

Movement Disorders: What the PCP needs to know

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Topics to be discussed:

- Hyperkinetic movement disorders
- Restless Leg Syndrome
- Two Rare but Treatable Movement Disorders

Objectives

- Describe the different hyperkinetic movement disorders
- Propose initial management of Essential Tremor
- Describe evaluation and treatment of Restless Leg Syndrome

Hyperkinetic Movement Disorders

- *Tremor* – rhythmic oscillation of a body part (e.g. hand, foot, tongue, head).
- *Chorea* – spontaneous brief, irregular randomly flowing involuntary movements that are NOT rhythmic. Pts may appear ‘fidgety’ or restless.
 - Pts with chorea often incorporate the involuntary mvt into a voluntary mvt such as crossing/uncrossing legs, rubbing chin (parakinesis)
- *Dyskinesia*- intermittent choreiform mvts affecting face, limb, or trunk that occur in some PD pts as side effect of dopamine.
 - Tardive dyskinesia- persistent choreiform mvts, especially affecting mouth or tongue assoc. with exposure to dopamine blocking agents (neuroleptics, metoclopramide)

Weiss, Howard MD. Clinical Pearls in Tremor and Other Hyperkinetic Movement Disorders. Semin Neurol 2016;36:335-341

Hyperkinetic Movement Disorders

- *Dystonia*- sustained or intermittent muscle contraction causing abnormal movement, postures or both. Often initiated or worsened by voluntary action.
 - May be very brief, resembling myoclonic jerk or causing tremor (Dystonic tremor)
 - Focal, segmental or generalized
- *Myoclonus* – rapid, brief, shock-like movements caused by sudden muscle contraction (positive myoclonus) OR sudden decrease in muscle tone (negative myoclonus) – asterixis.
 - Focal, segmental, or generalized

Weiss, Howard MD. Clinical Pearls in Tremor and Other Hyperkinetic Movement Disorders. Semin Neurol 2016;36:335-341

Hyperkinetic Movement Disorders

- *Tics* – repetitive, rapid, stereotyped unwanted muscle contractions causing abnormal movements (motor tics) or sounds (phonic tics).
 - Simple motor tics –can resemble myoclonus or choreic jerks; Examples: eye roll, eye blink, head toss
 - Complex motor tics - coordinated sequences of movement such as head shaking, self punching
 - Simple phonic tic – clearing throat, grunt
 - Complex phonic tic – identifiable verbalizations, including coprolalia.
- Premonitory sensory urges often precede tics, and are alleviated after the tic release.
 - This feature distinguishes tic from myoclonus, chorea or dyskinesia.

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Tremor

- The most common movement disorder in adults.
- Definition: Rhythmic involuntary oscillation of a body part
- Body parts affected: hands, head, chin, voice, palate, lower extremities
- Classified on basis of frequency (oscillations) and amplitude.
 - Parkinsonian rest tremor: 3-6Hz
 - Essential Tremor: 4 -12 Hz
 - Enhanced Physiologic Tremor: 8-12 Hz
- Tremor amplitude correlates with patient embarrassment or disability

Questions for Tremor Evaluation

1. Is the movement disorder actually tremor?
 - Action myoclonus and dystonia of upper limbs can mimic tremor
2. Is the tremor isolated, or are there accompanying neurologic abnormalities?
 - Parkinsonian features (bradykinesia, facial masking, shortened stride length, stopped posture, rigidity)
 - Cerebellar dysfunction – nystagmus, impaired ocular pursuits, dysmetria, overshoot, truncal ataxia and wide based gait.
 - Dystonia- look for a null point (body position with no tremor)

Questions for Tremor Evaluation

What are the features of the tremor?

- Time course / progression
- Acuity of onset
- Specific triggers- rest, with posture, with action,
- Need to ask the following:
 - detailed history of drug exposure
 - Medication list
 - Interventions that improve tremor (e.g, alcohol ingestion)
- Document any family history of tremor or other neurologic complaints in parents, siblings, and children.

Examining a patient with tremor

- Have patience, tremor may take 30sec or more to emerge
- Examine in different postures:
 - True rest position (arms lying at side or on lap, not on armrests of chair)
 - Hands pronated and resting – look and feel
 - Extend arms forward in outstretched position, hold ≥ 10 sec
 - Hold arms abducted at shoulders – wing beating position – for at least 10sec.
 - If head tremor – patient should lie down with head fully supported.
 - If resolves –essential tremor
 - If persists –dystonic tremor.
 - If voice tremor - hold a steady note such as "ahhhh" or "eeeeee"
 - If quivering – Essential tremor
 - If accompanied by hoarseness, straining, and voice breaks -spasmodic dysphonia.

