Rapid Relief from RLS Symptoms with Pramipexole: Results of a Large Polysomnographic Study

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Background

The restless legs syndrome (RLS) is one of the most frequent neurological diseases and affects 10%-15% of the US-population [1]. It is characterized by a desire to move the limbs associated with paresthesia and dysesthesia that is exacerbated by rest and relieved by activity. Motor restlessness and nocturnal worsening of symptoms are diagnostic of RLS [2]. More than 80% of RLS patients suffer from periodic leg movements (PLM) during time in bed which often result in significant disturbance of sleep [3].

Objective

To determine the optimal dose of pramipexole in patients with idiopathic restless legs syndrome (RLS) by polysomnography and evaluation of clinical improvement.

Methods

- Double-blind, placebo-controlled, single-centre, comprehensive polysomnographic study.
- Treatments:
  - Pramipexole 0.125 mg/day, 0.25 mg/day, 0.5 mg/day, 0.75 mg/day.
  - Placebo

  All pramipexole groups were started on 0.125 mg/day. For the higher dose groups, the dose was increased stepwise. The final dose was reached on day 5 (0.25 mg), day 9 (0.5 mg), and day 13 (0.75mg).
- Efficacy endpoints:
  - Primary endpoint: Reduction in the periodic limb movement index during time in bed (PLMI).
  - Secondary endpoints: Change in RLS symptom rating scale (RLSRS), and the clinical global impression scale for improvement (CGI-I).

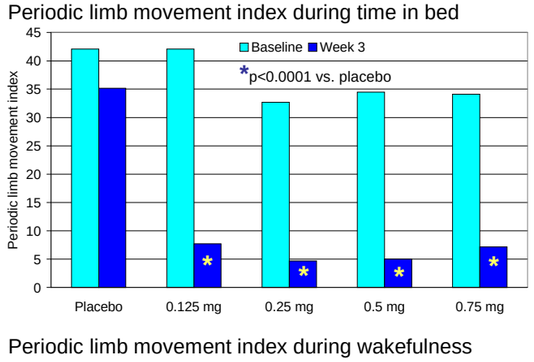
  Statistical methods: ANCOVA for PLMI on log-transformed data to account for non-normality with reporting of re-transformed means and Fisher's exact test.
- Safety assessments: physical examination, ECG, clinical laboratory tests, monitoring of adverse events.

Demographics and baseline characteristics

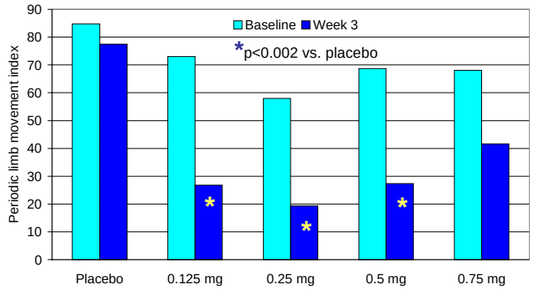
	Placebo N=22	0.125 mg/day N=21	0.25 mg/day N=22	0.5 mg/day N=22	0.75 mg/day N=22
Age, years (mean, SD)	53.3 (±11.1)	60.0 (±10.1)	54.8 (±10.9)	58.4 (±9.5)	54.5 (±12.2)
Female (%)	81.0%	71.4%	72.7%	81.8%	61.9%
BMI, kg/m^2 (mean, SD)	26.4 (±3.4)	25.5 (±3.2)	24.3 (±2.6)	25.6 (±3.4)	26.6 (±3.2)
Duration of RLS, years (mean, SD)	2.7 (±10.1)	5.1 (±11.1)	6.1 (±10.6)	5.3 (±10.6)	4.5 (±10.3)

Results

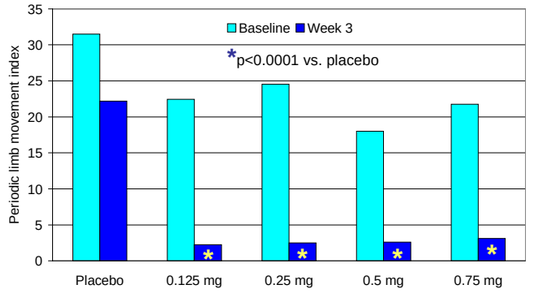
Periodic limb movement index during time in bed



