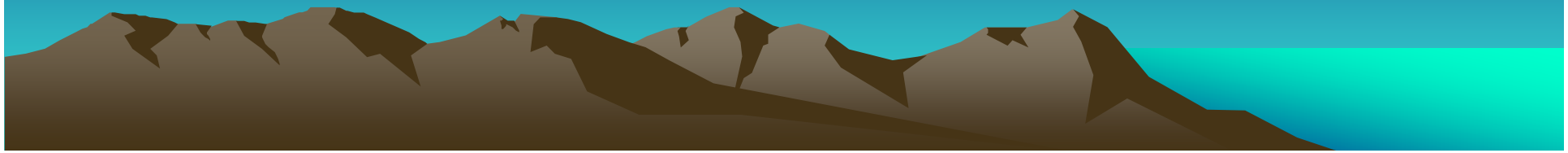
Restless Legs Syndrome: Impact, Recognition, and Management

Pierre Bou-Khalil, MD, FCCP, D'ABSM

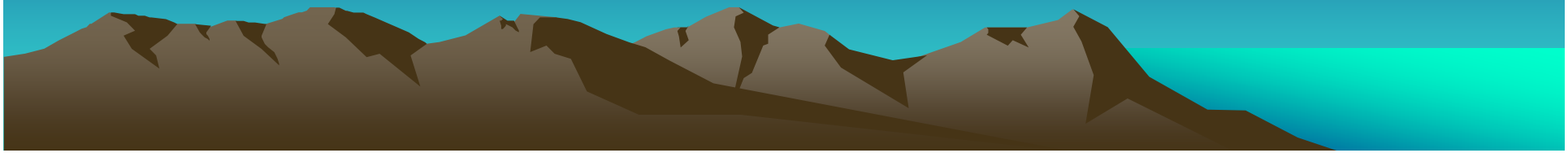
What is RLS and what is its impact?



Definition of RLS

RLS is characterized by disagreeable leg sensations that usually occur prior to sleep onset and are accompanied by an almost irresistible urge to move the legs.

Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group.



Impact

- RLS has been found to produce a chronic sleep loss more severe than in almost any other sleep condition
- It impairs quality of life as much or more than other chronic diseases, such as depression, congestive heart failure, and hypertension

Impact

- Therefore it is a common cause of sleep disruption that has a significant impact on daytime function.
- As such, RLS is important not only to sleep specialists, but also to primary care practitioners and a wide array of specialists who treat disorders that may cause or be associated with RLS.

Impact

- Sleep onset insomnia (difficulty falling asleep)
- Sleep loss resulting in daytime sleepiness
- Anxiety, depression, marital discord, social dysfunction, and even suicidal thoughts may occur in severe cases

Definition

- RLS is defined as a symptomatic ***urge*** to move the legs, usually accompanied or caused by uncomfortable or ***unpleasant*** sensations deep within the legs. These sensations begin or are ***worsened*** during periods of ***rest*** or inactivity and are partially or totally ***relieved*** by ***movement***.
- The sensations are worse or only ***present*** in the ***evening*** or ***night***
- RLS symptoms may also involve the arms or other body parts but the legs must be affected and are usually affected first and more severely than the other body parts

Periodic Limb movements

- Periodic limb movements of sleep (PLMS) were first documented in patients with RLS in 1965.
- PLMS were originally described as a rhythmic extension of the big toe and dorsiflexion of the ankle, with occasional flexion at the knee and hip, but they may vary considerably in their motor patterns.
- They tend to occur during sleep and are grouped into series with a periodic pattern of one movement usually occurring every 20–40 seconds.
- The quantification of PLMS is routinely performed in the sleep laboratory.
- **PLMS are not specific to RLS and can occur in several other sleep disorders, including narcolepsy and obstructive sleep apnea, as well as in isolation.**

RLS V/S PLMS

- RLS is a symptom
- RLS is diagnosed in the physician's office
- 80% of people who have RLS will have PLM's

- PLM's are an electromyographic finding
- PLM's are diagnosed in the sleep laboratory
- 30% of individuals who have PLM's have RLS symptoms

RLS V/S PLMS

- RLS is a symptom
- RLS is diagnosed in the physician's office
- 80% of people who have RLS will have PLM's

- PLM's are an electromyographic finding
- PLM's are diagnosed in the sleep laboratory
- 30% of individuals who have PLM's have RLS symptoms

Epidemiology

- RLS is a common disorder, occurring with an estimated prevalence to be between 2 and 15% in the general population.
- A Canadian survey of 2019 adults estimated the prevalence of RLS symptoms at 17% for women and 13% for men
- In a study from Japan, 4612 participants The prevalence of RLS ranged from 3% in women ages 20–29 years to 7% in women ages 50–59 years and correlated with age
- Symptoms often occur during middle age

Etiology

- RLS affects up to 19% of women during pregnancy; symptoms usually subside within a few weeks postpartum
- Fifty percent of patients with end-stage renal failure develop RLS that may improve after transplantation

Two forms of RLS

- Idiopathic:
  - Primary
  - familial hereditary cause. (earlier age of onset)
- Secondary (sporadic or symptomatic forms):
  - Renal failure
  - Iron deficiency
  - Neuropathy
  - Pregnancy
  - Diabetes
  - Rheumatoid arthritis

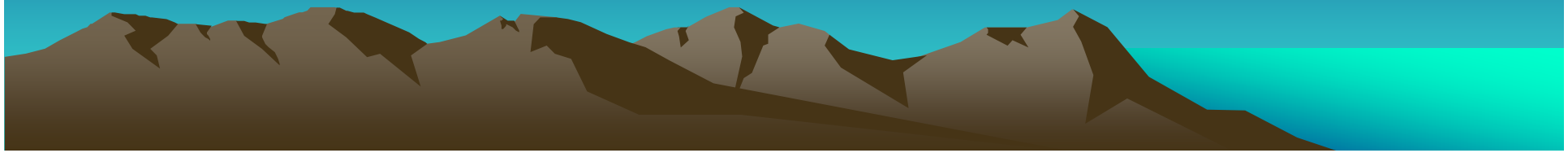
Etiology

- The most likely mechanism is related to dopaminergic dysregulation at the level of the spinal cord or higher in the central nervous system.
- Primary RLS (50%-60%) may include iron deficiency.
- Secondary RLS associated with iron deficiency, pregnancy, renal failure, repetitive blood donation, neuropathy, radiculopathy, myelopathy, and rheumatologic conditions.

