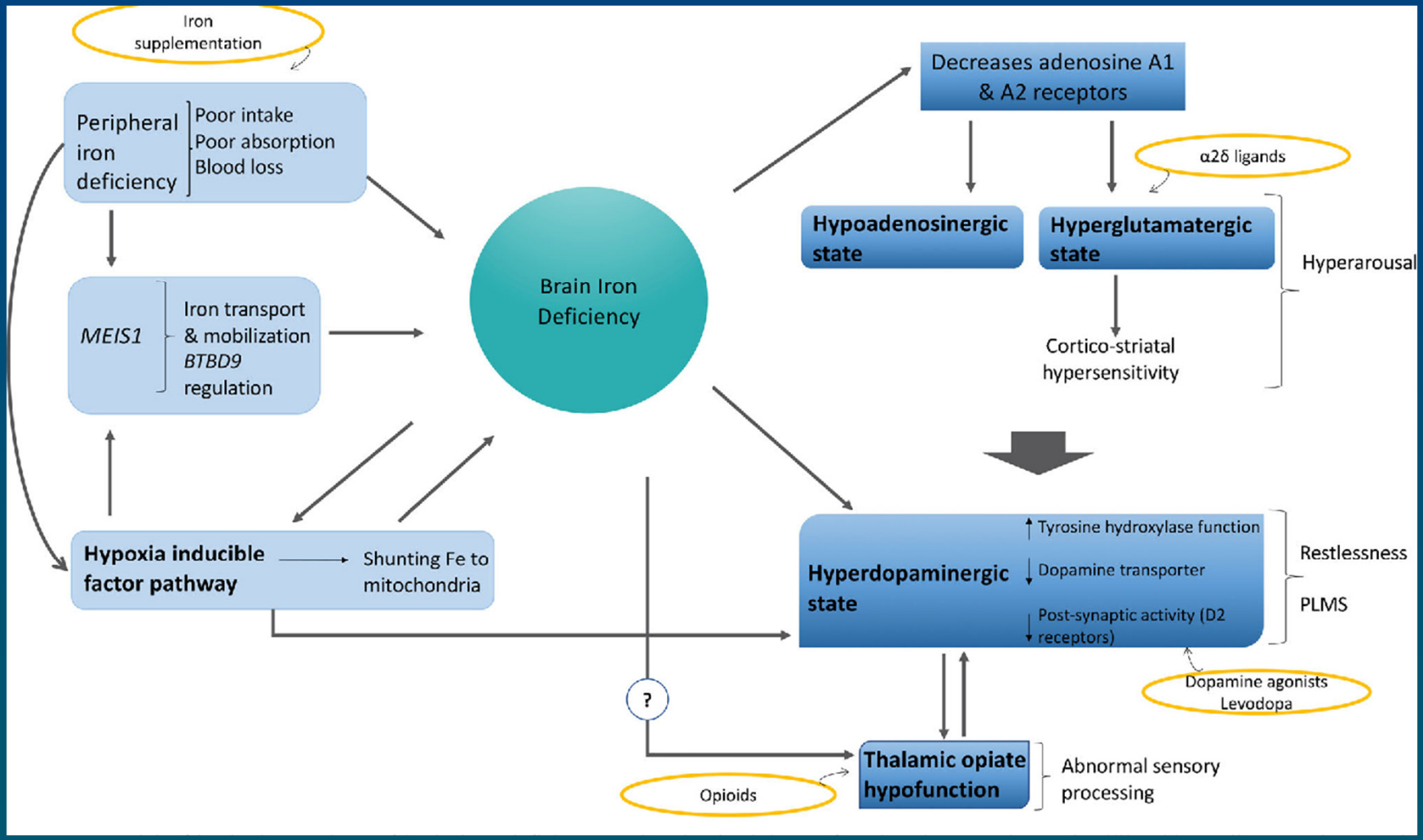
Iron Deficiency in the Choroid Plexus in RLS



Brain Iron Deficiency in RLS:

Effect on the Dopamine System

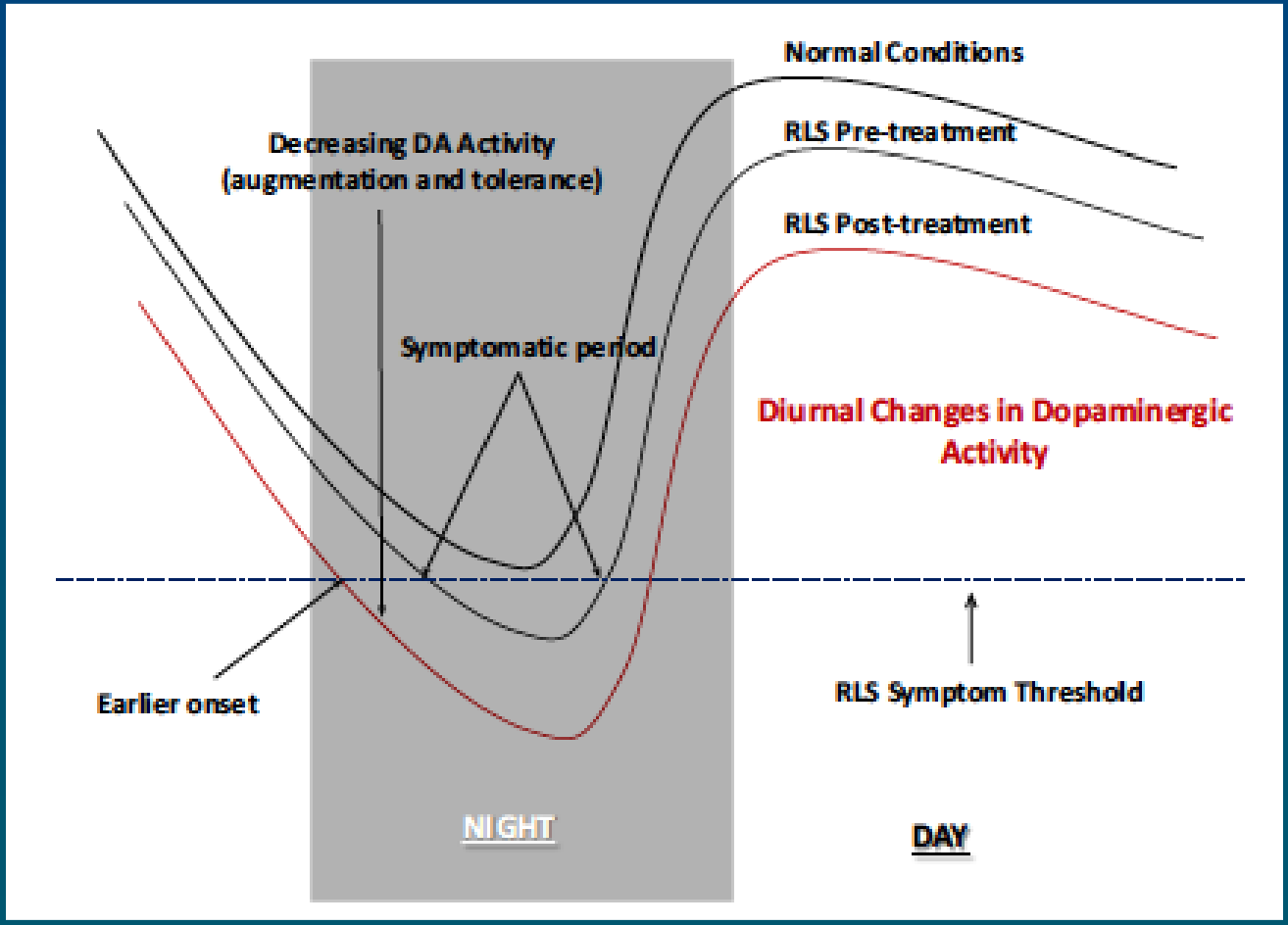
Pathophysiology of RLS and Site of Action of Therapeutic Compounds



