Ropinirole was an effective treatment for restless leg syndrome (RLS), but the magnitude of the effect was uncertain.

**Clinical Problem:** A 50 year old female with primary restless legs syndrome wants to know what treatments are available.

**Clinical Question:** Is ropinirole an effective and safe treatment for restless legs syndrome (RLS)?

**Search Strategy:**
PubMed: search terms – “Restless Legs Syndrome” (MeSH), limits RCTs or meta-analyses. 45 RCTs were found, but no meta-analyses. SUMSearch, limited to interventions only, failed to turn up any additional RCTs. No relevant guidelines or DARE/Cochrane abstracts more recent than 1999 were found. Very few RCTs compared study drugs head-to-head; most compared study drug to placebo. Several drugs had been studied (e.g., ropinirole, pergolide, gabapentin, valproic acid.) The evidence for ropinirole is reviewed here, as the TREAT RLS 1 study is the largest trial to date.

**Clinical Bottom Lines:**

1. Patients taking ropinirole, at doses up to 4.0 mg/day, reported a 3.01 (95% CI 0.99 to 5.03) improvement on the International Restless Leg Scale (IRLS) vs the placebo group at 12 weeks. The clinical significance and magnitude of this improvement is not known.

2. The ropinirole group vs the placebo group reported an improvement (“much or very much improved”) on the clinical global impression scale. ARR 12% (95% CI 0 to 24%), NNT 8 (95% CI 4 – 222). Given the wide confidence intervals, our level of certainty is low.

**The Evidence:**
Trenkwalder et al. report the results of a prospective double-blind randomized placebo-controlled trial in which 284 patients with primary RLS (per IRLSSG criteria) were given either placebo or ropinirole over a twelve week period. The primary endpoint was the mean change in International Restless Leg Scale (IRLS) total score at twelve weeks from baseline. Secondary endpoints were the mean change in IRLS total score at one week, the change in Clinical Global Impression - Improvement Scale score from baseline at weeks one and twelve, and the change in Medical Outcome Study scale, RLS Quality of Life questionnaire, and activity scale.

**Data:**

<table>
<thead>
<tr>
<th></th>
<th>Mean IRLS at initial visit</th>
<th>Mean IRLS at 1 week</th>
<th>Mean IRLS at 12 weeks</th>
<th>Absolute Improvement at 1 week (Ropinirole)</th>
<th>Absolute Improvement at 12 weeks (Ropinirole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole</td>
<td>24.4</td>
<td>16.3</td>
<td>13.5</td>
<td>3.05 (95% CI 1.38 to 4.72)</td>
<td>3.01 (95% CI 0.99 to 5.03)</td>
</tr>
<tr>
<td>Placebo</td>
<td>25.2</td>
<td>20.1</td>
<td>17.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Global Impression (CGI-I) scale:** proportion of enrollees who changed from “much improved” to “very much improved” at twelve weeks:

<table>
<thead>
<tr>
<th>Improvement in CGI-I Scale</th>
<th>Ropinirole Group: n = 146</th>
<th>Placebo Group: n = 137</th>
<th>ARR (95%CI)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53.4% (78)</td>
<td>40.9% (56)</td>
<td>12.5 (0 to 24)</td>
<td>8 (4 – 222)</td>
</tr>
</tbody>
</table>

**Other endpoints:**

a. Medical Outcome Study (sleep subscale): significant benefit for ropinirole.

b. Medical Outcome Study (SF-36): no significant difference.

c. RLS Quality of Life questionnaire: significant benefit for ropinirole.
d. Work Productivity and Activity Impairment: no significant difference.

**Side Effects: Subjects reporting severe adverse side effects**

*95% CI cross zero – side effect risk is not greater in treatment vs placebo group*

<table>
<thead>
<tr>
<th></th>
<th>Ropinirole Group n = 146</th>
<th>Placebo Group n = 138</th>
<th>ARH (Harm) 95%CI</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Adverse Side Effects</td>
<td>23.3% (34)</td>
<td>15.2% (21)</td>
<td>8% (-1 to 17%)</td>
<td>13 (-94 to 6)</td>
</tr>
</tbody>
</table>

**Comments:**

1) It is unclear where patients were recruited from i.e. family physicians, sleep clinics, movement disorder clinics. Patients recruited from a movement disorder clinic might be expected to be more resistant to treatment than patients from a family physician’s office. This might alter the applicability of the results of the trial (selection bias).

2) Many of the patients recruited into the trial were on medication for their RLS prior to entering the study. The exact medications were not provided in the article and it is unclear whether these patients were equally distributed between treatment groups. These patients are not naïve to treatment and will be comparing the effect of the study medication to that of the medication they were previously taking.

3) Efficacy and the absence of augmentation have not been demonstrated beyond twelve weeks by this trial. Another trial would be required to confirm these effects in the long-term.

4) There is a strong placebo effect in the treatment of restless legs syndrome.

**References:**


**Key Words:** Restless legs syndrome, ropinirole, treatment.

**Appraiser:** Alex Fraser and the UWO Evidence Based Neurology Group

**Date Appraised:** November 2004.

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**Appendix**

The TREAT RLS 2 study was recently published after the creation of this CAT (*Movement Disorders* 2004, 19:1414-1423). The results are listed below:

**Clinical Global Impression (CGI-I) scale; proportion of enrollees who changed from “much improved” to “very much improved” at twelve weeks:**

<table>
<thead>
<tr>
<th></th>
<th>Ropinirole Group: n = 131</th>
<th>Placebo Group: n = 136</th>
<th>ARR (95%CI) 95%CI</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in CGI-I Scale</td>
<td>59.5% (78)</td>
<td>39.6% (53)</td>
<td>20% (8 - 32)</td>
<td>5 (3 - 12)</td>
</tr>
</tbody>
</table>