**Essential Tremor (ET) - Treatment Options**

**What are some general characteristics of “Essential Tremor”?**

- **Most common** adult tremor (in elderly); autosomal dominant inheritance; offspring may have 50% chance of getting
- Affecting about 500,000 Canadians; starting at any age (Mean age 45yr; bimodal: 20s & 60s); equally men & women
- **Slowly progressive**, tremors esp. amplitude worsens over time; no bradykinesia, rigidity or postural instability. However, in cases with longstanding or severe ET, resting tremor may be seen (but without the other parkinsonian features).
- Often benign but can cause **functional** (occupation, activities, writing, drinking & eating) & **social impairment**

**What causes essential tremor?**

- **Primary – Idiopathic/Essential**: most common (>60% will have a positive family history); ??environmental toxins
- **Rule out**: metabolic disturbances, drug (eg. benz) or alcohol withdrawal, drugs, hypoglycemia, hyperthyroidism & panic disorder
- **Diagnosis**: Enhanced physiological tremor, Dystonic, Task-specific, Parkinsonian, Holmes (rubral tremor re: Wilson’s disease (consider if >40yr without family history of tremor, esp. if dystonia, dysarthria & psychiatric features; liver abnormalities & Kayser-Fleischer corneal rings).
- **Drugs** which exacerbate physiologic tremor: amiodarone, amphetamines, antipsychotics, beta agonists eg. salbutamol, caffeine, calcitonin, cocaine, cyclosporin, dopamine, ephedrine, lead, Li+; nicotine, procainamide, SSRIs, steroids, theophylline, thyroid hormones, TCAs & valproate.

**What non-pharmacological therapies can be recommended?**

- Tremor is often the sole symptom but may be worsened by stress, fatigue, cold & social interaction. **Alcohol**, which may relieve the tremor, must be used appropriately. Adequate **REST** is important. Adding **wrists** to a limb may reduce amplitude of the tremor. **Relaxation** techniques such as meditation, yoga, hypnosis and biofeedback may help.

**When should drug treatment be considered for ET?**

- Consider “no drug treatment” or “treatment only for specific events” (e.g. party, special events) if not severe.
- If disabling only during periods of stress & anxiety consider "PRN" use of propranolol or benzodiazepines
- Consider regular drug therapy if ET **significantly impacts daily activity or psychologic distress.** Meds don't cure or slow progression

**What are the primary drug treatments options for treating ET?**

- Beta-blockers & anticonvulsants **alone or in combination** are the mainstays of therapy (>50% of the pts have symptomatic benefit). Dosages may have to be increased with time. Clonazepam, topiramate, gabapentin & botulinum toxin injections may be useful in select cases. Surgical intervention, if tremors are refractory to medical management, may be indicated.

表1: Drug Regimen Options in ET

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dose (po in ET)</th>
<th>$/month</th>
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<tr>
<td><strong>Beta-blockers</strong></td>
<td><strong>Propranolol</strong></td>
<td>10-20mg po bid initially</td>
<td>~$10</td>
<td>Cl: asthma, uncompensated heart failure, ↓ heart rate (&lt;50), ↓ BP (&lt;90mmHg). SE: wheezing, headache, dizziness, ↓ BP/Dx, ↓ amplitude not frequency of tremors (Also sotalol 60-160mg; non-selective &amp; antihistamnic)</td>
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<td><strong>Anticonvulsants</strong></td>
<td><strong>Primidone</strong></td>
<td>62.5mg hs (~63.5mg qd)</td>
<td>~$10</td>
<td>SE: Dizziness/vertigo, ataxia/unstable gait, drowsiness, headache, polyuria &amp; rash. <strong>Combination</strong> propranolol &amp; primidome occasionally useful.</td>
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<td><strong>Benzodiazepines</strong></td>
<td><strong>Clonazepam</strong></td>
<td>0.25-0.5mg tid</td>
<td>~$16</td>
<td>Limited benefit on tremor, but has hypnotic effect &amp; may help ↓ anxiety. SE: tolerance, falls, dependence, daytime sedation &amp; abuse / addiction potential</td>
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<td><strong>Botulinum Toxin A</strong></td>
<td><strong>Botulinum</strong></td>
<td>Head: 50-100units Max 400</td>
<td>~$4 per UNIT</td>
<td>SE: Hand tremor; muscle weakness &amp; paresthesia. SE: Voice tremor; breathlessness, hoarseness &amp; swallowing difficulties. Option: disabling head or voice tremor</td>
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**What are the primary drug treatments options for treating ET?**

- Beta-blockers & anticonvulsants **alone or in combination** are the mainstays of therapy (>50% of the pts have symptomatic benefit). Dosages may have to be increased with time. Clonazepam, topiramate, gabapentin & botulinum toxin injections may be useful in select cases. Surgical intervention, if tremors are refractory to medical management, may be indicated.