Dopamine Dysregulation in RLS

- Although RLS appears to involve a decreased DA signal (DA agonists improve & DA antagonists worsen symptoms), symptoms reflect **decreased post-synaptic DA signalling:**
- Evidence of a **pre-synaptic hyperdopaminergic state:**
  - Increased tryosine hydroxylase activity and dopamine synthesis (1° or 2°/compensatory changes?)
- **Circadian dynamics of DA regulation**: Post-synaptic downregulation of D2 receptors, due to a hyperdopaminergic state, may result in low DA signalling when DA levels are low in the evening, leading to a relative nighttime DA activity deficit.

Proposed Circadian Changes in the Dopaminergic Output Signal in RLS



Neurophysiology of RLS

- Increased excitability in cortical neurons, particularly in the motor cortex, and reduced inhibition in spinal cord pathways
  - Reduction in short-interval intracortical inhibition (TMS)
  - Supra-spinal GABA-mediated disinhibition and spinal cord hyperexcitability
  - EEG spectral analysis of waking-rest conditions indicates a state of hyperarousal
  - Abnormalities show a circadian distribution and can be reversed by dopamine agonist treatment

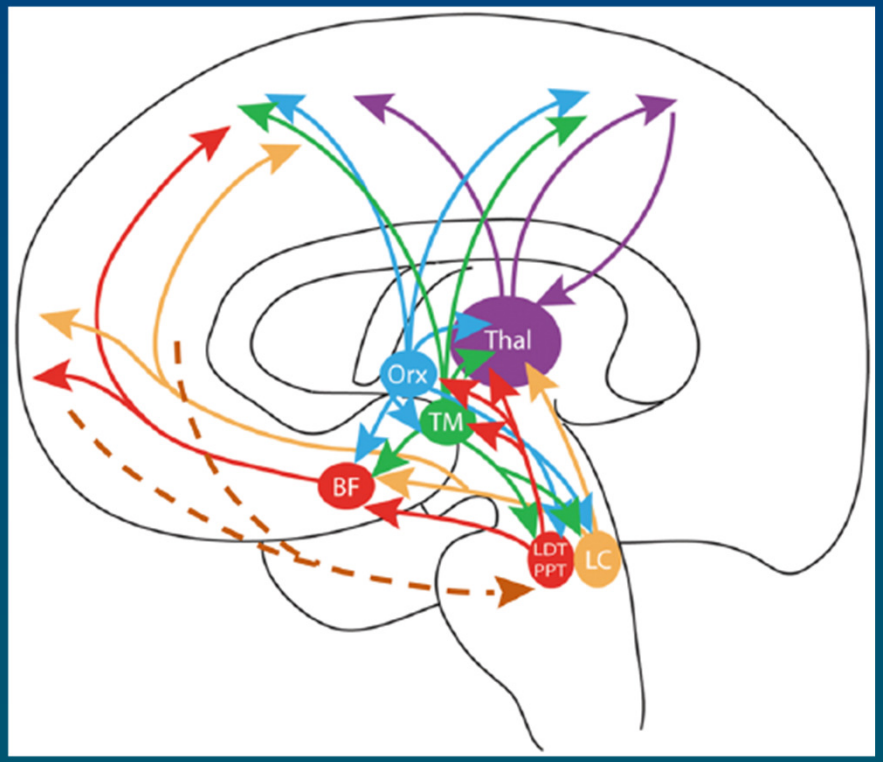
Magalhaes SC, et al 2015; Lanza G et al, 2015; Heide AC et al, 2014

Adenosine, Glutamate and Hyper-Arousal in RLS/PLMS

- Brain iron deficiency decreases adenosine A1 receptors (more than A2 receptors), resulting in:
  - a hypo-adenosinergic state
  - A hyperglutamatergic state, with increased cortico-striatal terminal hypersensitivity

➢ **The hypoadenosinergic and hyperglutamatergic states may explain the neurophysiologic changes and hyper-arousal in RLS/PLMS**