Genetics

- Molecular genetic studies have identified at least three major susceptibility loci
  - Canadian chromosome 12q13-23 (autosomal recessive inheritance pattern)
  - Italian 14q13-21 region (autosomal dominant inheritance pattern)
  - American 9p24-22 (autosomal dominant inheritance pattern)
- RLS may ultimately prove to have a polygenic basis and complex interactions of genes with environmental factors

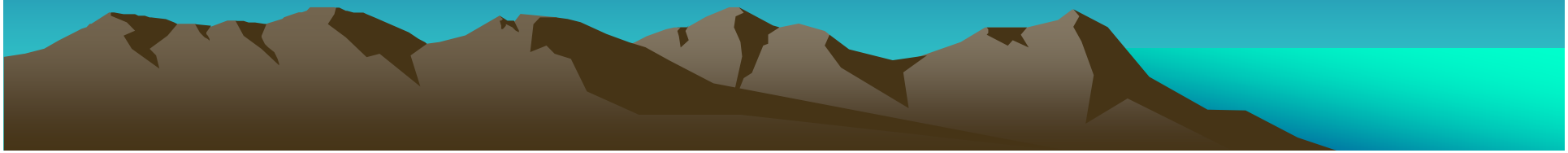
Diagnosis



Diagnosis

- It's a clinical diagnosis made in the office, not in the sleep laboratory

- The diagnosis is based on a careful history that elicits the 4 classic features.



Diagnosis

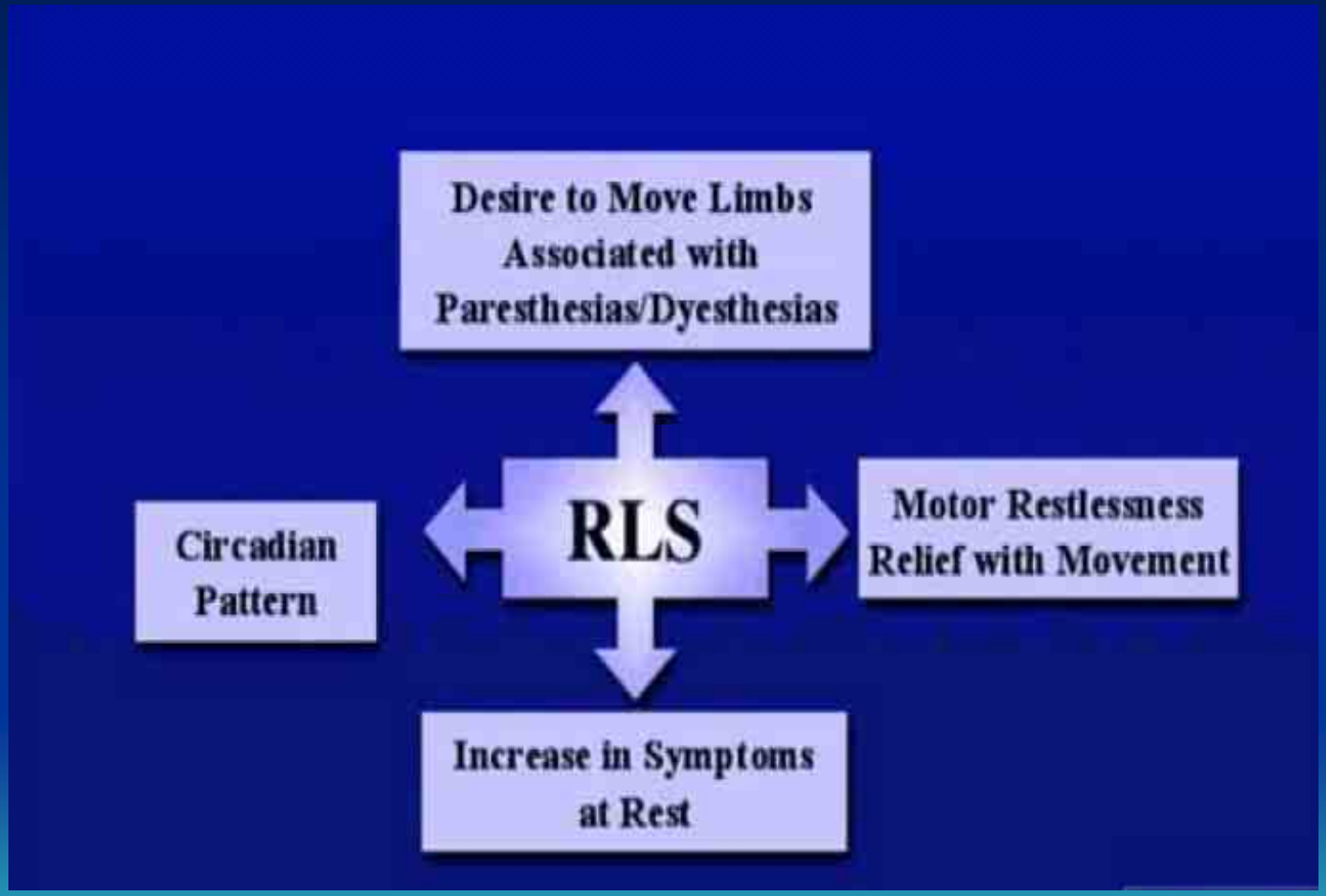
- The patient must experience an urge to move the legs (an akathisia focused on the legs). This urge is commonly accompanied by an unpleasant sensation (a paresthesia)
- Symptoms occur when the patient is at rest either sitting or lying down (For a diagnosis of RLS, the symptoms must not start while the patient is walking)

Diagnosis

- The symptoms must be at least partly relieved by movement, usually movement of the affected leg
- RLS symptoms must be worse in the evening and night than at other times of the day

Allen, RP, Picchietti, D,. Hening, WA, Trenkwalder, C, Walters, AS, & Montplaisir, J.
Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology.
A report from the restless legs syndrome dialynosis and epidemiology workshop at the National Institutes of Health.
Sleep Medicine 2004, 4, 101-119

Diagnosis

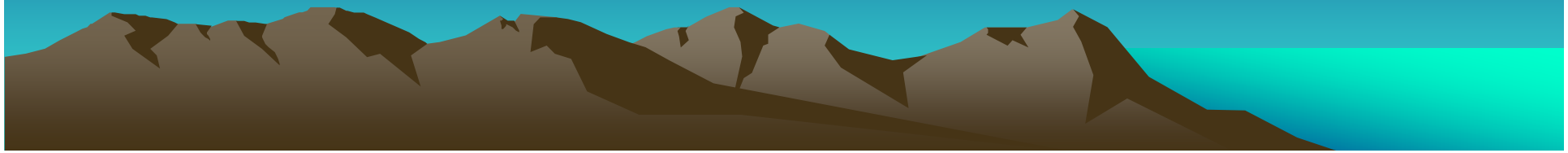

Desire to Move Limbs Associated with Paresthesias/Dyesthesias
Circadian Pattern
RLS
Motor Restlessness Relief with Movement
Increase in Symptoms at Rest

Diagnosis

- In uncertain clinical cases, three additional features may support, but are not essential for, the diagnosis :
  - Family history
  - The presence of periodic limb movements, which is seen in the majority of patients who have RLS
  - A response to dopaminergic agents.