(Deep brain stimulation (DBS) to Vim nucleus of the thalamus has similar efficacy to thalamotomy of the Vim to improve contralateral limb tremor, but DBS has fewer serious SE.)

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**BP=blood pressure**   **CI=contraindication**   **ET=Essential Tremor**   **Li=lithium**   **Pts=patients**   **SE=side effects**

**Other Possible Options:** amantadine (100mg bid or 600mg tid); clonazepam (0.5-2mg daily); clobazam (2.5-50mg bid), lioresal (5-10mg hs or 20-40mg prn), methylphenidate (10-80mg daily), ritalin (10-80mg daily), topiramate (25-400mg daily); zoloft (50-200mg daily)

**NOT recommended:** acetazolamide, isoniazid, pindolol & triazolone.

**Drug treatment by ET type:** Limb Hand: propranolol, primidone, anticonvulsants, benzodiazepines; Head: propranolol, BTX; Voice: BTX

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**ET Websites:** www.essentialtremor.org

**Specific drug charts at www.RxFiles.ca**
Restless Legs Syndrome (RLS) - Treatment Options

What are the diagnostic criteria for "restless legs"? {Also known as: Ekbom's syndrome} 
- Distressing desire to move legs or other body parts; often accompanied by uncomfortable sensations (e.g. creeping) 
- Symptoms brought on by, or worsen with rest (sitting or lying down). Overall prevalence is ~10% in general population. 
- Urge and sensation is relieved with movement or reduced temporarily (e.g. walking, stretching) 
- Symptoms worsen in evening or at night (often worst between midnight-4am; thus causing major disruption of sleep) 
- Optional: involuntary limb movements while awake; periodic limb movements while sleep (as per patient or partner)

What causes restless legs?
- **Primary – Idiopathic:** most common (~ 50% will have a positive family history) 
- **Secondary, non-drug:** uremia, diabetes, peripheral neuropathy, iron deficiency serum ferritin, pregnancy, Mg++, K+, Ca++ 
- **Drug causes:** antihistamines, antinauseants, antipsychotics, dopamine antagonists, L-threonine, metoclopramide, SSRI's & TCAs, CCBs. Other: Discontinuation of opioids may precipitate RLS. Caffeine containing products.

What non-pharmacological therapies can be recommended? 
- **Avoiding** caffeine/chocolate, alcohol, smoking cessation; keeping a regular sleep routine, rubbing limbs, walking / exercise (combination resistance and aerobic), stretching; doing mentally alerting activities, warm or cool baths.
- **Pneumatic compression devices effective:** worn for 1hr upon symptom onset, inflated to 40cm H2O air pressure for 5 seconds during every minute

When should drug treatment be considered for restless legs? 
- **Consider** "no drug treatment" or "treatment only for specific events" (e.g. air travel, theatre) if not severe. 
- **Treat intermittently** for intermittent symptoms. Levodopa's fast onset makes it suitable for intermittent use. 
- **Consider regular** drug treatment if RLS significantly impacts daily activities or disturbs sleep.

What are the primary drug treatment options for treating RLS?
- Dopaminergic therapy is often the current drug treatment of choice. "Rebound" and "Augmentation" can arise with dopaminergic agents, especially levodopa (LD). Rare: ↑gambling behavior {Other drugs have also been studied; see Table 1.} 
- **Rebound:** worsening of symptoms when LD levels fall, usually during night or early day 
  - Management Options: 1) Repeat dose; 2) Add Levodopa CR to IR 
- **Augmentation:** appearance of more severe RLS symptoms earlier in day, before dose. 
  - Management Options: 1) If on LD, switch to dopamine agonist