Terms Used to Describe the Components of Tremor

- **Rest tremor:** Tremor of a body part that is not undergoing voluntary muscle contraction.
- **Postural tremor:** Tremor occurs when holding a body part motionless against gravity.
- **Kinetic Tremor:** Tremor during active voluntary movement.
 - *Task-specific Tremor:* appearance of kinetic tremor during the performance of highly specific, skilled movements (eg. writing)
 - *Intention tremor:* the pronounced exacerbation of kinetic tremor toward the end of a goal-directed movement. Intention tremor worsens as body part nears target

Major Tremor Syndromes

Tremor Syndrome	Rest	Posture Action	Tremor Frequency	Relative Occurrence
Essential Tremor	+/-	++	5-8 Hz	Common
Parkinsonian Tremor	++	+/-	4-6 Hz	Common
Enhanced physiologic tremor		++	8-13 Hz	Common
Psychogenic tremor	+	+	Variable	Less Common
Cerebellar tremor		+	2-4 Hz	Less Common
Drug-Induced tremor	+	+	4-8 Hz	Less Common
Dystonic tremor	+/-	+	4-8 Hz	Uncommon
Holmes tremor	+	+	2-3 Hz	Uncommon
Orthostatic tremor			13-18 Hz	Uncommon
Task-specific tremor		+	4-8 Hz	Uncommon

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Physiologic Tremor

- Present in healthy people of all ages
- Amplitude is so small that it is generally unnoticed- or only seen with fine/precise movements (threading needle)
- Enhanced Physiologic tremor (EPT)- amplitude of physiologic tremor increases and becomes clinically apparent.
 - Occurs in periods of anxiety or stress
 - Usually a postural tremor in outstretched hands, bilateral, symmetrical.
 - Limb weights reduce both amplitude and frequency of EPT.
 - Limb weights reduce only amplitude of Essential Tremor

Factors that Induce Enhanced Physiologic Tremor (also exacerbate involuntary movements in patients with movement disorders)

- Stress
- Anxiety
- Fever
- Cold (shivering)
- Excitement
- Anger
- Fear
- Fatigue
- Mental activity

Medications and conditions that cause Enhanced Physiologic Tremor

- Lithium
- Sodium Valproate
- Tricyclic antidepressants
- Bronchodilators (theophylline, terbutaline)
- Psychostimulants [cocaine, amphetamines, MDMA(ecstasy)]
- Amiodarone
- Mexiletine
- Steroids
- Cyclosporine
- Caffeine
- Hypoglycemia
- Hyperthyroidism
- ETOH or Drug Withdrawal
- Toxins (mercury, lead)

Essential Tremor

- Postural, kinetic. Frequency 8-12Hz, small amplitude increasing with severity
- Hands, head, voice legs, face, trunk
- Usually symmetric, almost always more noticeable with action vs with posture or rest
- Increased incidence with age
- Writing is shaky, spills drink or food
- Often improves with alcohol
- Mild ataxia can be seen (trouble with tandem gait)
- Does not increase mortality

Essential Tremor (cont'd)

- Strong Familial
 - Autosomal dominant inheritance
 - Heritability 45-90%
 - Variable penetrance
 - Non-Mendelian (unlikely this is single gene, at least 3 chromosomal regions)
- Patients use strategies to mitigate tremor – bracing elbow on wall and holding wrist to apply mascara; using opposite hand to brace writing hand; holding spoon with whole fist

• Movement Disorder Review by University of Kansas 12/2017

Essential Tremor Functional Disability

- Handwriting
- Drinking liquids
- Fine manipulations
- Eating
- Dressing
- Speaking
- Embarrassment → avoid going out/socializing → depression

Archimedes spiral



Normal



Parkinson's disease



essential tremor

First Line Medications for Essential Tremor

- **Beta-blockers: non-selective: need beta-2 effect**
 - Propranolol Immediate-release (IR)
 - PRN 10-40mg
 - Twice daily, up to 240mg total
 - Propranolol LA
 - Start 60mg qAM, up to 240-320mg/day
- **Primidone (barbiturate)**
 - Start with ½ of 50mg tab in evening, titrate up as needed/tolerated to 250mg (can go up to 750mg)
 - Side effects: sedation, dizziness/clumsiness