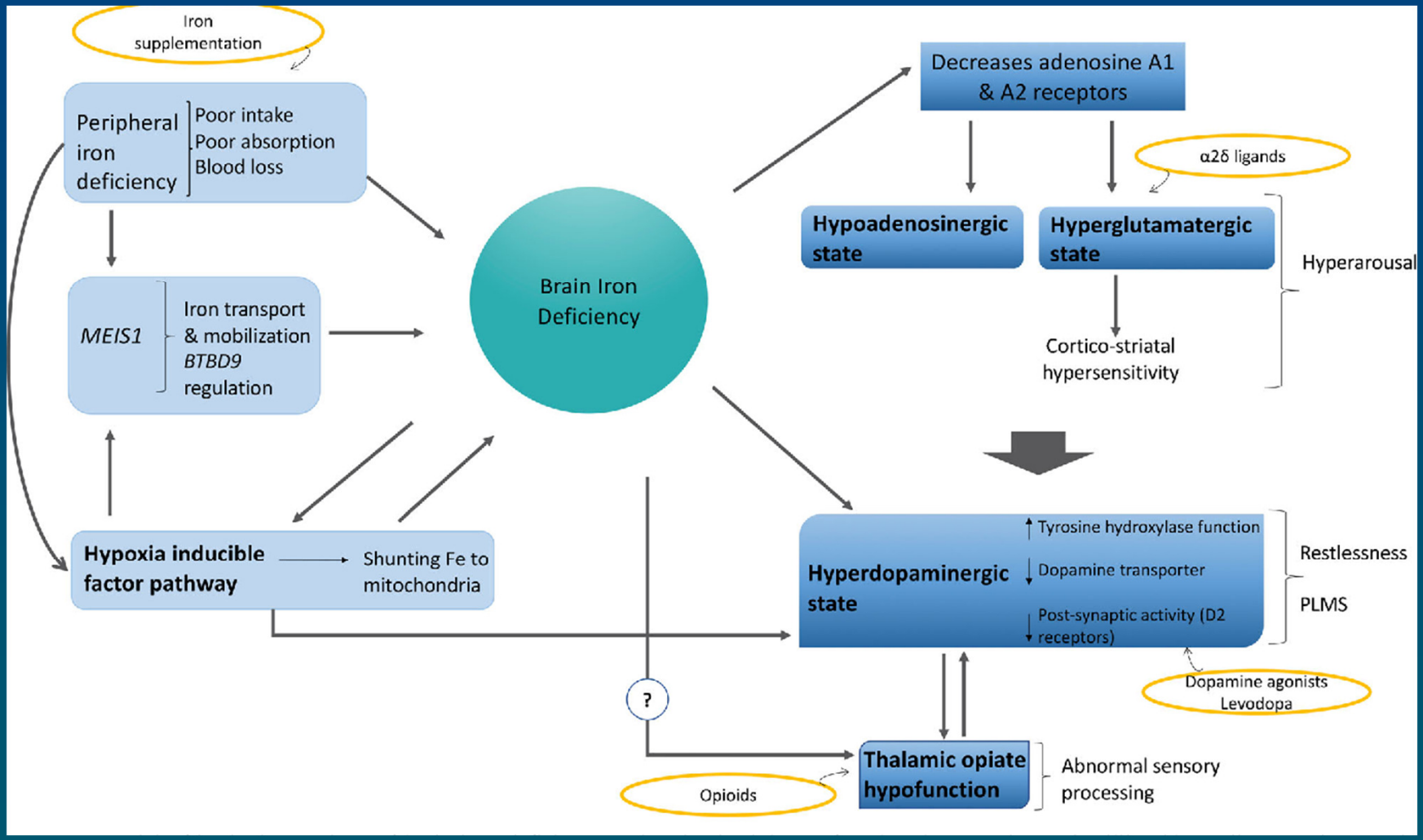
The Ascending Arousal Systems Involved in the Homeostatic Sleep Function of Adenosine



Scheme of the highly interconnected multiple ascending arousal systems, which are directly or indirectly inhibited by adenosine. These include the ascending reticular activating system, the corticopetal basal forebrain systems, and the ascending hypothalamic histamine and hypocretin/orexin ascending arousal systems.