Diagnosis

- Other supportive features:
  - Generally chronic course, often progressive
  - Sleep disturbance and its consequences
  - Normal neurologic examination in idiopathic cases

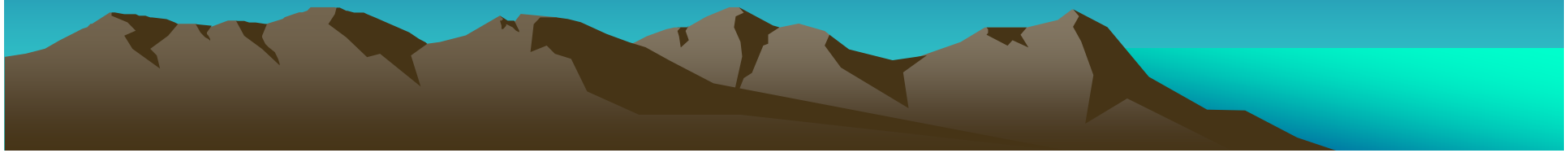


Diagnosis Summary

- RLS develops with rest, inactivity, and relaxation (conditions that induce drowsiness), while it is suppressed by activity, alertness, and arousal.
- In addition, RLS tends to follow a circadian pattern with intensified symptoms later in the usual day-night cycle.
- RLS symptoms peak late in the evening around bedtime and last through about half of the night (*from approximately 22:00 to 4:00*).
- In contrast, there appears to be a relatively protected period when symptoms are minimal in the late morning and early afternoon (*approximately 8:00 to 13:00*).

History

- Exploration of the four cardinal features of RLS including
  - unpleasant sensations in the extremities
  - motor restless precipitated by inactivity
  - symptoms relieved by activity
  - symptoms become worse at night



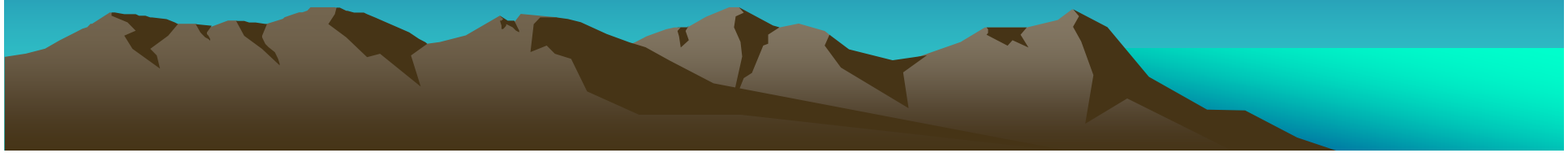
Aggravating Factors

Numerous factors may aggravate RLS and PLMD including:

- Tricyclics, serotonin reuptake inhibitors, monoamine oxidase inhibitors, and metaclopramide
- Antihistamines/over-the-counter cold remedies
- Antiemetics (e.g., compazine)
- Withdrawal from neuroleptics, sedatives, or hypnotics

Aggravating Factors
(Cont.)

- Sleep deprivation and fatigue
- Caffeine, alcohol
- Lack of exercise or excessive exercise
- Exposure to a very cold or warm environment



Past Medical History

- Associated conditions such as pregnancy, anemia, and renal failure
- Anxiety or depression
- If the patient is a child, a careful assessment of language and conceptual skills development
- Family history (30-60% have a symptomatic first-degree family member).

Physical Examination

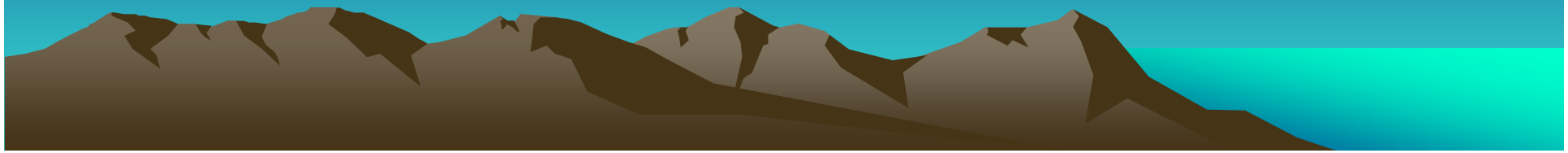
- Neurological examination, including evaluation for spinal cord and peripheral nerve function
- Sensory and motor exam, checking for position/vibration sense, sensation to pain and temperature, deep tendon reflexes, and muscle strength

Physical Examination

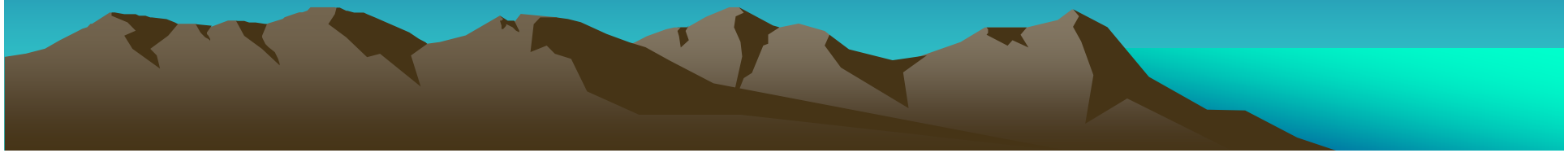
- Peripheral vascular examination, including peripheral pulses, capillary filling, hair distribution on extremities, and presence or absence of ulcers.
- Signs of congestive heart failure and arthritis
- **The physical examination is often within normal limits**

Laboratory Features

- Because RLS requires clinical diagnosis, laboratory study is not a major part of evaluation and management.
- **All patients should be checked, however, for iron deficiency**
- Most laboratory studies will be directed to causative or comorbid conditions such as renal failure.



Treatment

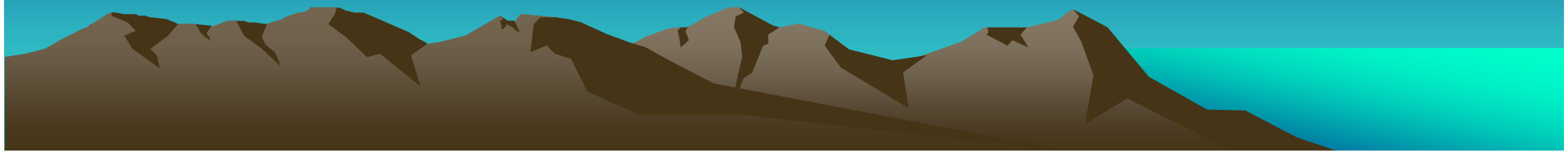


Goals of RLS therapy

- Reduce its symptoms:
  - Decreasing the number of nights with RLS symptoms.
  - Decreasing the severity of RLS symptoms.
  - Decreasing nighttime awakenings.
- Improve quality of life:
  - Improve the activities of daily living.
  - Decrease daytime somnolence.
  - Improve the quality of sleep.