American Academy of Neurology Guidelines Treatment of Essential Tremor (2011)

AAN Guidelines	Treatment
Effective	Primidone, Propranolol
Probably Effective	Topiramate, Gabapentin, Atenolol, Sotalol, Alprazolam
Possibly Effective	DBS, thalamotomy, botulinum toxin type A, Clonazepam, nadolol, nimodipine
Ineffective	Acetazolamide, isoniazid, mirtazapine, nifedipine, pindolol, trazodone, verapamil, levetiracetam, 3,4-diaminopyridine, flunarizine
Insufficient Evidence	Amantadine, clonidine, pyridoxine, metoprolol, nicardipine, olanzapine, quetiapine, clozapine, phenobarbital, pregabalin, zonisamide, gamma knife

Medications for Essential Tremor

Drug	Initial Dose	Maximal Dose	Side Effects
Propranolol	20-80mg/day in 2 divided doses	120-320mg/day in 1-2 doses	↓HR, ↓BP, erectile dysfunction, fatigue, exacerbate asthma or depression
Primidone	25mg qhs	250mg-750mg qhs or 2 divided doses	Sedation, ataxia, confusion, dizziness, fatigue, nausea, flu-like symptoms
Gabapentin	300-900mg/day in 3 divided doses	1200-3600mg/day in 3 divided doses	Ataxia, dizziness, nausea, sedation, wt.gain.
Levetiracetam	500mg/day	2000mg/day in 2 divided doses	Dizziness, drowsiness, fatigue, irritability
Topiramate	25-50mg qhs or 2 divided doses	150-300mg/day in 2 divided doses	Acute angle closure glaucoma, paresthesias, cognitive difficulty, drowsiness
Zonisamide	25mg qhs	200mg qhs or 2 divided doses	Headache, drowsiness, fatigue, paresthesias. CANT USE if SULFA allergy

Frucht, Steven M.D. Evaluation of Patients with Tremor. *Practical Neurology*. May 2018

Surgical Treatment of Essential Tremor

- **Thalamotomy**

- Craniotomy – stereotactic techniques create lesion in ventral intermediate nucleus of thalamus (VIM) under electrophysiologic guidance
- Gamma Knife - uses radiation delivered to the intracranial target (not used much)
 - Radiation side effects and theoretical risk of secondary tumor formation
- Focused ultrasound (7/2016)- uses high-energy ultrasound beams to create the lesion.
 - Neither of these latter two methods requires craniotomy, but still considered invasive procedures, as brain tissue is destroyed.
 - Electrophysiologic guidance is not possible with gamma knife or ultrasound
 - Ultrasound contraindicated in patients who cannot have MRI
- Side effects of thalamotomy
 - Numbness, headache, cognitive deterioration, gait/balance disturbance

Surgical Treatment of Essential Tremor

- **Deep Brain Stimulation (DBS)**

- electrodes implanted in Thalamic VIM nucleus using stereotactic methods.
- electrodes connected to a pulse generator implanted in the chest wall below the clavicle. High-frequency electrical stimulation is applied to modify the activity of the target region of the brain.
- Computerized programming of the pulse generator with a handheld device to optimize the electrode montage, voltage, pulse frequency, and pulse width.
- No universal formula for programming, each patient must participate in the transaction to inform the programmer when the best settings have been achieved.
- Regular follow-up visits for program checks are necessary to maintain the best clinical benefit and to monitor battery life (usually two to five years)

Deep Brain Stimulation for Tremor (cont'd)

- Side effects: most related to equipment malfunction or lead displacement. Many side effects transient and resolved with stimulator adjustment or with time.
- One procedure-related death reported due to perioperative intracerebral hemorrhage
- dysarthria, disequilibrium, paresthesias, weakness, headache, intracranial or subdural hemorrhage, ischemic changes, generalized seizures, and decreased verbal fluency.
- Overall, DBS tends to have fewer side effects than thalamotomy

Schuurman PR, Bosch DA, Bossuyt PM. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med.* 2000;342(7):461

Tremor of Parkinson's Disease

- Rest, postural
- Frequency 4-6 Hz; variable amplitude (often starts small gets bigger as patient keeps moving)
- Hands, legs, chin involvement
- Not evident in all patients
- May diminish with advancing disease