Ferre 2010; Brown et al, 2012

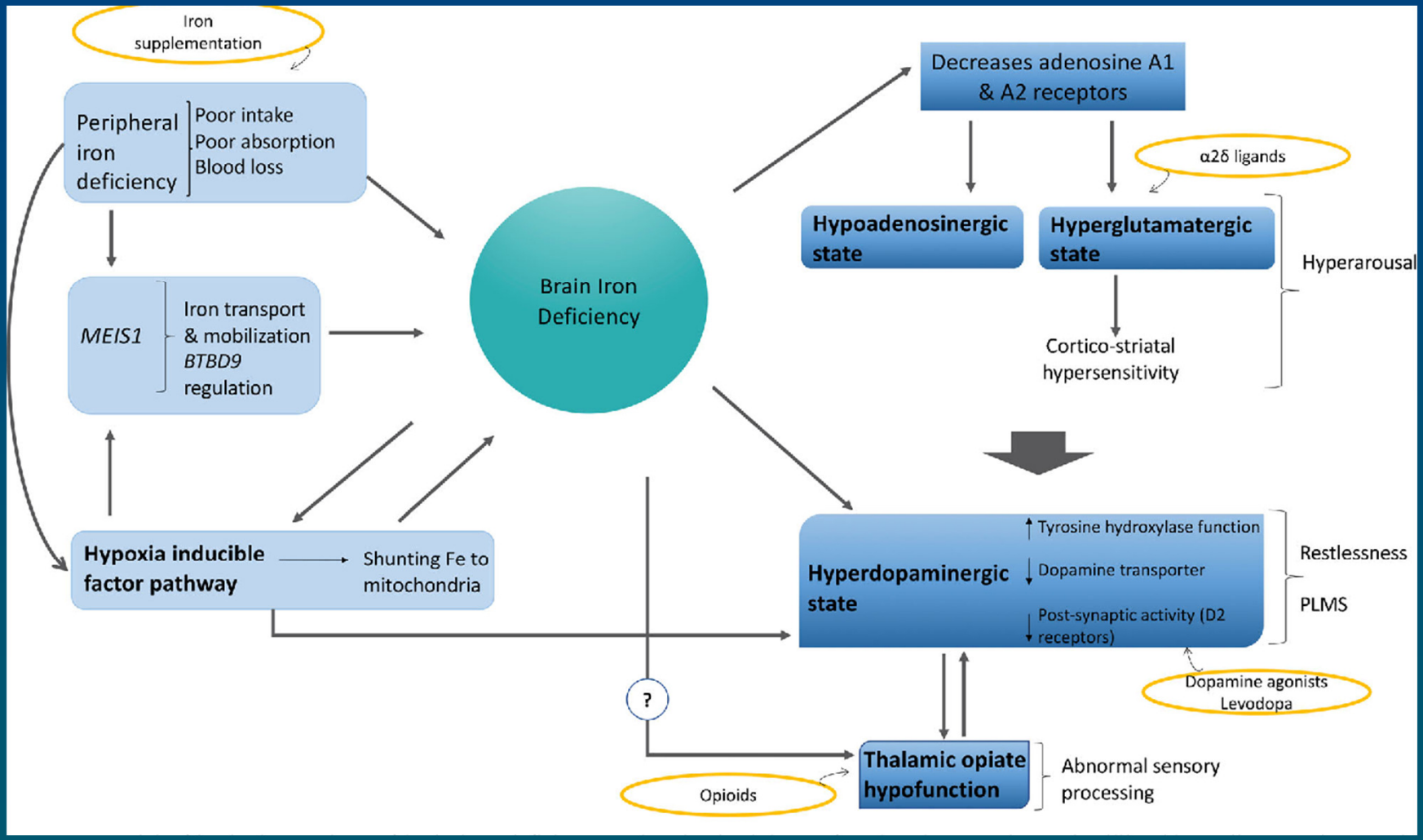
Pathophysiology of RLS and Site of Action of Therapeutic Compounds



Opioid Abnormalities in RLS

- PM studies show a deficiency of beta-endorphin and met-enkephalin in the thalamus (but not the SN) in RLS
- Opioid withdrawal can provoke RLS, and opioid medications can improve RLS
- The beneficial effects of opioids appear to be mediated through the DA pathway: Sx. improvement with opioids is blocked by both DA antagonists and naloxone, while the effect of DA agonists is not affected by naloxone.
- DA inhibits opiates, so the hyperdopaminergic state in RLS may lead to a decrease in endogenous opiates; AND, endogenous opiate activity may inhibit DA. Thus a hyperdopaminergic state due to BID may inhibit endogenous opiate activity, leading to further DA release

Pathophysiology of RLS and Site of Action of Therapeutic Compounds



Treatment Options in RLS: Non-Pharmacological Measures

- Good sleep hygiene (avoid day-time naps; regular bedtime)
- Aerobic and resistance training exercises
  - One RCT showed that engaging in lower body resistance training and walking on a treadmill for 30 mins 3x/week improved RLS symptoms [1]
- Avoidance of alcohol, caffeine and nicotine
- Found to be useful in small studies: pneumatic compression devices, acupuncture, and near infra-red light [2]
- Tactile and temperature stimulation, including massage or hot baths can temporarily decrease symptoms
- First FDA-approved device to improve sleep in patients with RLS: The Relaxis pad – provides vibrational counter-stimulation to provide external stimulus to the legs [3]

[1] Aukerman MM et al, 2006; [2] Wijemanne S, Jankovic J ,2015; [3] http://dev.sensorymedical.com

Management of RLS

Modality/Strategy	Measures	Examples/Agents
Nonpharmacologic strategies	Nonpharmacologic measures	Sleep hygiene, circadian re-entrainment, and so forth
	Iron replacement	Oral or intravenous preparations
Pharmacologic strategies	Dopaminergic agents	Ropinirole, pramipexole, rotigotine, levodopa/carbidopa
	Apha-2-delta calcium channel ligands	Gabapentin, gabapentin enacarbil (prodrug of gabapentin), pregabalin
	Opioid agents	Tramadol, oxycodone, hydrocodone, or methadone
	Benzodiazepines	Temazepam, zolpidem, zaleplon, eszopiclone
	Others	Carnitine, and so forth

Clinical Features Guiding Choice of Initial Agent for Chronic Persistent RLS

Dopamine agonists	α-2-δ Ligands
Very severe RLS/WED	Comorbid pain
Comorbid depression or dysthymia	Comorbid anxiety
Obesity/metabolic syndrome	Comorbid insomnia
	Previous impulse control disorder or addiction

RLS = restless legs syndrome; WED = Willis-Ekbom disease.

