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Treatment of Restless Leg Syndrome with Pergolide

Earley CJ, Yaffee JB, Allen RP. Randomized double-blind placebo-controlled trial of pergolide in restless leg syndrome. Neurology 1998; 51:1599-602.

Clinical question **Is pergolide effective in the treatment of restless leg syndrome?**

Background Restless leg syndrome (RLS) affects between 2% and 15% of the population. Disturbances in the dopaminergic system are thought to play a role in the etiology of RLS. Levodopa, which demonstrated significant benefit in small randomized controlled trials, can cause a paradoxical worsening of symptoms (levodopa augmentation). Other agents that augment dopaminergic action (pramipexole, ropinirole, bromocriptine, and pergolide), as well as the anticonvulsant gabapentin, are currently being investigated for the treatment of RLS.

Population studied Patients presenting to a sleep center who met standard criteria for the disease and who had a minimum of 15 periodic limb movements of sleep per hour (PLMSs/hr) were considered for enrollment. The first 16 consecutive patients presenting to the center who met these inclusion criteria and who had not previously been treated with pergolide were enrolled. Seven of those 16 had not previously been treated for RLS, 5 were being treated with levodopa/carbidopa, 2 with propoxyphene, and 1 each with clonazepam and alprazolam.

Study design and validity Patients stopped their previous treatment regimens for RLS 4 days before the baseline assessment. They were then randomized in a double-blind fashion to pergolide or placebo. During the first 14 days, patients in each group were instructed to increase the dose taken at dinner and at bedtime until (1) the patient felt the benefits from the medication were adequate; (2) the maximum dose had been reached (0.65 mg per day); or (3) adverse effects occurred. After day 14, the dose remained constant for 5 days. The final pergolide dose could be from 0.05 mg twice daily to 0.3 mg at dinner and 0.35 mg at bedtime. All-night polysomnograms and a log of RLS symptom duration were obtained at baseline and on day 17 or 18.

Outcomes measured The primary outcome was the global improvement score (0% to 100% improvement) on day 18. Secondary outcomes included the number of PLMSs per hour and the number of hours per day with RLS symptoms.

Results Baseline characteristics (PLMSs per hour, sleep efficacy, age, and symptom duration) were not statistically different between groups. The median final daily dose of pergolide in the treatment group was 0.35 mg (7 capsules). Global improvement scores were 61% improved in the pergolide group compared with 19% in the placebo group (P = .009). The placebo group showed no statistically significant change from baseline for any of the secondary outcome variables. For patients treated with pergolide, however, the PLMSs decreased from 48.9 per hour to 14.5 per hour (P <.001) and the duration of RLS symptoms decreased from 7.0 hours per day to 1.8 hours per day (P = .036). Mild adverse events were common in both groups (unfortunately, "mild" was not defined by the authors). Adverse events rated as "severe" occurred in 4 patients in the pergolide group (stomach pain, increased dreaming, and constipation) compared with 2 in the placebo group (bad taste in the mouth and itchy eyes). RLS rebound or augmentation was not seen in either group. None of the patients discontinued treatment or had to decrease the dose of medication because of adverse events.

Recommendations for clinical practice **This study demonstrates the efficacy of pergolide in the treatment of RLS. Unfortunately, the number of patients studied was small and the follow-up period was short. It is still unknown whether treatment of RLS with pergolide will result in the same augmentation of RLS symptoms seen with levodopa/carbidopa. Given the difficulty of treating RLS, the known adverse effects of augmentation seen with levodopa/carbidopa, and the significant improvements in both objective and subjective measures seen in this clinical trial, long-term trials comparing the efficacy of pergolide with other agents that augment dopamine are needed.**

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Initiating Warfarin Therapy

Crowther MA, Ginsberg JB, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. Arch Intern Med 1999; 159:46-8.