Dopaminergic Agents in Treating Restless Legs Syndrome

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Summary and Conclusions

SBU's appraisal of the evidence

Restless legs syndrome (RLS) is a neurological disorder associated with uncomfortable and occasionally painful creeping sensations in the legs and/or arms. Restless legs syndrome can be categorized as primary or secondary, depending on the onset mechanism. Dopaminergic agents, which include dopamine agonists[1] and levodopa, are used to ameliorate the symptoms of RLS.

- In people with moderate to severe primary RLS, treatment with dopamine agonists relieves symptoms and improves quality of life in the short term. However, side effects can lead to terminating treatment in some cases. The benefits and risks of treatment in the longer term are not established.
- Some evidence suggests that levodopa treatment can reduce periodic limb movements (PLM) during sleep and improve sleep and quality of life in patients, but the scientific evidence is insufficient to draw conclusions on the risks for side effects of levodopa.
- The scientific evidence is insufficient to draw conclusions on the cost-effectiveness of dopaminergic agents.

1 *The conclusions on dopamine agonists apply to the drugs pramipexole, ropinirole, and rotigotine.*

Technology and target group

The most common symptom in RLS is creeping sensations (paresthesias) affecting the lower legs. The symptoms usually appear during rest, in the evening, and at night, causing a strong urge to move the affected part of the body to relieve the symptoms.

A genetic association is suspected in primary RLS, and several genes with a probable association to RLS have been identified. The secondary form of the disorder is probably caused by another underlying disease, or a deficiency in certain vitamins or minerals.

The prevalence of RLS, including all forms of the disorder, is estimated at 5% to 10% of the adult population in Europe and North America. An estimated one fourth of people with RLS have symptoms severe enough to require medication. This corresponds to approximately 200 000 individuals in Sweden. Twice as many women as men are affected, and the disorder is more common in older people than in younger people.

The causes of RLS remain largely unknown. Research suggests that the condition could be partly attributed to the malfunction of certain dopamine-releasing parts of the central nervous system, which could possibly disrupt movement functions in the body, thereby causing the symptoms. The dopaminergic activity can be amplified with dopamine-receptor-activating drugs (dopamine agonists) or levodopa.

Depending on their chemical structure, dopamine agonists can be divided into two different pharmacological groups: ergot-derived and nonergot-derived. Three nonergot dopamine agonists – pramipexole, ropinirole, and rotigotine – are currently approved in Sweden for treating RLS. Treatment involving dopamine agonists aims to ameliorate disease symptoms and is used mainly for patients with moderate to severe primary RLS. Levodopa is also used for milder discomfort and in secondary RLS. Levodopa, however, is not registered in Sweden as a treatment for RLS.

Primary questions

- Does treatment with dopaminergic agents relieve patient-assessed symptoms of RLS?
- Does treatment with dopaminergic agents improve sleep, reduce daytime tiredness, and/or improve quality of life in people with RLS?
- What side effects are associated with treatment?
- What does treatment with dopaminergic agents cost? Is it cost-effective?

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Patient benefit

Dopamine agonists

- ❑ Dopamine agonists relieve symptoms[2] in patients with moderate to severe primary RLS (Evidence Grade 1)*. The effect is moderate in comparison to placebo, and most studies have not followed patients for more than 3 months. Treatment with dopamine agonists also results in increased sleep time and improved sleep quality and leads to improving quality of life (Evidence Grade 2)*. Dopamine agonists, however, have side effects that have caused some patients to terminate their participation in studies prematurely. Evidence concerning the longer-term side effects of RLS is limited.

SBU bases its assessment on 10 randomized controlled trials (RCTs) involving the use of dopamine agonists to treat moderate to severe primary RLS. Of these RCTs, 3 involved pramipexole, 4 involved ropinirole, 2 involved rotigotine, and 1 involved cabergoline. The first three drugs are nonergot dopamine agonists, while the fourth is ergot-derived. In total, the studies included nearly 4000 patients.

A meta-analysis shows that average symptom relief was just over 50% after treatment with nonergot dopamine agonists and 35% after placebo treatment. The studies also show that treatment with these drugs improves sleep and quality of life and reduces daytime tiredness.

Overall, the rate of side effects in the studies averaged 75% in the treatment groups and 63% in the placebo groups. The side effects were usually mild to moderate, but severe side effects were also reported. Patients who received active treatment had a greater tendency to terminate a study prematurely due to adverse effects (on average 12% in the treatment groups and 7% in the placebo groups).