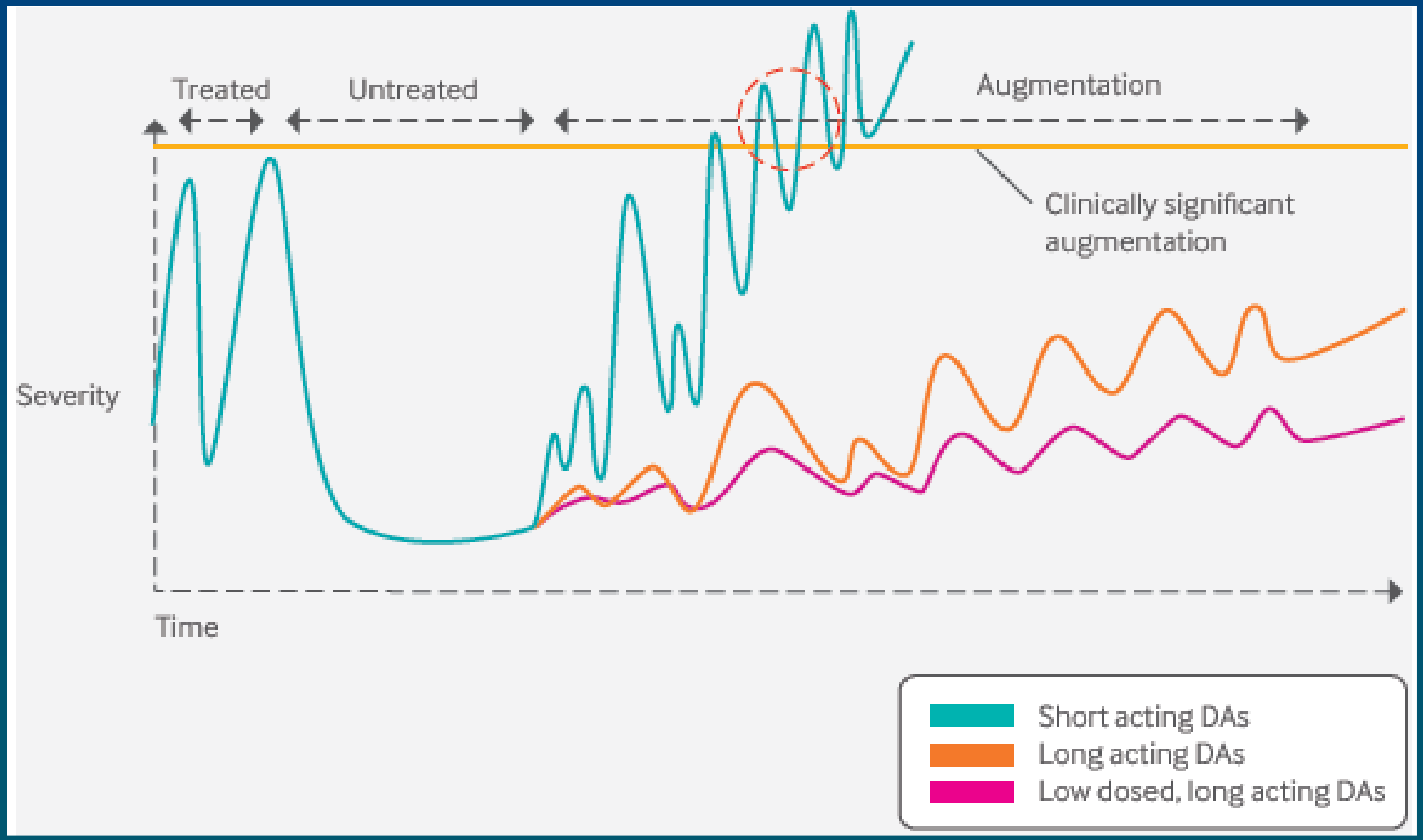
Dopamine Agonists Used in the Treatment of RLS

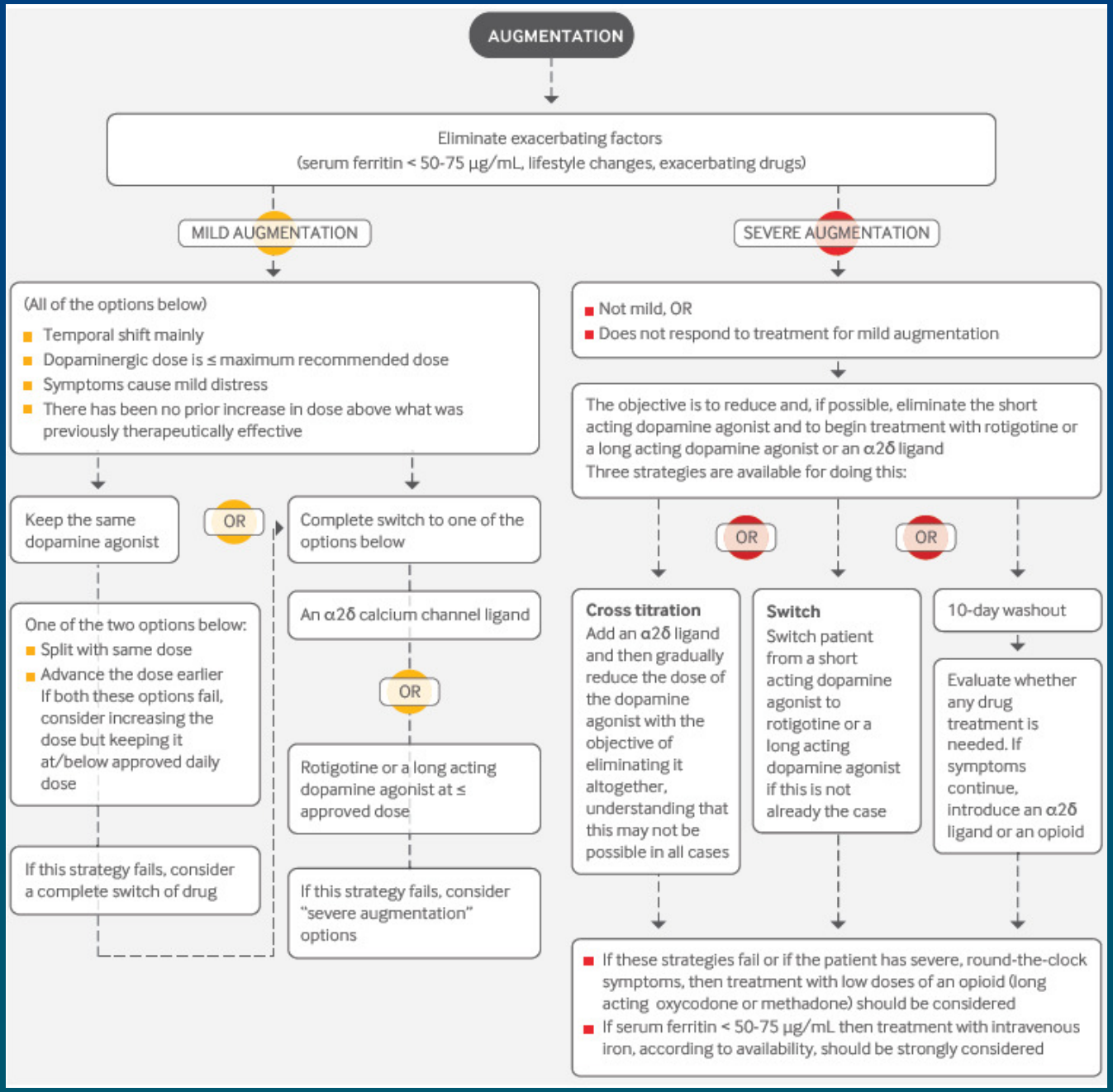
	Initial Dose	Maximum recommended dose	Half-lives
Pramipexole	0.125mg/day	0.75mg/day	8-12 h
Ropinirole	0.25mg/day	4mg/day	6h
Rotigotine	1mg/day	3mg/day	24hr transdermal system