Treatment

- Before beginning treatment of RLS, it is important to determine whether the disorder is idiopathic or secondary.
- It is worth attempting to resolve a causative condition -- such as iron deficiency



Treatment

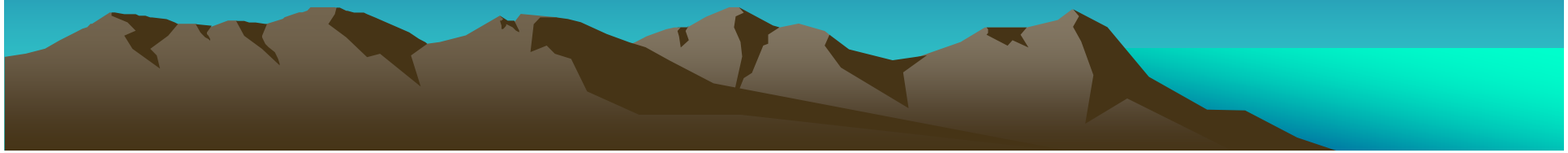
- Second step second step before treatment is to determine whether there are factors that may be aggravating RLS:
  - Pharmaceutical: Antiemetics, antidepressants, centrally active antihistamines
  - Dietary: caffeine, alcohol etc…
  - Sleep deprivation
- Third step is nonpharmacological therapies

Nonpharmacologic Therapies

- There have been no systematic trials of nonpharmacologic therapies for RLS patients
- Patient education, support groups etc…
- Good sleep hygiene, including rising and going to bed at the same times each day.
- Avoidance of tobacco, alcohol, caffeine, antihistamines, antiemetics (e.g., compazine), metaclopramide (reglan)
- Exercise for 30 minutes three times per week
- Other recommendations include hot baths, massage, stretching, and moderate exercise

Pharmacologic Treatment

- It is easiest to divide RLS patients into 3 categories:
  - Those with intermittent or situational symptoms
  - Those with daily symptoms
  - Those who have failed prior first-line therapies



Intermittent RLS

- Medications that can be taken as needed
  - Levodopa with decarboxylase inhibitor (carbidopa or benserazide)
  - Mild-to-moderate-strength opioid (codeine, propoxyphene, tramadol, hydrocodone, oxycodone)
  - Sedative-hypnotic
  - Dopamine agonist: low dose, if tolerated

Daily Symptoms

- Dopamine agonists
  - Non-ergoline
    - Ropinirole (0.25-6 mg/day) (*Requib*)
    - Pramipexole (0.125-1.5 mg/day) (*Sifrol/Mirapex*)
  - Ergoline
    - Pergolide (0.05-1.5 mg/day) considered an option in cases where there are unremitting side effects from the other dopaminergic agents
- Anticonvulsants
  - Gabapentin (300-2700 mg/day) (*Neurontin*)
  - Carbamazepine (200-400 mg at bedtime)

Daily Symptoms

- Opioids
  - Tramadol (100-400 mg/day)
  - Codein 15mg-60 mg at bed time
  - Less tolerance and abuse as compared to patient with chronic pain
- Benzodiazepines
  - Clonazepam (0.5-4 mg/day)

Refractory Cases

- Change to a different dopamine agonist
- Switch to an opioid or anticonvulsant
- Add a second medication, possibly with reduced agonist dose
- Consider a drug holiday: may be covered by opioid or different agonist high-potency opioids for severe, resistant cases; for example, methadone (5-40 mg/day)

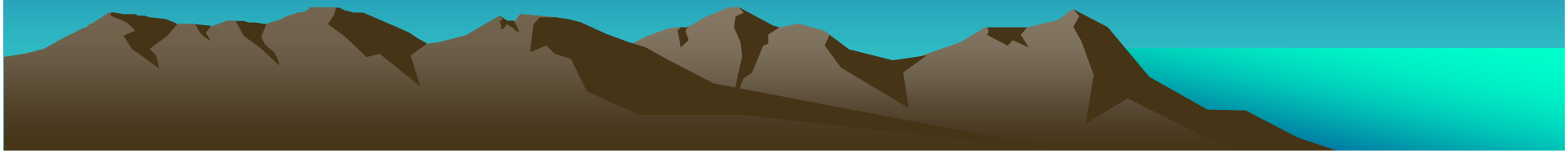
Dopaminergic Medications

Carbidopa/levodopa

- 90% efficacy rate
- 25/100 mg at dinner and bedtime
- Maximal does 50/100 mg three to four times a day
- Frequently dosed in continuous-release formulation (CR) (Start 25/100 max 50/200)
- Can be used with other medications.

Carbidopa-levodopa

- Approximately one half of patients eventually require change of medication.
- 80% risk o developing augmentation when the dose exceed two 25/100 tablets



Dopamine Agonists

Pramipexole (Sifrol)

- 0.125 to 0.5 mg before bedtime or in divided dosages at dinner and before bedtime (2 hours before expected symptoms)
- Maximal dose 1.5 mg in two to three divided doses
- Rebound/augmentation less common

Ropinirole (Requib)

- 0.375 to 1.5 mg before bedtime or in divided dosages at dinner and before bedtime
- Maximal dose 4 mg in two to three divided doses
- Rebound/augmentation less common

Side Effects of Dopaminergic Medications

Side effects may include:

- Nausea
- Orthostatic hypotension
- Insomnia
- Sleepiness (sleep attacks similar to those seen in narcolepsy)
- Constipation
- Hallucinations
- Dyskinesia
- Fluid retention
- Nasal Stuffiness