Cardinal Motor Features of Parkinsonism

- **Bradykinesia** – slowness of movement and small movements. Reduced blinking, face expression and gesturing. Hypophonia, micrographia, ↓ arm swing, start hesitation, shuffling steps, freezing
- **Tremor:** (usually resting) “pill-rolling,” often involves thumb.
- **Postural Instability:** retropulsion on pull test. Falls, stooped, flexed posture.
- **Rigidity-** resistance to passive manipulation that is NOT velocity or direction dependent (unlike spasticity)

Differentiating PD vs Essential Tremor

Clinical features	Parkinson disease tremor	Essential tremor
Age at onset	>50 years	Bimodal 2nd and 6th decade
Gender	Male ≥ Female	Male = Female
Family history	~10 to 15 percent	~50 percent
Asymmetry	+++	+
Frequency	4 to 6 Hz	6 to 12 Hz
Character	At rest	Postural, kinetic
	Supination-pronation	Flexion-extension
Distribution	Hands, legs, chin, tongue	Hands, head, voice
Associated features	Bradykinesia, rigidity, postural instability, micrographia	Mild gait disorder or cerebellar signs in a minority

Jankovic J. Essential tremor: clinical characteristics. Neurology 2000; 54(11 Suppl 4):S21.

Psychogenic Tremor

- Abrupt tremor onset
- Waxing and waning history
- Periods of remission
- History of movement of tremor from 1 body region to another
- Equal severity of tremor at rest, posture, and action
- Variability in tremor frequency and axis of oscillation
- Unusual involvement of noncontiguous body areas
- Accompanying inconsistent exam findings: give-way weakness, inconsistent slowness

Orthostatic Tremor

- Unusual tremor affecting trunk and legs
- Specifically triggered by standing
- Patients report 'trouble standing', may be unaware of tremor
- Tremor abates when walking
- Touching wall or anything solid may also abate tremor
- Female > Male preponderance. Onset usually in 50's (13-85y/o)
- High and low frequencies described
- Treatment: Clonazepam, Gabapentin, DBS to thalamic VIM

Cerebellar Tremor

- Accompany disorders affecting cerebellar neurons
 - Spinocerebellar ataxia, Olivopontocerebellar degeneration, cerebellar stroke
- Accompany disorders affecting afferent or efferent connections to cerebellum
 - Multiple sclerosis
 - Brainstem strokes
- Tremor is coarse, slow (3Hz), affects proximal muscles (ie. Wing-beating tremor). Postural, kinetic or in severe cases at rest
- Usually other cerebellar signs – dysmetria, dysdiadochokinesia
- Treatment – no pharmacology. DBS thalamic VIM in select patients

Holmes Tremor

- First described in 1904 by Gordon Holmes as a 3–4 Hz flexor-extension oscillation, present at rest, exacerbated with posture changes and intensified with action.
- **Current Definition: rest and intention tremor with sometimes irregular amplitude. Postural tremor is also present in many patients.**
- Prior names: rubral, mesencephalic, or thalamic tremor
 - terms no longer used because typical cases have been described with lesions located in other areas, and red nucleus experimental lesions fail to induce persistent tremor
- Assumed that a double lesion is required to develop HT:
 - the dopaminergic nigrostriatal system
 - cerebello-thalamo-cortical or dentate-rubro-olivary pathways

Gajos A, Bogucki A, Schinwelski M, et al. The clinical and neuroimaging studies in Holmes tremor. Acta Neurol Scand 2010;122:360–366

Holmes Tremor

- Associated symptoms: hemiparesis, ataxia, hypoesthesia, dystonia, cranial nerve involvement, and dysarthria
 - Other symptoms/signs were vertical gaze disorders, bradykinesia/rigidity, myoclonus, and seizures. Most of the patients had lesions involving more than one area.
 - MRI usually shows lesion in thalamus or midbrain/pons or cerebellum but in some cases no lesion is identified.
- Tremor onset between 1-24 months after a CNS insult. delayed onset might be due to neuronal plastic changes. Cases of years later (5,19,23yrs!)
- Treatment: Levodopa (only ~50% respond). DBS or thalamotomy VIM.