Augmentation

- The earlier onset of symptoms in the evening (or afternoon), increase in symptoms, and spread of symptoms to involve other extremities
- Occurs in up to 82% with carbidopa-levodopa; 15%-40% with oral DA agonists; 5-15% with rotigotine
- Generally milder with agonists and may take many months to develop (cf. few weeks with carbidopa-levodopa)
- With agonists, is predicted by a +ve FH and normal NCV/EMG; higher dose may be a risk factor
- Mechanism unclear
- Mild forms manageable by adding an earlier dose; usually resolves with medication cessation
- Some patients require a different drug class (e.g. gabapentin/opiate) or rotation of drugs of differing classes

Therapeutic Response During Treatment with Dopamine Agonists




AUGMENTATION
Eliminate exacerbating factors
(serum ferritin < 50-75 µg/mL, lifestyle changes, exacerbating drugs)
MILD AUGMENTATION
SEVERE AUGMENTATION
(All of the options below)
Temporal shift mainly
Dopaminergic dose is ≤ maximum recommended dose
Symptoms cause mild distress
There has been no prior increase in dose above what was previously therapeutically effective
Keep the same dopamine agonist
OR
Complete switch to one of the options below
One of the two options below:
Split with same dose
Advance the dose earlier
If both these options fail, consider increasing the dose but keeping it at/below approved daily dose
If this strategy fails, consider a complete switch of drug
An α2δ calcium channel ligand
OR
Rotigotine or a long acting dopamine agonist at ≤ approved dose
If this strategy fails, consider "severe augmentation" options
Not mild, OR
Does not respond to treatment for mild augmentation
The objective is to reduce and, if possible, eliminate the short acting dopamine agonist and to begin treatment with rotigotine or a long acting dopamine agonist or an α2δ ligand
Three strategies are available for doing this:
OR
OR
Cross titration
Add an α2δ ligand and then gradually reduce the dose of the dopamine agonist with the objective of eliminating it altogether, understanding that this may not be possible in all cases
Switch
Switch patient from a short acting dopamine agonist to rotigotine or a long acting dopamine agonist if this is not already the case
10-day washout
Evaluate whether any drug treatment is needed. If symptoms continue, introduce an α2δ ligand or an opioid
If these strategies fail or if the patient has severe, round-the-clock symptoms, then treatment with low doses of an opioid (long acting oxycodone or methadone) should be considered
If serum ferritin < 50-75 µg/mL then treatment with intravenous iron, according to availability, should be strongly considered

Alpha-2-Delta Ligands Used in the Treatment of RLS

	Starting dose <65 yrs	Starting dose >65 yrs	Usual effective dose
Gabapentin	300 mg	100mg	900-2400mg
Pregabalin	75mg	50mg	150-450mg
Gabapentin Enacarbil	600mg	300mg	600mg

Alpha-2-Delta Ligands for RLS
Gabapentin

- Multiple mechanisms of action; used off-label for RLS
- 4 older studies at doses of 800mg – 1855 mg/day showed efficacy, particularly in patients undergoing hemodialysis
- Because of renal excretion, use lower doses in hemodialysis patients (200-300mg post-dialysis)
- Can be particularly useful in patients with pain as a primary RLS symptom

Garcia-Borreguero et al, 2002; Thorp et al, 2001

Gabapentin Enacarbil

- An actively transported extended-release pro-drug of gabapentin
- Low inter-patient variability, well-sustained plasma levels
- Three randomized, double-blind, placebo-controlled studies showed
  ↓ RLS symptoms and IRLS score
- Response to GEn may be reduced when used after long-term (>5yrs) dopamine agonist treatment
- Improves all IRLS items: sleep disturbance, day-time tiredness, RLS severity, impact on daily affairs and mood disturbance (at both 600mg and 1200mg once daily doses, over 12 weeks)

Pregabalin

- Binds to $\alpha 2\delta$ subunit in voltage-gated calcium channels.
- Similar to gabepentin but is more rapidly and readily absorbed and has a higher binding affinity for $\alpha 2\delta$
- 3 randomized controlled trials showed pregabalin effective for RLS at doses between 150-450mg/day
- A randomized, double-blind, placebo-controlled, crossover trial showed that pregabalin was non-inferior to pramipexole for the overall management of RLS symptoms; pregabalin also increased slow-wave sleep and decreased the number of awakenings [1]

[1] Garcia-Borreguero et al. Sleep 2014;37:633-43

Pregabalin versus Pramipexole

- Greater improvement in the CGI at 12 and 52 weeks with pregabalin 300mg/day compared with pramipexole 0.25mg but not 0.5mg/day [1]
- Augmentation was less frequent with pregabalin (2.1%) than pramipexole 0.5mg (7.7%) but not 0.25mg/day (5.3%) [1]
- Pregabalin was associated with an increased rate of dizziness, somnolence, weight gain, & suicidal ideation [1]

[1] Allen RP, et al. N Engl J Med 2014;370:621-31

Opioids for RLS

- 2nd line therapy, for severe RLS, first described as a treatment option by Willis in 1684 – may work via the DA system
- Low-potency opioids (e.g. 30 – 60mg codeine qhs) are useful for treatment of intermittent RLS
- Tramadol is the only nondopaminergic drug occasionally associated with augmentation
- High-potency opioids, e.g.oxycodone, hydrocodone, or methadone (5-20mg in single or divided doses), are highly effective and can be helpful in refractory RLS/for severe augmentation (In a double-blind, randomized, crossover trial, oxycodone improved RLS symptoms and significantly reduced PLMS and arousal index)
- Long-term data show minimum risk of dependency, addiction or tolerance; may cause daytime somnolence, constipation, nausea, worsening of OSA, or induction of central sleep apnea. Consider oxycodone/naloxone.