Augmentation

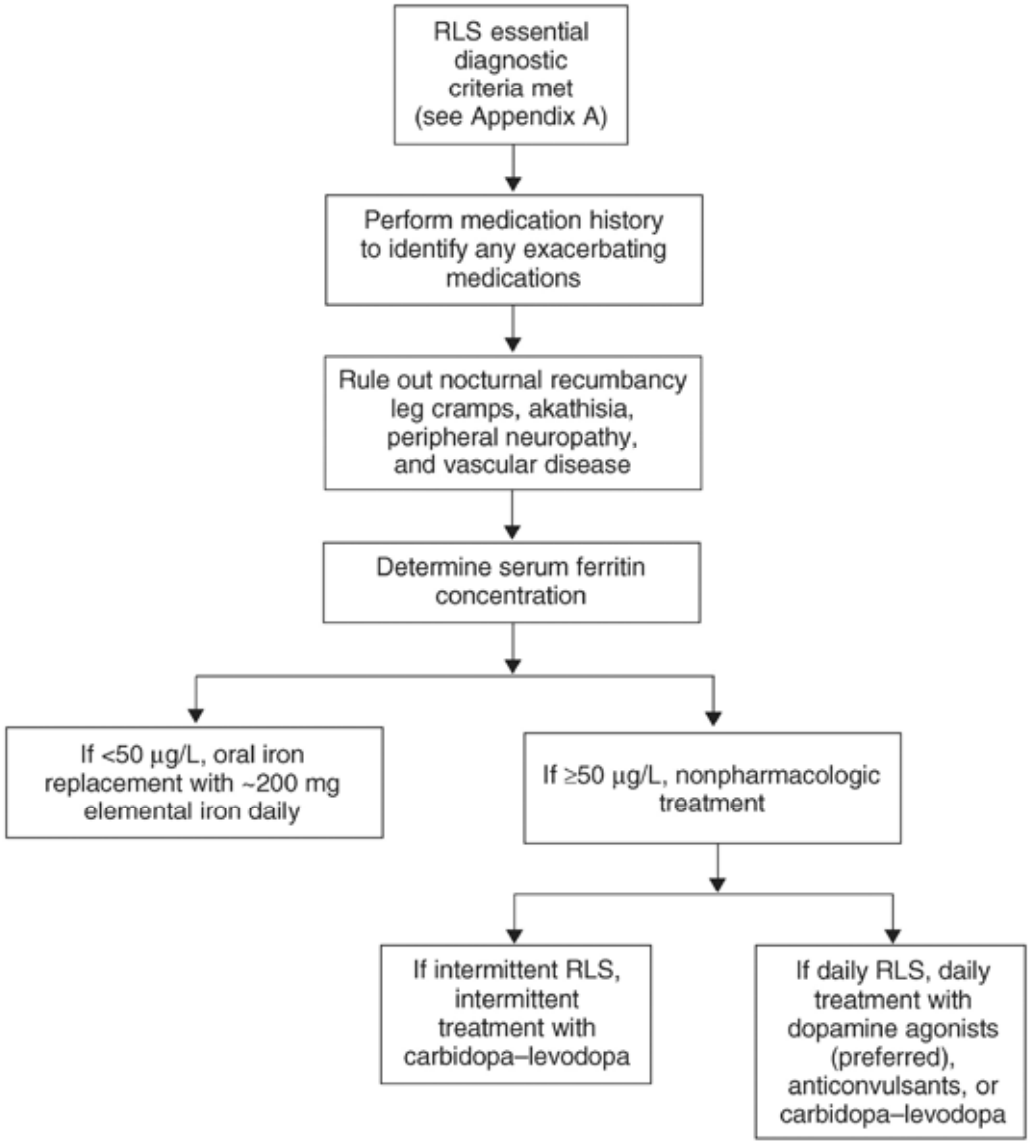
- It is an iatrogenic worsening of RLS. It is characterized by worsening of untreated clinical symptoms and decreased responsiveness to medication.
- The key feature, however, is an earlier onset of more severe symptoms.
- Some authors suggested that 50–85% of patients receiving levodopa will develop augmentation, with an increased risk if the patient receives more than 200 mg of levodopa daily
- Augmentation is always identified within two months of treatment initiation
- Augmentation is usually treated by either changing to a different medication or giving doses earlier during the day

Special populations

- **Pregnant Women.** Opioids may present the least potential harm to the fetus. Iron and vitamin (folate) repletion should be considered.
- **Children.** Drug treatment of children should be done cautiously if behavioral measures such as sleep hygiene, and restriction of caffeinated beverages such as sodas fail.
- **Depressed Patients.** Treatment of these patients can present a dilemma, since antidepressants may exacerbate RLS, although the degree of this problem is not well studied (Buspar may help in this situation)

General Considerations

- The dopamine agonists -- as well as other classes of RLS medications -- should be gradually titrated from a minimal dose.
- Maximal agonist doses are generally well below those used for Parkinson's disease and this may help reduce the problematic side effects seen in patients with Parkinson's disease, including somnolence and sleep attacks, dyskinesias, and hallucinations/psychosis

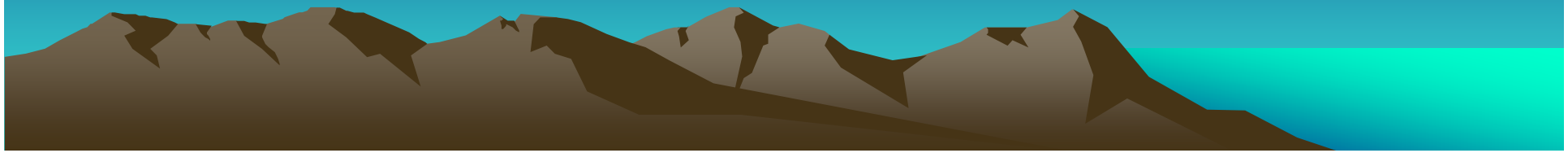


Conclusion

- RLS is a common disorder thought to involve abnormal iron metabolism and dopaminergic systems.
- RLS is underdiagnosed
- Nonpharmacologic therapy should be suggested for all patients with RLS, but pharmacologic therapy may be required, and evidence is strongest for levodopa and dopamine agonists.

Conclusion

- Common
- Important cause of reduced quality of life
- Easy to diagnose (RLS)
- Easy to treat (usually)
- Gratifying response to treatment

