



A good sleep would be dop(aminergic) doc! Pramipexole in restless legs syndrome

Clinical Question: Is pramipexole effective for the treatment of restless legs syndrome (RLS)?

Bottom Line: Systematic review of twelve randomized controlled trials demonstrates 63% of patients using pramipexole report feeling much or very much better compared to 41% on placebo over 3-26 weeks. Lower doses (example 0.25/0.5mg) may have equivalent efficacy to higher doses with less risk of augmentation (paradoxical worsening of symptoms with treatment), although up to ~40% of patients may experience augmentation after 1 year.

Evidence:

- Systematic review 12 randomized, controlled trials (RCTs), 3286 patients, average age 49-58 years, pramipexole 0.125 - 1.5mg/d versus placebo for 3 - 26 weeks.¹
 - Pramipexole significantly increased proportion of patients reporting:
 - Improved symptoms ("very much better" or "much better"):
 - 63% versus 41%; number needed to treat (NNT)=5.
 - ≥50% reduction in International Restless Leg Score (IRLS):
 - 62% versus 38%, NNT=5.
- Five RCTs report pramipexole dosing comparisons.
 - Multiple outcomes assessed.²⁻⁶
 - Patient Global Impression Improvement ("much or very much better") at 3-6 weeks with:^{2,4}
 - 0.25mg: 73%,
 - 0.5mg: 77-79%,
 - 0.75mg: 57%-68%.
- Adverse events:
 - Meta-analyzed by PEER, statistically significant increase versus placebo at 3-26 weeks for:
 - Nausea: 8 RCTs, 2050 patients:^{2,7-13}
 - Pramipexole 14% versus placebo 5%, number needed to harm (NNH)=13.
 - Fatigue: 6 RCTs, 1596 patients:^{2,7,8,10,11,13}
 - Pramipexole 10% versus placebo 6%, NNH=23.
 - No statistically significant increase in dizziness, somnolence or headache compared to placebo.

Context:

- Non-pharmacologic treatment options should be tried first. Limited evidence supports options such as exercise, standard acupuncture, and compression devices.¹⁴
- If ferritin <50-75ug/L, iron supplementation may be beneficial.^{15,16}
- Other dopaminergic drugs (example ropirinole) have demonstrated similar efficacy.¹⁵
- Augmentation may be difficult to identify (example a patient stable for 6 months asks for more medication).¹⁶ Risk increases with higher doses of pramipexole¹⁶ and duration of treatment:¹⁶⁻¹⁸
 - <1 year: up to 8%,
 - ≥1 year: up to 42%.
- Management of augmentation includes: Modified dosing (example split or earlier dose), alternate pharmacotherapies (example pregabalin or gabapentin), and minimizing exacerbating drugs (examples antihistamines, dopamine-receptor blockers, or serotonergic antidepressants).^{3,16}

Authors:

Rodger Craig MPH, Michael Wollin BSc, Christina Korownyk MD CCFP

Disclosures:

Authors do not have any conflicts of interest to declare.

References:

1. Liu GJ, Wu L, Lin Wang S, *et al.* Clin Ther. 2016; 38(1):162-179.e6.
2. Partinen M, Hirvonen K, Jama L, *et al.* Sleep Med. 2006; 7(5):407-417.
3. Allen RP, Chen C, Garcia-Borreguero D, *et al.* N Engl J Med. 2014; 370(7):621-631.
4. Inoue Y, Kuroda K, Hirata K, *et al.* Neuropsychobiology. 2011; 63(1):35-42
5. Winkelmann JW, Sethi KD, Kushida CA, *et al.* Neurology. 2006; 67(6):1034-1039.
6. Jama L, Hirvonen K, Partinen M, *et al.* Sleep Med. 2009; 10(6):630-636.
7. Ferini-Strambi L, Aarskog D, Partinen M, *et al.* Sleep Med. 2008; 9:874-881.
8. Hogl B, Garcia-Borreguero D, Trenkwalder C, *et al.* Sleep Med. 2011; 12:351-360.
9. Ma JF, Wan Q, Hu XY, *et al.* Sleep Med. 2012; 13:58-63.
10. Montagna P, Hornyak M, Ulfberg J, *et al.* Sleep Med. 2011; 12:34-40.
11. Inoue Y, Hirata K, Kuroda K, *et al.* Sleep Med. 2010; 11:11-16
12. Garcia-Borreguero D, Patrick J, DuBrava S, *et al.* Sleep. 2014; 37:635-643.
13. Oertel WH, Stiasny-Kolster K, Bergtholdt B, *et al.* Mov Disord. 2007; 22:213-219.
14. Harrison EG, Keating JL, Morgan PE. Disabil Rehabil. 2019; 41(17):2006-2014.
15. Winkelmann J, Allen RP, Högl B, *et al.* Mov Disord. 2018; 33(7):1077-1091.
16. Garcia-Borreguero D, Silber MH, Winkelmann JW *et al.* Sleep Med. 2016; 21:1-11.
17. Lipford MC, Silber MH. Sleep Med. 2012; 13(10):1280-5.
18. Allen RP, Ondo WG, Ball E, Calloway, *et al.* Sleep Med. 2011; 12(5):431-9.