Willis, 1685; Walters et al, 1993; Kaplan et al, 1993; Ondo et al; Walters et al, 2001

Benzodiazepines and Benzodiazepine Receptor Agonists for RLS

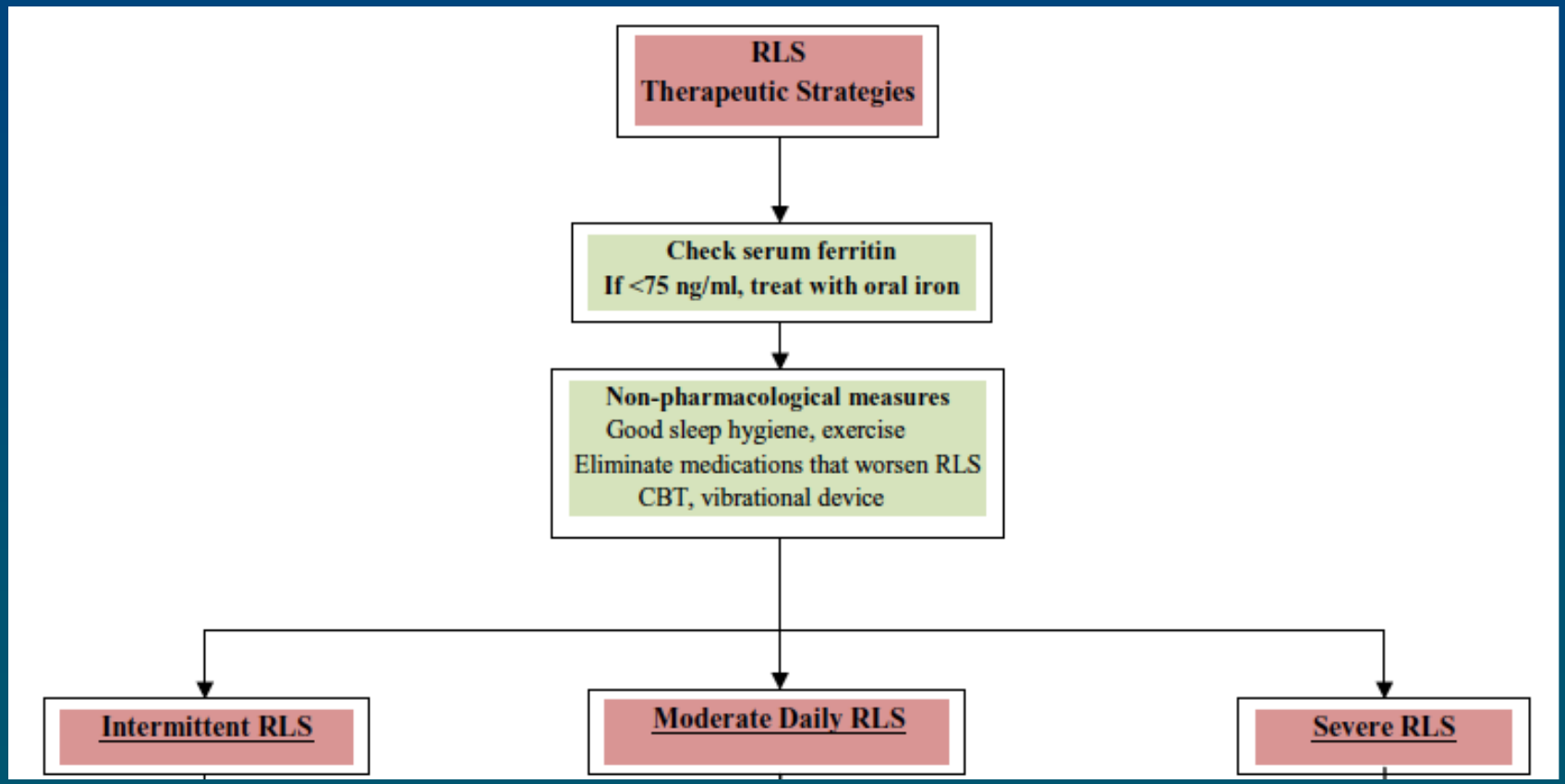
- Earliest agents used, still in widespread use (Zolpidem 5-10mg; zaleplon 5-10mg; temazepam 15-30mg; eszopiclone 1-3mg)
- Do help facilitate sleep (improve insomnia), but seldom improve the primary features of RLS; no good controlled trials
- Can be used successfully in mild cases of RLS and, especially, as adjunct therapy for residual insomnia
- AEs include drowsiness, unsteadiness and cognitive impairment