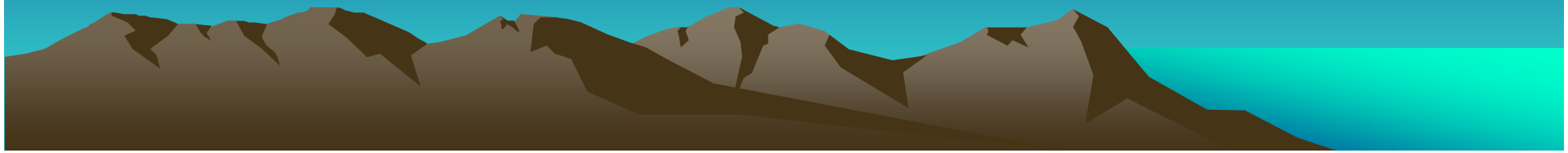


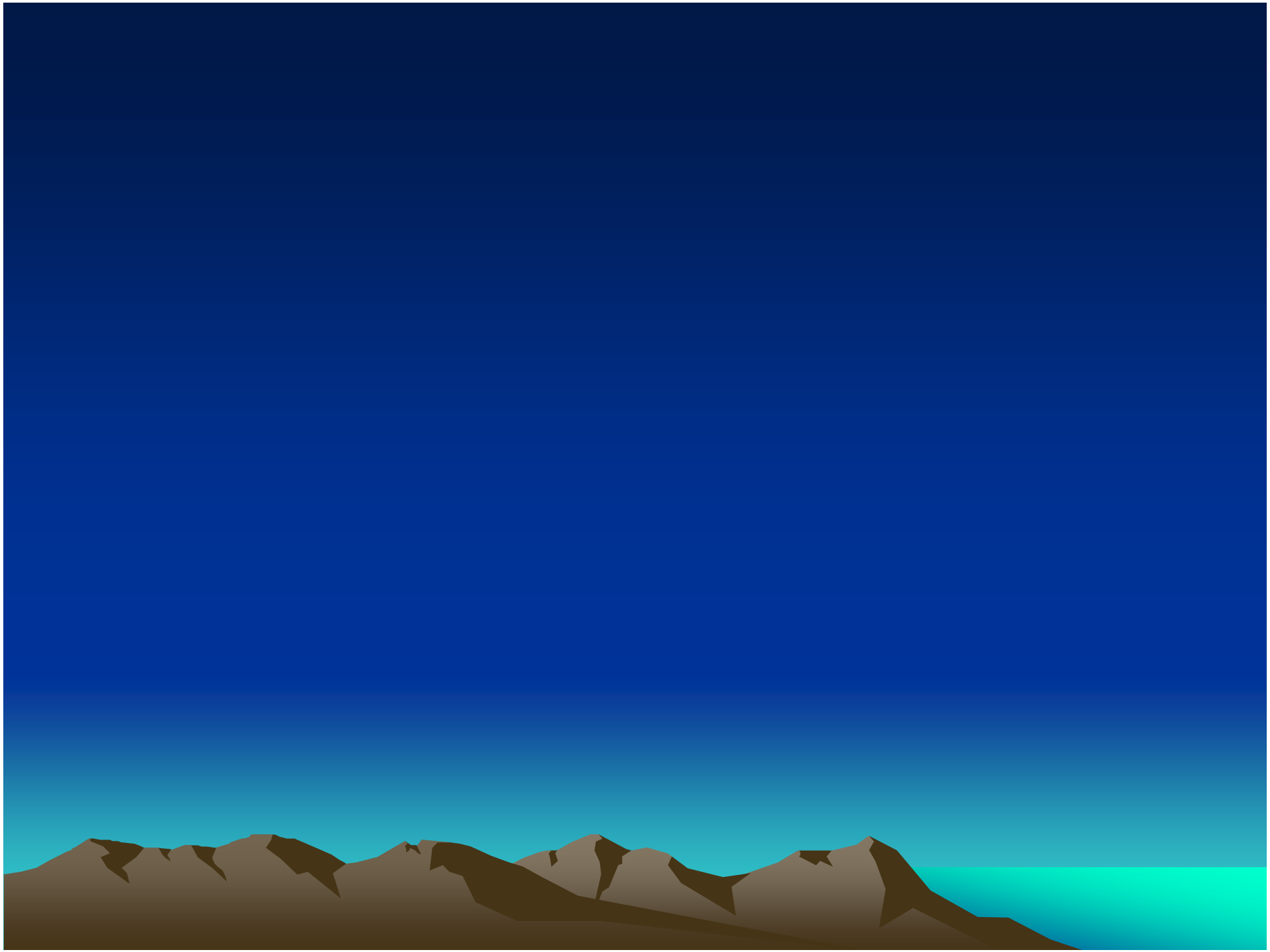
Summary

- RLS was first described in the 17th century and rediscovered in 1945 byKarl Ekbom
- RLS is a common disorder, occurring in about 10% of the population.
- Patients with RLS often describe the urge to move, uncomfortable sensations, and pain, which begin or worsen during rest or inactivity such as lying or sitting.
- Symptoms of RLS make sleeping difficult for many patients, and significant daytime difficulties result from the condition.
- RLS can either be primary or arise from secondary causes that lead to iron deficiency. There is a familial component in primary RLS, but its underlying mechanisms remain unknown.
- Of individuals with conditions associated with iron-deficiency states, including pregnancy, renal failure, and anemia, 25–30% may develop RLS.
- The goals of RLS treatment include improving its symptoms and the patient's quality of life.
- There are limited data on the treatment of RLS.
- Pharmacologic therapies
  - include iron replacement,
  - dopaminergic agents (e.g., levodopa),
  - dopamine agonists,
  - anticonvulsants,
  - opioids, and
  - benzodiazepines.
- There have been no systematic trials of nonpharmacologic therapies for RLS, but good sleep hygiene and avoidance of alcohol, caffeine, and nicotine may improve symptoms.

- “Wherefore, in some, whilst they would indulge sleep, in their beds, immediately follow leapings up of the Tendons, in their Arms and Legs, with Cramps, and such unquietness and flying about of their members, that the sick can no more sleep, than those on the Rack

-Thomas Willis, 1672





Impact

- It does appear that individuals with restless legs syndrome are about 3-5 times more likely to have major depressive disorder or panic disorder in their lifetime
- Individuals with restless legs syndrome are 4-10 times more likely to have major depressive disorder or panic disorder during the past 5 months

Depression and RLS

- about 10% to 20% of people with *DSM-IV* major depressive disorder and/or panic disorder meet the criteria for restless legs syndrome
- Unfortunately are rarely diagnosed.
- Probably due to symptomatic overlap between restless legs syndrome and major depressive disorder
  - Insomnia, dysphoria, poor concentration, and low energy.

Selected Differential Diagnoses

- Claudication
- Painful legs and moving toes
- Akathisia (motor restlessness)
- Nocturnal legs cramps

Features of Restless Legs Syndrome Symptoms that Differentiate Them From Mimics

- **Location of symptoms:** RLS symptoms are usually diffuse and deep within the limb, as opposed to very focal or superficial
- **Duration of symptoms:** RLS symptoms are usually somewhat persistent, lasting 5 or 10 minutes or longer, while mimics may be transitory (lasting seconds)
- **Speed of relief with activity:** RLS symptoms are quickly relieved with activity, unless movement is a major problem; mimics may persist
- **Relief with change of position:** Relief for RLS symptoms usually demands continued activity, simple positional change gives at best transitory or incomplete relief
- **Provocation by rest:** RLS symptoms are brought on by the resting state, no matter the bodily position (while sitting or lying), and do not require a specific position (eg, the legs bent or crossed)

Special populations

- **Pregnant Women.** Opioids may present the least potential harm to the fetus. Iron and vitamin (folate) repletion should be considered.
- **Children.** Drug treatment of children should be done cautiously if behavioral measures such as sleep hygiene, and restriction of caffeinated beverages such as sodas fail.
- **Depressed Patients.** Treatment of these patients can present a dilemma, since antidepressants may exacerbate RLS, although the degree of this problem is not well studied (Buspar may help in this situation)

Pathophysiology of Secondary RLS

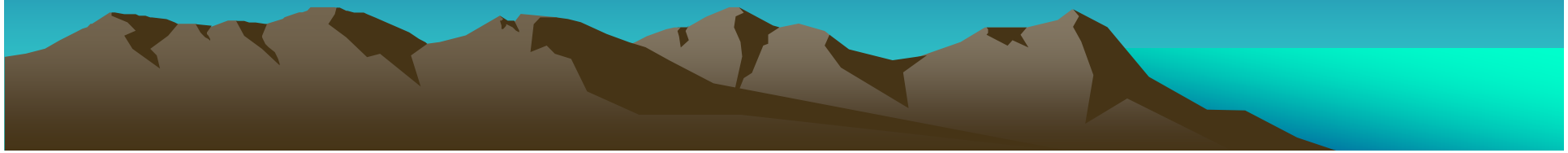
- Of individuals with conditions associated with iron-deficiency states, including pregnancy, renal failure, and anemia, 25–30% may develop RLS.
- Individuals with renal failure or who are pregnant may have RLS symptoms without significant anemia but with deficient iron stores (defined by a serum ferritin concentration of <50 µg/L).
- Oral and i.v. iron therapy may improve or resolve RLS symptoms in patients with clear iron-deficiency anemia and also in RLS of pregnancy and renal disease where iron stores may be reduced without obvious anemia.