• Raina GB, Cersosimo MG, Folgar SS et al. Holmes tremor: Clinical description, lesion localization and treatment in a series of 29 cases. *Neurology*. 2016 86:931-938

Dystonic Tremor

- 2 Types: 1) Tremor in a body part that is affected by dystonia.
 - Neck (cervical dystonia), arm (limb dystonia)
 - Frequency and amplitude variable, irregular
- 2) Tremor assoc. with dystonia – tremor in body part which is not dystonic
- Can resemble essential tremor
- Usually postural or task specific but sometimes occur at rest, in which state they tend to be jerky and irregular.
- The use of an alleviating maneuver (geste antagoniste, sensory trick) can be helpful in distinguishing dystonic tremor from other tremor syndromes, such as ET.
 - In dystonic head tremor, for example, moving an hand to the face or head in a specific plane can alleviate the cervical dystonia symptoms, including head tremor.

Differential Diagnosis of Tremor

Tremor	Description
Essential tremor	Bilateral postural or kinetic tremor of the hands and forearms (≥ 4 Hz; usually 6 to 12 Hz) or isolated head tremor without evidence of dystonia. Absence of other neurologic signs or recent trauma preceding the onset of tremor.
Physiologic tremor	Enhanced physiologic tremor. High frequency (10 to 12 Hz), presence of known cause (eg, medications, hyperthyroidism, hypoglycemia).
Parkinson disease	Mixture of rest and action tremors; occasionally action tremor alone. Leg or foot tremor more common than with essential tremor, usually does not produce head tremor. Frequency 4 to 6 Hz.
Orthostatic tremor	Postural tremor in the torso and lower limbs while standing; may also occur in the upper limbs. Suppressed by walking. Tremor is high frequency (14 to 20 Hz) and synchronous among ipsilateral and contralateral muscles.
Cerebellar tremor	Postural, intention, or action tremor. Relatively low frequency (3 to 4 Hz). Associated with ataxia and dysmetria.
Drug induced tremor	Lithium, VPA, Amiodarone, Beta adrenergic agonists, Cyclosporine, Terbutaline, Theophylline, Dopamine receptor blockers,
Holmes tremor	Mixture of rest, postural, and intention tremor with frequency of 2 to 4 Hz. Associated with signs of brainstem or cerebellar damage.

Question

- Occasional quick single jerks of either upper extremity, with no premonitory sensation or urge, are most consistent with which of the following?
 - A. Dystonia due to Haldol
 - B. Myoclonus due to Sertraline
 - C. Tremor due to lithium
 - D. Tics in Tourette syndrome
 - E. Tremor due to Depakote

Answer

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Myoclonus

- Sudden, brief shock –like involuntary movements
- Important causes
 - Drugs: SSRI, TCA, Lithium, opioids, stimulants, Gabapentin
 - Epileptic myoclonus
 - Renal and liver disease, hyperthyroidism
 - Neurodegenerative disorders (AD, CJD, some parkinsonian disorders)
 - Anoxic brain injury

Other Myoclonic Syndromes

- Opsoclonus-myoclonus:
 - Paraneoplastic – SCLC (most common), also non-SCLC, breast, ovarian, adenocarcinoma, melanoma, bladder
 - Parainfectious – Lyme, West Nile, HIV, EBV, CMV, post-streptococcal, enterovirus
 - Neuroblastoma in children
- Palatal myoclonus: brainstem lesion
- Spinal segmental myoclonus
- Myoclonus-dystonia
- Progressive myoclonic epilepsies

Myoclonus Treatment

- Treat underlying cause
 - Check CMP, TSH, Vit E level, Drug/tox screen, EEG, Brain/spinal cord imaging
 - In select cases paraneoplastic Ab panel, infection work up
- No FDA approved agent for non-epileptic myoclonus.
 - Anticonvulsants used off label:
 - Valproic Acid
 - Levetiracetam
 - Clonazepam

Question

- Woman has a creepy crawly feeling in her lower extremities as the day advances, improved by walking. What is the best explanation for her symptoms?
 - A. She has an abdominal aortic aneurysm.
 - B. She is pregnant
 - C. She has light menses
 - D. She does not have a family history of similar symptoms
 - E. She takes Tylenol as needed

Answer

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Restless Leg Syndrome

5 Essential Criteria for restless leg syndrome:

- Urge to move the legs usually/not always accompanied by or caused by uncomfortable and unpleasant sensations in the legs
- Urge to move or the unpleasant sensations:
 - begin or worsen during periods of rest or inactivity
 - are partially or totally relieved by movement
 - are worse in the evening or night vs during the day
 - Not solely accounted for as symptoms due to another condition