Iron Treatment in RLS

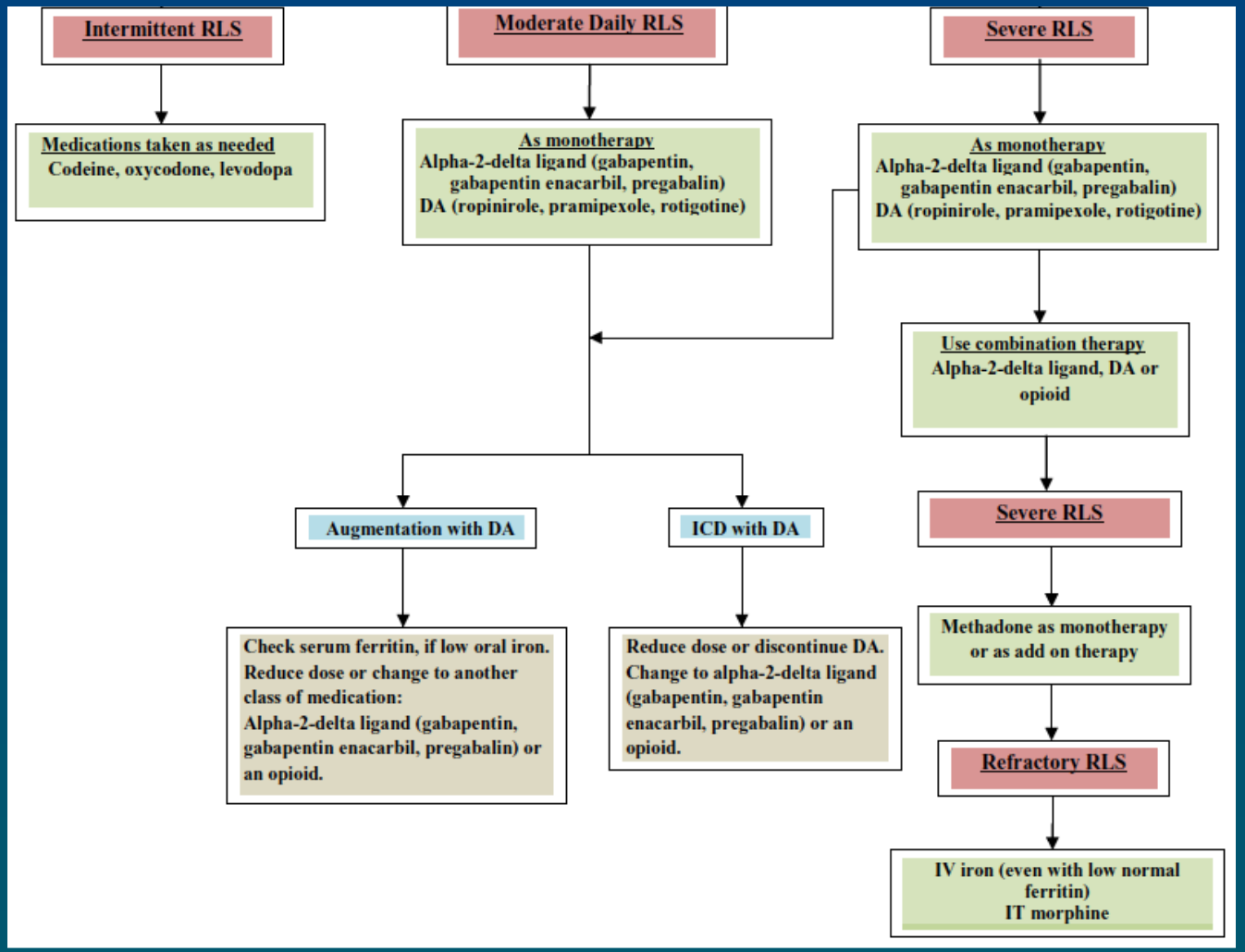
- IV iron is effective for RLS[1,2] but is not currently recommended as a general treatment
  - Potential problems:
    - Practical issues
    - Potential for hypersensitivity reactions
    - Increased rate of iron excretion following IV administration [2,3]
- Oral iron supplementation is effective in patients with lower serum ferritin and is recommended if serum ferritin is below 50 mg/l [4]

[1]Nordlander, 1953; [2]Earley et al, 2004; [3]Earley et al, 2005; [4]Lesage and Hening, 2004

Treatment Algorithm in RLS



Treatment Algorithm in RLS



RLS and its Management in Special Populations

RLS in Pregnancy

- Prevalence: 20-27%, 2-3 times higher than in non-pregnant women
- Predictive factors include:
  - Hx of RLS in previous pregnancy or of RLS prior to pregnancy
  - FH of RLS
  - Multiparity
  - Anemia or low iron level
  - Low folate level
  - High estrogen level
- Rx options :
  - Consider fully replenishing iron stores prior to pregnancy
  - Folate replacement may be beneficial
  - For severe cases: ± Dopaminergic agents, anti-epileptic agents (gabapentin, gabapentin enacarbil, pregabalin, carbamazepine, oxcarbazepine), benzos.
- Prognosis is good and most patients recover quickly; a small number may develop chronic idiopathic RLS

RLS in Childhood

- Approx 35% of RLS patients have onset by age 20; 10% have onset before age 10
- Prevalence : approx. 2% in school-age children and adolescents; likely under-diagnosed.
  - ✓Classic RLS symptoms
  - ✓"Growing pains"
  - ✓ADHD phenotype (25%)[1]
    - ❖ 12-35% of children with ADHD meet criteria for RLS
- Serum ferritin < 50ug/L in 83%, these subjects improving with oral or IV iron; FH +ve in 72%
- NB: Efficacy of dopaminergic therapy for RLS/PLMS in children; clonidine useful at bedtime for sleep-onset insomnia; gabapentin can improve sleep quality and reduce sensory symptoms

Picchietti D, et al 2007; [2]Lewin et al; 2004; Wagner et al, 2004

RLS - Summary

- RLS is a common disorder, characterised by an uncontrollable urge to move the legs combined with uncomfortable leg sensations, typically occurring in the evening or when at rest, and temporarily relieved by movement
- Diagnosis of RLS is based on history, but lab tests, including iron studies, are essential to rule out secondary RLS; remember other predisposing neurological and medical conditions, and iatrogenic causes
- Brain iron deficiency and abnormalities in dopaminergic, adenosinergic and glutamatergic neurotransmission play a central role in RLS pathogenesis
- Treatment depends on the severity and frequency of RLS symptoms, comprises non-pharmacological and pharmacological interventions and needs to be tailored to the patient, (consider age, co-existing conditions, and co-medication)
- Dopaminergic agonists, alpha-2-delta calcium channel ligands and opioids are commonly used for Rx; augmentation is the main complication of long-term dopaminergic treatment of RLS.