Pathophysiology of Primary RLS

- The mechanisms underlying primary RLS remain unknown.
- Because they frequently coexist and respond to the same medications, it is reasonable to presume that RLS and periodic limb movement disorder (PLMD) likely have a shared, but not identical, pathophysiology

Definitions

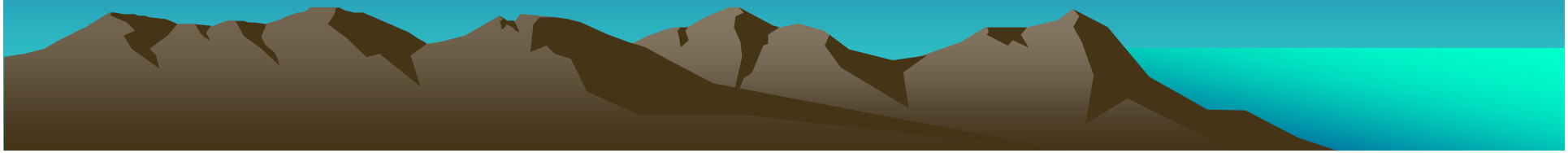
- Activities to maintain alertness, such as engaging in conversations or playing video games, can reduce the severity of symptoms



- The relationship between iron deficiency and RLS/PLMD may lie in iron's importance role in dopamine signaling; iron is an essential co-factor for enzymatic conversion of tyrosine into L-dopa (via tyrosine hydroxylase).

Pharmacologic Therapies

- Experts recommend iron supplementation if ferritin concentrations are below 50 µg/L



Abnormalities in Iron Metabolism

- Reversible forms of RLS - pregnancy, renal failure, and anemia - are characterized by iron deficiency and respond to iron therapy.
- Thus, abnormalities in iron metabolism may play a pathogenic role.
- Insufficient iron stores in selected areas of the brain (substantial nigra and putamen) have been described.

Allen, RP, Barker, PB, Wehrl, F, Song, HK, & Warly, CJ MRI measurement of brain iron in patients with restless legs syndrome. Neurology 2001; 56: 263-265

Synonyms

- Restless limb syndrome
- Growing pains
- Night kicking
- Night walker syndrome

Iron

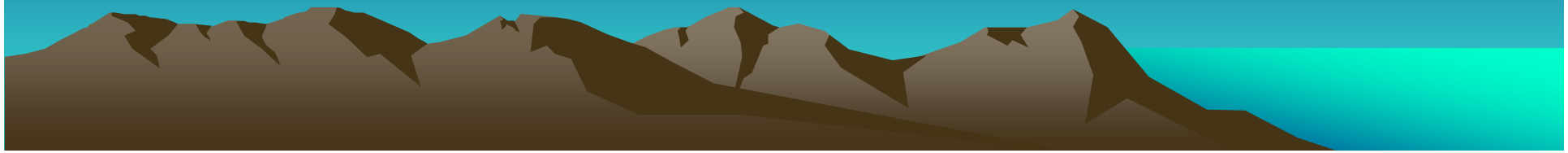
- Ferrous sulfate 325 mg tid with 100 mg of vitamin C with meals for patients who have serum ferritin below 50 µm/mL even in the absence of iron-deficiency anemia. Iron can cause constipation and abdominal discomfort; hence, it is best to take it with meals or to lower the dose if poorly tolerated.
- Recheck ferritin levels in 3 mo and stop iron therapy if serum ferritin above 50 to avoid iron overload.

Carbidopa-levodopa

- 25/100 carbidopa-levodopa at bedtime (one tablet). Dose may be increased as needed.
- Augmentation develops in up to 80% of patients especially of daily dose exceeds two 25/100 tablets. Approximately one half of patients eventually require change of medication.

Pramipexole

- 0.125 mg at bedtime. The dose may be increased as necessary by 0.125 mg every 3 days. The dose may be increased up to 2 mg.
- Augmentation can be easily overcome with an additional 0.125 dose several hours before bedtime



Ropinirole

- 0.25 mg at bedtime to be increased in 0.25 mg increments every 3 days. The dose may be increased up to 2–4 mg/d.
- The adverse effects include nausea, vomiting, fluid retention, nasal stuffiness and daytime sleepiness. These side effects are common to all dopamine agonists (ropinrole, pramipexole and pergolide).

Pramipexole & Ropirenol

- Are usually well tolerated
- Nausea is very frequent when you initiate treatment with dopaminergic agonists. It's usually not very severe, and it takes place usually in the first 2-3 weeks of treatment and it decreases with time, so if you do slow titration you may avoid the occurrence of nausea.
- Long-term studies show that pramipexole remains effective over a long period of time.

Pergolide

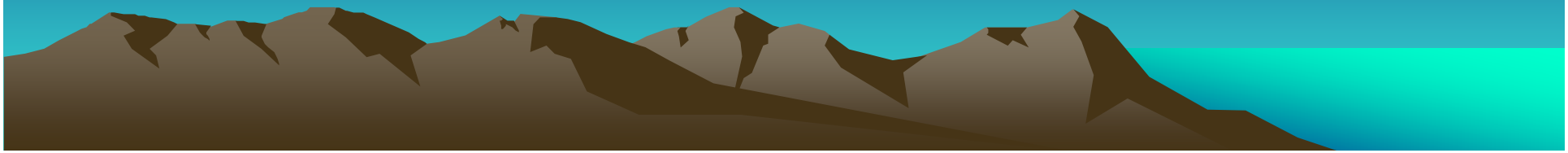
- 0.05 mg at bedtime to be increased in 0.05 mg increments to efficacy. The effective dose is up to 0.5 mg.
- This medication has been associated with increased incidence of cardiac valve fibrosis. Thus, ropinrole and pramipexole are preferred over pergolide.

Neurontin

- 300 mg at bedtime, increase in 300 increments
- Excessive sedation limits usefulness. Dependence may be an issue.
- 300mg increments weekly to efficacy. The dose may be increased up to 1800 mg.
- The medication can cause somnolence and dizziness in the elderly if dose is not titrated upward slowly

Clonazepam

- 0.5 mg at bedtime to be increased gradually up to 2 mg/d.

