ROPINIROLE

THERAPEUTICS

Brands
• Requip, Adartrel

Generic?
Yes

Class
• Dopamine agonist, non-ergot

Commonly Prescribed for
(FDA approved in bold)
• Parkinson’s disease (PD)
• Restless legs syndrome (RLS)

How the Drug Works
• Dopamine agonist, with high affinity for the D2 receptor. This action is likely the main reason for effectiveness in PD. Also binds with high affinity to D3 receptors, but the importance of this is unclear. The mechanism of action for RLS is probably related to D2 receptor agonism

How Long Until It Works
• PD – weeks
• RLS – days to weeks

If It Works
• PD – may require dose adjustments over time or augmentation with other agents. Most PD patients will eventually require carbidopa-levodopa to manage their symptoms
• RLS – safe for long-term use with dose adjustments

If It Doesn’t Work
• PD – Bradykinesia, gait and tremor should improve. Non-motor symptoms including autonomic symptoms such as postural hypotension, depression, and bladder dysfunction do not improve. If the patient has significantly impaired functioning, add carbidopa-levodopa with or without ropinirole
• RLS – Rule out peripheral neuropathy, iron deficiency, thyroid disease. Change to another drug such as a benzodiazepine. Antiepileptic drugs (AEDs) such as gabapentin or carbamazepine may also be beneficial. In severe cases consider opioids

Best Augmenting Combos for Partial Response or Treatment-Resistance
• For suboptimal effectiveness add carbidopa-levodopa with or without a COMT inhibitor. MAO-B inhibitors may also be beneficial
• For younger patients with bothersome tremor: anticholinergics may help
• For severe motor fluctuations and/or dyskinesias with good “on” time, functional neurosurgery is an option
• Depression is common in PD and may respond to SSRIs
• Cognitive impairment/dementia is common in mid-late stage PD and may improve with acetylcholinesterase inhibitors
• For patients with late-stage PD experiencing hallucinations or delusions, withdraw ropinirole and consider oral atypical neuroleptics (quetiapine, olanzapine, clozapine). Acute psychosis is a medical emergency that may require hospitalization
• For RLS, can change to a different dopamine agonist or add another drug such as a benzodiazepine. AEDs such as gabapentin or carbamazepine may be beneficial. In severe cases consider opioids

Tests
• None required

ADVERSE EFFECTS (AEs)

How Drug Causes AEs
• Direct effect on dopamine receptors

Notable AEs
• Nausea/vomiting, dizziness, hallucination, constipation, somnolence, abdominal pain/discomfort, diaphoresis, anxiety, viral infection, pharyngitis, dyskinesias, and orthostatic hypotension

Life-Threatening or Dangerous AEs
• May cause somnolence or sudden-onset sleep, often without warning. Occurs more often than with ergot agonists or carbidopa-levodopa. Rare syncope or cardiac arrhythmias, most commonly bradycardia
ROPINIROLE (continued)

**Weight Gain**
- Unusual

**Sedation**
- Common

**What to Do About AEs**
- Nausea can be problematic when initiating drug – titrate slowly
- Hallucinations or delusions may require stopping the medication
- Warn patients about the risks of sleeping while driving

**Best Augmenting Agents for AEs**
- Amantadine may help suppress dyskinesias
- Orthostatic hypotension: adjust dose or stop antihypertensives, add supplemental salt, and consider fludrocortisone or midodrine
- Urinary incontinence: reducing PM fluids, voiding schedules, oxybutynin, desmopressin nasal spray, hyoscyamine sulfate, urological evaluation

**DOSING AND USE**

**Usual Dosage Range**
- PD – 3–24 mg daily, divided into 3 daily doses or once daily with XL formulation
- RLS – 4 mg or less 1–3 hours before bedtime