Table 1: Drug Regimen Options in RLS

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug Name</th>
<th>Dose (po) in RLS*</th>
<th>$/month</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine Agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st line in moderate to severe RLS; Gradually ↑dose (2-3days) NNT=6; NNH=77 to DEC SE: nausea, dizziness, fatigue, somnolence ...</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levodopa (LD) 35</td>
<td><strong>Levodopa</strong>/benserazide</td>
<td>50/125 mg hs</td>
<td>$17</td>
<td>(≤400/100 mg); fast onset ~20min if asc; useful for intermittent pm treatment; Rebound &amp; Augmentation common if ≥200mg &amp; requires discontinuation</td>
</tr>
<tr>
<td>Levodopa (LD) 35</td>
<td><strong>Carbidopa/levodopa</strong></td>
<td>1/2, 100/25 mg tab hs (may give regular &amp; CR tabs together for rapid &amp; sustained effect)</td>
<td>$15</td>
<td>FDA approved; RCT evidence, Level A; 12wks Typical dose =2mg/kg/day; t½ =6hrs</td>
</tr>
<tr>
<td>LD/benserazide</td>
<td><strong>Prolopa</strong></td>
<td>15-30 mg hs</td>
<td>$12</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines 15</td>
<td><strong>Clonazepam</strong></td>
<td>0.25-1 mg hs</td>
<td>$15</td>
<td>Hypnogenic effect; limited benefit on sleep. Problems with tolerance, falls, dependence &amp; daytime sedation.</td>
</tr>
<tr>
<td>Antiepileptics 12</td>
<td><strong>Temazepam</strong></td>
<td>15-30 mg hs</td>
<td>$12</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Gabapentin</strong></td>
<td>600-2400 mg; trials: 1,800 mg/day</td>
<td>$10-16</td>
<td>Limited data, maybe effective; consider if pain; CNS effects (daytime sedation, etc.) Valproic acid may also be effective.</td>
</tr>
<tr>
<td>Opioids 27</td>
<td><strong>Oxycodone IR or oxyContin</strong></td>
<td>5-10 mg q12h</td>
<td>$60</td>
<td></td>
</tr>
<tr>
<td>Other opioids options; codeine 10-60mg/day; propoxyphene</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*Ac: before meals; CR: controlled release; HS: bedtime IR: immediate release; LD: Levodopa RLS: Restless Legs Syndrome SE: side effects t½: half-life Other options: bromocriptine (long- vs short-acting); dopa; gabapentin; pergolide; pramipexole; pergolide; bupropion *Dosing: HS effective for most, some may require daytime (e.g. afternoon) dose. If Depression may consider bupropion. 13

RLS Differential Diagnosis:
- Periodic limb movements of sleep (PLMS): often occurs in addition to RLS. Involves involuntary movements during sleep; brief awakenings or arousal from sleep (unaware).
- Nocturnal leg cramps: always involve a specific muscle; they usually require stretching of the muscle more than non-specific movement to relieve symptoms; usually unilateral
- Peripheral neuropathy: not usually associated with restlessness or helped by movement; does not worsen in evening or hs; sensations (numbness, tingling, or pain). May coexist with vessel disease (varicose veins, deep vein thrombosis); usually accompanied by swollen legs & a change in skin color
- Akathisia (often drug-induced): usually involves spontaneous movement of the whole body without sensory complaints; lacks a circadian pattern.
- Intermittent claudication: usually worsens with exercise & improves with rest.
- Rapid eye movement (REM) sleep behavior disorder: complex, often violent, motor behaviors associated with dreams (dream may not be recalled). Typically after age 60+
- Painful legs and moving toes: rare disorder not involving an urge to move limb

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**RX Files Q&A Summary**

Loren Regier BSP BA, Brent Jensen BSP

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**RLS Websites:**
Essential Tremor (ET) & Restless Legs Syndrome (RLS) - Treatment Options

Additional References:
Health Canada. Aug/07; Eli Lilly Canada advises Healthcare Professionals that they will cease sale of Permox August 30, 2007 due to risk of cardiac valvulopathy.
Pharmacists Letter’s: Mirapex (Pramipexole) for RLS Nov/O6.
Trenkwalder C, et al. Controlled withdrawal of two for short-term use) are effective in relieving the symptoms. Transdermal oestradiol is ineffective for PLMD.
Winkelman JW, Allen RP, Tenzer P, Hening W. Syndrome (RLS) is associated with prevalent coronary artery disease and cardiovascular disease. This association appears stronger in those with greater frequency or severity of RLS symptoms.
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References


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- Newsletters, Q&As, Trial Summaries, Charts; participation in continued professional learning (http://www.usask.ca/cme/)
- Contributions to Canadian and international evidence informed drug therapy discussions and academic detailing developments.