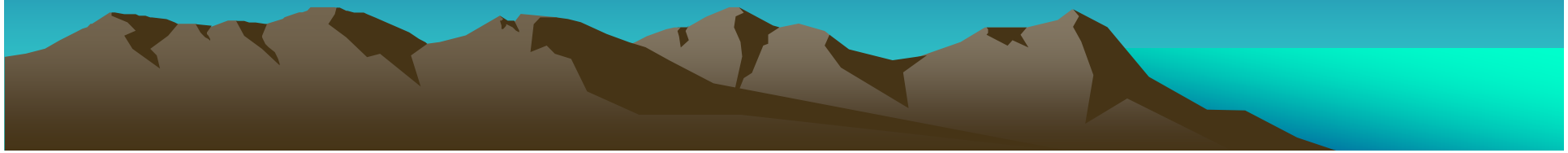


Propoxyphene hydrochloride/napsylate

- 65–130 mg of propoxyphene napsylate and 100–200 mg of propoxyphene hydrochloride is the usual starting dose at bedtime that may be increased on a weekly basis to efficacy.
- Sedation may be a limiting factor in addition to drug abuse potential. Constipation may be an issue.

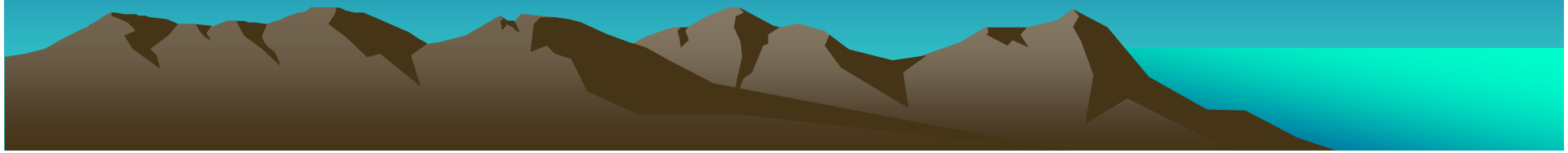
Oxycodone

- 5 mg at bedtime and increase in 5 mg increments up to 20 mg/d.
- Excessive sedation, constipation and significant abuse potential may limit usefulness.



Clonidine

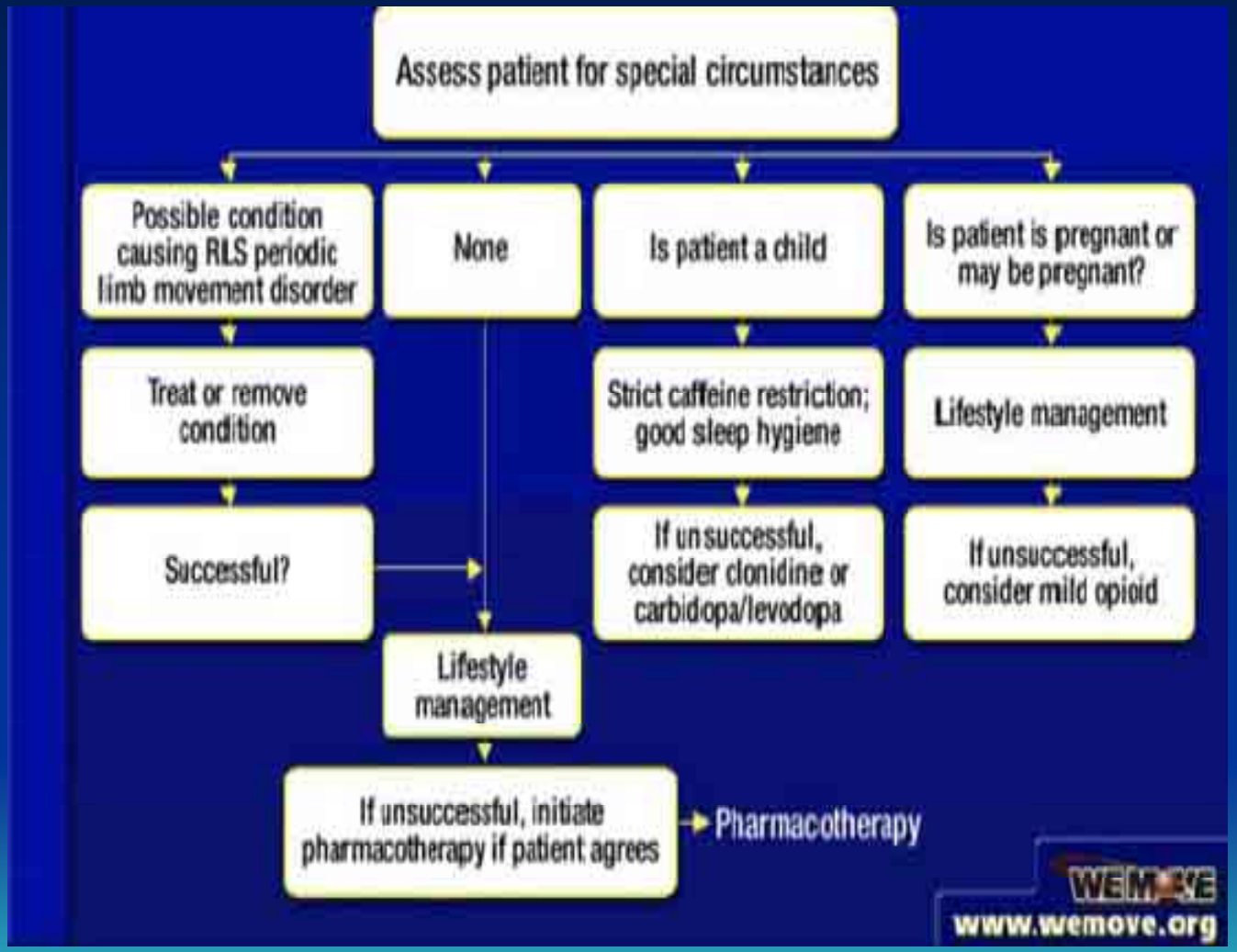
- Initial dose: 0.1 mg PO qhs
- Can increase daily dose weekly by 0.1 mg; not to exceed 1 mg/d
- Average effective dose is 0.5 mg/d



Bromocriptine mesylate

- Parlodel
- Dopamine D2 receptor agonist that has been found to be effective in RLS.
- However, usually poorly tolerated because of nausea and orthostatic hypotension.

- Other dopamine agonists such as pergolide or pramipexole preferred.
- **Adult Dose**7.5 mg PO qd am and hs


Assess patient for special circumstances
Possible condition causing RLS periodic limb movement disorder
None
Is patient a child
Is patient is pregnant or may be pregnant?
Treat or remove condition
Strict caffeine restriction; good sleep hygiene
Lifestyle management
Successful?
If unsuccessful, consider clonidine or carbidopa/levodopa
If unsuccessful, consider mild opioid
Lifestyle management
If unsuccessful, initiate pharmacotherapy if patient agrees
Pharmacotherapy
www.wemove.org