Periodic limb movement index during wakefulness

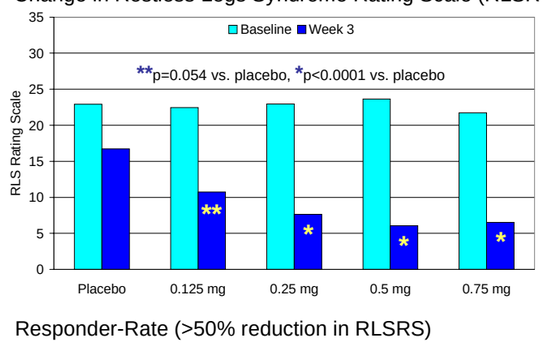


Periodic limb movement index during sleep

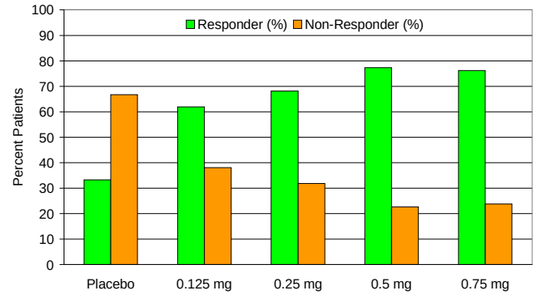


Results

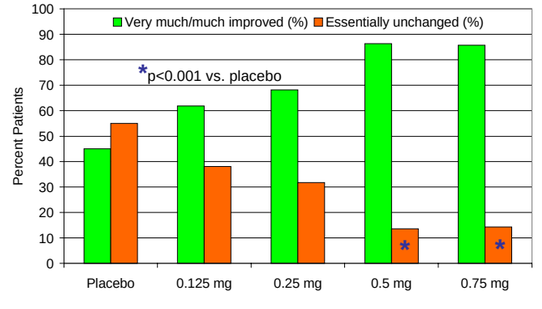
Change in Restless Legs Syndrome Rating Scale (RLSRS)



Responder-Rate (>50% reduction in RLSRS)



Clinical Global Impression of Improvement at Week 3



Safety

Incidences of the most frequent adverse events *

	Placebo N=22	0.125 mg/day N=21	0.25 mg/day N=22	0.5 mg/day N=22	0.75 mg/day N=22
Total with any adverse event (%)	72.7%	81.0%	77.3%	81.8%	59.1%
Headache	36.8%	4.8%	18.2%	31.8%	22.7%
Fatigue	22.7%	23.8%	13.6%	27.3%	9.1%
Nausea	4.5%	19.0%	13.6%	4.5%	22.7%
Nasopharyngitis	0%	4.8%	9.1%	9.1%	4.5%
Influenza	0%	0%	9.1%	0%	9.1%

* occurring in more than 5% of all patients

Summary and Conclusion

Pramipexole showed excellent efficacy over the range of 0.125 mg/day to 0.75 mg/day within 3 weeks of therapy. A statistically significant difference of pramipexole versus placebo was observed in the reduction of periodic limb movements during time in bed, p<0.0001. As reflected in the high responder rates (>50% reduction of RLSRS) and in the clinical global impression of improvement, the severity of the restless legs symptoms was significantly reduced by pramipexole treatment. Clinical efficacy was most prominent in the 0.5 mg/day and 0.75 mg/day dose groups. Safety and tolerability were favorable in all dose groups. No serious adverse events occurred during the study.
This thorough polysomnographic study with a fixed dose regimen confirms the findings of Montplaisir 1999[4].

References

1 Silber MH, Girish H, Izurieta R. Pramipexole in the management of restless legs syndrome: an extended study. Mayo Clin Proc. 1997; 72(3): 261-4

2 Walters AS for the International Restless Legs Syndrome Study Group. Toward a better definition of restless legs syndrome: Mov Disord 1995;10: 634-12

3 Trenkwalder C, Walters AS, Hening W. Periodic limb movments and restless legs syndrome. Neurol Clin 1996; 14(3): 629-50

4 Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. Neurology 1999; 52(5): 938-43

Acknowledgement

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