Observation times in the studies are relatively short, and few studies report more than 3 months of follow up. Hence, knowledge is limited regarding the drugs' longer-term effects on RLS and the risk for delayed side effects. Due to the risks for cardiac-related side effects, particular caution should be exercised in using ergot agonists.

The findings suggest that the three dopamine agonists, ie, pramipexole, ropinirole, and rotigotine, have similar effects in terms of symptom relief and side effects. However, studies that compare these drugs with each other are lacking.

Levodopa

- ❑ Compared to placebo, treatment with levodopa reduces periodic limb movements during sleep in patients with primary or secondary RLS (Evidence Grade 3)*. Treatment with levodopa also has positive effects on patients' sleep and quality of life (Evidence Grade 3)*. Scientific evidence is insufficient* to draw conclusions on the side effects of levodopa.

Four randomized, placebo-controlled trials of levodopa treatment have been included in the assessment. All of these studies appeared in older publications (1988–1999) and mainly assessed the surrogate endpoint of periodic limb movements (PLM) during sleep. In addition to patients with primary RLS, the studies also included patients with secondary forms of the disorder.

The results suggest that the number of PLM per hour decreases with levodopa treatment compared to placebo. However, the relevance of the effects is difficult to judge since baseline values were reported in only one of the studies. Further, the results suggest that levodopa treatment has positive effects on patients' sleep and quality of life. The scientific evidence is insufficient to assess the effects of levodopa treatment on patient-assessed sensory symptoms (creeping sensations).

Further studies are essential to establish the effectiveness, and the side effects, of levodopa in treating RLS.

Ethical aspects

Knowledge is limited about potential, delayed side effects of dopaminergic agents in treating RLS. Few treatment options are currently available for patients with more severe RLS, and dopaminergic agents usually comprise first-line treatment. However, there is a risk of widening treatment indications (ie, prescribing dopamine agonists to patients with milder symptoms, where the disorder is not associated with long-term complications or increasing morbidity). From an ethical standpoint it is important that patients who have the greatest need for pharmacotherapy have access to this treatment.

Economic aspects

- ❑ Scientific evidence is insufficient* to draw conclusions on the cost-effectiveness of dopaminergic agents.

The cost of regular treatment with dopamine agonists can be estimated at 3000 to 4000 Swedish kronor (SEK) per patient and year. Calculated per patient responding to treatment, the cost is substantially higher and is estimated at SEK 25 000 to SEK 40 000, depending on how response is defined. The cost of treatment with levodopa can be estimated at SEK 500 to SEK 1500 per patient and year, depending on the dose and regularity of treatment. This estimate, however, does not account for those who respond to treatment.

2 *Assessed according to the IRLS rating scale.*

*** Criteria for Evidence Grading SBU's Conclusions**

Evidence Grade 1 – Strong Scientific Evidence. The conclusion is corroborated by at least two independent studies with high quality, or a good systematic overview.
Evidence Grade 2 – Moderately Strong Scientific Evidence. The conclusion is corroborated by one study with high quality, and at least two studies with medium quality.
Evidence Grade 3 – Limited Scientific Evidence. The conclusion is corroborated by at least two studies with medium quality.
Insufficient Scientific Evidence – No conclusions can be drawn when there are not any studies that meet the criteria for quality.
Contradictory Scientific Evidence – No conclusions can be drawn when there are studies with the same quality whose findings contradict each other.