Allen et al on behalf of RLS Study Group. Sleep Med 2014

Supportive of an RLS Diagnosis

- Periodic limb movements (during wakefulness or sleep)
- Response to dopaminergic therapy
- Positive family history of RLS in 1st degree relative
- Lack of expected daytime sleepiness

Allen et al on behalf of RLS Study Group. Sleep Med 2014

Restless Leg Syndrome

- “can’t get comfortable”
- “just need to move”
- “can’t fall asleep”
- “ I just feel antsy”
- “crampy, itchy calves”
- “Tingling in legs”
- “dread going to bed at night”
- Avoid long car rides or airplanes
- Avoid going to movie theatre

RLS: A Heterogeneous Disorder

- Genetics
- Iron
- Dopamine

RLS

Genomewide Association Studies

- 4 single nucleotide polymorphisms account for 70% of population risk for RLS
 - BTBD9 (6p)
 - MEIS1 (2p)
 - MAP2K5/LBXCOR1 (15q)
 - PDPRD
- 5 genetic loci found (RLS1-RLS5) but gene mutation not known

• Winkelmann et al *Nat Gen* 2007;39:1000-06. Stefansson et al. *NEJM* 2007;357:639-47; Schormair et al. *Nat Gen* 2008;40:946-8

Iron and RLS

- Systemic iron deficiency associated with RLS
 - Anemia
 - Pregnancy
 - Blood donors
- Severity of RLS correlates with degree of ferritin reduction
- Replacement of iron improves symptoms of RLS

Manconi et al *Neurology* 2004;63:1065-69; Earley et al *Sleep Med* 2004;5:231-5

Mizuno et al. *J Sleep Res* 2005; 14:43-47

Dopamine and RLS

- Dramatic response to dopaminergic agents
 - Levodopa and dopamine agonists
 - Low doses
- Exacerbated by centrally active dopamine receptor antagonists
- RLS common in Parkinson disease
 - Caveat: more frequent in PD with low ferritin

Medications That May Worsen RLS

- Antidepressants
 - Serotonin reuptake inhibitors
 - Norepinephrine reuptake inhibitors
 - Antihistamines
- Dopamine receptor antagonists
 - Antipsychotics
 - Anti-emetic/GI motility drugs
 - prochlorperazine, promethazine, metoclopramide
 - Dopamine depleters
 - Tetrabenazine, Reserpine

Treatment of RLS

- Non-Pharmacological
 - Correction of underlying medical condition
 - Iron supplementation (ferritin <75 mcg/L)
 - Assess for cause of iron deficiency
 - Treat with Ferrous sulfate 325mg QD or QOD + Vit C 100-200mg (or glass of OJ) to enhance absorption
 - IV iron supplementation if not responding or ferritin very low
 - Follow ferritin level to avoid iron overload
 - Remove medication triggering or enhancing RLS
 - External Pneumatic compression devices

Winkelman JW et al Practice guideline summary. Treatment of RLS in Adults: Report of the Guideline Development, Dissemination and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2016;87(24):2585.

Dopamine Agonist for RLS

DA Agonist	Initial daily dose	Minimal interval to assess effect before increasing dose	Usual effective daily dose range	FDA
Pramipexole (IR)	0.125 mg 2 to 3 hours before bedtime	2-3 days	0.25 to 0.5mg	Approved
Ropinirole (IR)	0.25 mg 1 to 3 hours before bedtime	2 to 3 days	2 to 4 mg	Approved
Rotigotine transdermal patch	1 mg per 24 hour patch	5 to 7 days	2 to 3 mg per 24 hour patch	Approved

Dopaminergic Agonists Adverse Effects

- Nausea, dizziness, somnolence, headache
- Orthostatic hypotension
- Rebound (occurs during the night)
- Augmentation
- Impulse control disorders



Augmentation Screening Questions

- Do RLS symptoms appear earlier than when the drug was first started?
- Are higher doses of drug now needed, or do you need to take the drug earlier in the day to control symptoms?
- Has the intensity of symptoms worsened since starting the drug?
- Have symptoms spread to other body parts (arms, torso) since starting the drug?