**Dosage Forms**
- Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg
- Extended-release tablets: 2 mg, 4 mg, 8 mg

**How to Dose**
- PD (Immediate release): Start at 0.25 mg 3 times daily. Each week increase each dose by 0.25 mg until reaching 1 mg 3 times daily at week 4. After week 4 increase each dose by 0.5 mg per week if needed until taking 9 mg/day, then by 1 mg each dose until taking a maximum of 24 mg/day in 3 divided doses to reach desired clinical effect
- PD (Extended release): Start at 2 mg/day for 1–2 weeks, then increase by 2 mg every week until symptomatic relief or maximum of 24 mg/day

- RLS: take 1–3 hours before bedtime. Start at 0.25 mg, and increase to 0.5 mg in 2–3 days. After 1 week increase to 1.0 mg and after that increase by 0.5 mg every week until at 4 mg at bedtime

**Dosing Tips**
- Slow titration will minimize nausea and dizziness

**Overdose**
- Symptoms include somnolence, agitation, orthostatic hypotension, abdominal pain, nausea, or dyskinesias. For cases of excessive CNS stimulation, neuroleptics can be effective

**Long-Term Use**
- Safe for long-term use. Effectiveness may decrease over time in PD (years) and RLS (months)

**Habit Forming**
- No

**How to Stop**
- Taper and discontinue over a period of 1 week. PD and RLS symptoms may worsen, but serious AEs from discontinuation are rare

**Pharmacokinetics**
- Extensive metabolism in liver by CYP 1A2 enzyme. 55% bioavailability. Half-life is 6 hours

**Drug Interactions**
- Increases the effect of levodopa
- Estrogen, especially ethinyl estradiol, can reduce clearance of drug
- CYP1A2 inhibitors (ciprofloxacin, cimetidine, diltiazem, erythromycin, mexiletine, fluvoxamine, tacrine) increase ropinirole concentration
- Dopamine antagonists such as phenothiazines, metoclopramide diminish effectiveness
- Use with caution in patients on antihypertensive medications due to risk of orthostatic hypotension
- Smoking induces CYP1A2 and increases drug clearance
Other Warnings/Precautions

- Dopamine agonists can precipitate impulse control disorders, such as pathological gambling

Do Not Use

- Hypersensitivity to the drug

SPECIAL POPULATIONS

Renal Impairment
- Dose does not seem to be affected but not studied in patients with severe disease

Hepatic Impairment
- Drug has hepatic metabolism but impairment does not appear to affect drug clearance. Use with caution

Cardiac Impairment
- Infrequently causes cardiac arrhythmias, rarely ventricular tachycardia. Use with caution

Elderly
- There is reduced drug clearance, but no dose adjustment needed as the dose used is the lowest that provides clinical improvement

Children and Adolescents
- Not studied in children (PD is rare in pediatrics)

Pregnancy
- Category C. Teratogenic in some animal studies. Use only if benefits of medication outweigh risks

Breast Feeding
- Inhibits prolactin secretion. Unknown if excreted in breast milk

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- PD: may delay need for carbidopa-levodopa and decreases risk of motor dyskinesias by 30%. This is especially important in younger PD patients. Available in 1/day dosing. Unlike ergot-based agonists, no known risk of fibrotic complications
- RLS: less risk of dependence compared to opioids or benzodiazepines and less augmentation than levodopa

Potential Disadvantages

- Less effective than carbidopa-levodopa for PD with more AEs such as hallucinations, somnolence and orthostatic hypotension. Patients with significant motor disability will require carbidopa-levodopa

Primary Target Symptoms

- PD – motor dysfunction including bradykinesia, hand function, gait and rest tremor
- RLS – pain, insomnia

Pearls

- Excellent drug for young patients with early PD. Favorable long-term AEs
- First-line treatment for RLS with less augmentation or “rebound” than carbidopa-levodopa
- AE profile differs from pramipexole. Less often associated with postural hypotension, dyskinesias and edema, but more likely to cause dizziness, syncope, nausea or respiratory problems
- For patients with mildly symptomatic disease, dopamine agonists are also appropriate for initial therapy, but for patients with significant disability, use carbidopa-levodopa early
ROPINIROLE (continued)

Suggested Reading