References

1. Ekbom K, Leissner L, Olsson JE, Widner H. Restless legs – vanligt sjukdomstillstånd som ofta missas. Möjligheter till framgångsrik behandling finns idag. Läkartidningen 2006;103(4):207-11.
2. Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. Mov Disord 2008;23(16):2267-302.
3. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, Trenkwalder C; International Restless Legs Syndrome Study Group. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4(2):121-32.
4. Hays RD, Stewart AL. Sleep measures. In: Stewart AL, Ware JE, editors. Measuring functioning and well-being: The Medical outcomes study approach. Durham, NC: Duke University Press; 1992. p 235-59.
5. Abetz L, Vallow SM, Kirsch J, Allen RP, Washburn T, Earley CJ. Validation of the Restless Legs Syndrome Quality of Life questionnaire. Value Health 2005;8(2):157-67.
6. Kohnen R, Benes H, Heinrich CR, Kurella B. Development of the disease-specific Restless Legs Syndrome Quality of Life (RLS QoL) questionnaire. Mov Disord 2002;17(Suppl 5):743.
7. Läkemedelsverket. Läkemedelsbehandling av restless legs syndrom – RLS – Ny rekommendation. Information från Läkemedelsverket nr 3, 2009.
8. Trenkwalder C, Stiasny K, Pollmächer T, Wetter T, Schwarz J, Kohnen R et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. Sleep 1995;18(8):681-8.
9. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165(11):1286-92.
10. Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Med 2004;5(3):237-46.
11. Bogan RK, Fry JM, Schmidt MH, Carson SW, Ritchie SY. Ropinirole in the treatment of patients with restless legs syndrome: a US-based randomized, double-blind, placebo-controlled clinical trial. Mayo Clin Proc 2006;81(1):17-27.
12. Ferini-Strambi L, Aarskog D, Partinen M, Chaudhuri KR, Sohr M, Verri D et al. Effect of pramipexole on RLS symptoms and sleep: a randomized, double-blind, placebo-controlled trial. Sleep Med 2008;9(8):874-81.
13. Kushida CA, Geyer J, Tolson JM, Asgharian A. Patient- and physician-rated measures demonstrate the effectiveness of ropinirole in the treatment of restless legs syndrome. Clin Neuropharmacol 2008;31(5):281-6.
14. Oertel WH, Benes H, Garcia-Borreguero D, Geisler P, Högl B, Saletu B et al. Efficacy of rotigotine transdermal system in severe restless legs syndrome: a randomized, double-blind, placebo-controlled, six-week dose-finding trial in Europe. Sleep Med 2008;9(3):228-39.
15. Oertel WH, Stiasny-Kolster K, Bergtholdt B, Hallström Y, Albo J, Leissner L et al. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). Mov Disord 2007;22(2):213-9.
16. Trenkwalder C, Benes H, Grote L, Happe S, Högl B, Mathis J et al. Cabergoline compared to levodopa in the treatment of patients with severe restless legs syndrome: results from a multi-center, randomized, active controlled trial. Mov Disord 2007;22(5):696-703.
17. Trenkwalder C, Benes H, Poewe W, Oertel WH, Garcia-Borreguero D, de Weerd AW et al. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2008;7(7):595-604.
18. Trenkwalder C, Garcia-Borreguero D, Montagna P, Lainey E, de Weerd AW, Tidswell P et al. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. J Neurol Neurosurg Psychiatry 2004;75(1):92-7.
19. Walters AS, Ondo WG, Dreykluft T, Grunstein R, Lee D, Sethi K. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. Mov Disord 2004;19(12):1414-23.
20. Winkelman JW, Sethi KD, Kushida CA, Becker PM, Koester J, Cappola JJ et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology 2006;67(6):1034-9.
21. Oertel WH, Benes H, Garcia-Borreguero D, Geisler P, Högl B, Trenkwalder C et al. One year open-label safety and efficacy trial with rotigotine transdermal patch in moderate to severe idiopathic restless legs syndrome. Sleep Med 2008;9(8):865-73.
22. Baker WL, White CM, Coleman CI. Effect of nonergot dopamine agonists on symptoms of restless legs syndrome. Ann Fam Med 2008;6(3):253-62.
23. Hansen RA, Song L, Moore CG, Gilsenan AW, Kim MM, Calloway MO et al. Effect of ropinirole on sleep outcomes in patients with restless legs syndrome: meta-analysis of pooled individual patient data from randomized controlled trials. Pharmacotherapy 2009;29(3):255-62.
24. Antonini A, Poewe W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. Lancet Neurol 2007; 6(9):826-9.
25. Simonis G, Fuhrmann JT, Strasser RH. Meta-analysis of heart valve abnormalities in Parkinson's disease patients treated with dopamine agonists. Mov Disord 2007;22(13):1936-42.
26. Läkemedelsverket. Läkemedelsbehandling vid Parkinsons sjukdom – Behandlingsrekommendation. Information från Läkemedelsverket nr 2, 2008.
27. Fulda S, Wetter TC. Where dopamine meets opioids: a meta-analysis of the placebo effect in restless legs syndrome treatment studies. Brain 2008;131(Pt 4):902-17.
28. Benes H, Kurella B, Kummer J, Kazenwadel J, Selzer R, Kohnen R. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. Sleep 1999;22(8):1073-81.
29. Brodeur C, Montplaisir J, Godbout R, Marinier R. Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind, controlled study. Neurology 1988;38(12):1845-8.
30. Walker SL, Fine A, Kryger MH. L-DOPA/carbidopa for nocturnal movement disorders in uremia. Sleep 1996;19(3):214-8.
31. Lees M, Roberts G, Tabberer M, DasGupta R, Finnern HW. Cost-effectiveness of licensed treatment options for restless legs syndrome in the UK and Sweden. Curr Med Res Opin 2008;24(10):2919-30.

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The complete report is available in Swedish.