Treatment of Augmentation

- Check ferritin, review concomitant meds
- Split dose of Dopamine agonist (if early and mild symptoms)
- Switch to extended release Dopamine agonist or rotigotine patch (early symptoms)
- Reduce and discontinue dopamine agonist
- Add alpha 2-delta ligand
- If ineffective, consider opioid treatment
 - Methadone

Alpha-2 Delta Calcium Channel Ligands

	Initial daily dose	Minimal interval to assess effect before increasing dose	Usual effective daily dose range	FDA
Gabapentin(IR)	100-300mg 2 hours before bedtime	5-7 days	600-1800mg on 2 divided doses	Not approved
Gabapentin Enacarbil (ER)	0.25 mg 1 to 3 hours before bedtime	2 to 3 days	600mg -2400mg	Approved
Pregabalin (IR)	50-75mg 1-3hrs before bedtime	5 to 7 days	150-450mg	Not approved

Factor that impacts the choice of agent for RLS	Treatment choice
Time of day (daytime disturbance)	Long-acting agent (preferred) Twice a day dosing of a short-acting agent
Sleep disturbance disproportionate to other symptoms of RLS	Alpha-2-delta ligand
Comorbid insomnia	Alpha-2-delta ligand
Pregnancy risk	Avoid both dopaminergic agents and alpha-2-delta ligands Consider the use of iron
Impaired renal function	Avoid pramipexole Avoid or dose-adjust alpha-2-delta ligands
Increased risk for falls	Dopamine agonist
Painful restless legs	Alpha-2-delta ligand
Comorbid pain syndrome	Alpha-2-delta ligand
History of or current impulse control disorder	Alpha-2-delta ligand
History of or current alcohol or substance abuse	Avoid drugs that are hepatically metabolized (eg, ropinirole, rotigotine patch)
Severe symptoms of RLS	Dopamine agonist
Excess weight, metabolic syndrome, or obstructive sleep apnea	Dopamine agonist
Comorbid depression	Dopamine agonist
Comorbid generalized anxiety disorder	Alpha-2-delta ligand
Hepatic impairment	Avoid ropinirole Use caution with rotigotine patch

Garcia-Borreguero D, Kohnen R, Silber MH, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. *Sleep Med* 2013; 14:675.

Other Treatments for RLS

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

Management of Intermittent RLS (<2 times / year)

- Medications (as needed intermittently)
 - Carbidopa-Levodopa
 - Very effective
 - 50-600mg levodopa at bedtime
 - Short term side effects minimal
 - Nausea, vivid dreams
 - Chronic use associated with augmentation
 - Dopamine Agonists
 - Alpha-2 Delta Calcium Channel Ligands

Rare But Treatable

- QUESTION: A 10yr old previously healthy girl develops a stiff twisted foot with clumsy gait. Which of the following measures is the most important?
 - A. Check CSF cultures; Rx vancomycin and ceftriaxone
 - B. Check ASO (strep) titers; Rx pimozide
 - C. Check Huntington gene; Rx clonazepam
 - D. Check 24hr urine copper; Rx trial of L-dopa
 - E. Check Lyme titer

Answer

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 - B. Check ASO (strep) titers; Rx pimozide
 - C. Check Huntington gene; Rx clonazepam
 - D. Check 24hr urine copper; Rx trial of L-dopa
 - E. Check Lyme titer

Wilson's Disease

- Autosomal recessive defect in ATP7B, a copper transporter
- Copper builds up in brain, liver, cornea and other tissues
- Age of onset b/w 5-35 (mean age 13yrs) but variable
- Neurologic symptoms: dysarthria, gait change, tremor, dystonia, parkinsonism (suspect in any movement disorder!)
- Psychiatric disease and/or dementia common
- Liver disease
- **Prognosis good if diagnosed and treated early**
- Penicillamine, Trientine (Cu chelation). Low Cu diet. Zinc
- Liver transplant sometimes required
- Can be fatal if untreated!

Wilson's Disease Diagnostic Tests

- 24hour urine copper (high)
- Serum ceruloplasmin (low in 90% cases)
 - Not sensitive test
- Kayser-Fleischer ring (Cu deposits around iris)
- Brain MRI: signal abnormalities in basal ganglia, also thalamus, midbrain, other



Dopa-Responsive Dystonia

- A treatable genetic condition
- Child or young adult with twisted foot, gait abnormality (often labeled as cerebral palsy”) often worse in evening
- May present with juvenile parkinsonism
- Responds beautifully to low dose levodopa
- Prognosis excellent if treated

The END

