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Q / What drugs are effective for periodic limb movement disorder?

EVIDENCE-BASED ANSWER

A / CLONAZEPAM improves subjective sleep quality and polysomnogram (PSG) measures of leg movements more than placebo (strength of recommendation [SOR]: **B**, a small randomized controlled trial [RCT]); temazepam produces similar results (SOR: **C**, extrapolated from a small comparison trial).

Melatonin and L-dopa consistently improve certain PSG measures, but their

effect on subjective sleep quality varies; valproate improves only subjective measures; apomorphine injections reduce limb movements but not awakenings (SOR: **C**, very small crossover and cohort trials).

Estrogen replacement therapy is ineffective for periodic limb movement disorder (PLMD) associated with menopause (SOR: **B**, RCT).

Evidence summary

Although PLMD often occurs in association with restless legs syndrome, sleep apnea, narcolepsy, and other sleep disorders, it is itself an intrinsic sleep disorder characterized by stereotyped limb movements and sleep disruption.¹ Most treatment studies of PLMD report both subjective and objective measures of sleep quality. Two commonly used objective measures, obtained by PSG, are the periodic leg movement (PLM) index and the PLM arousal index. The **TABLE** summarizes the evidence of medication trials.

Clonazepam improves subjective sleep measures, leg movements

Three comparative trials evaluated clonazepam against placebo, temazepam, and cognitive behavioral therapy (CBT).¹⁻³ In the placebo-controlled and temazepam trials, clonazepam significantly improved subjective sleep parameters and leg movements.^{1,2} However, the studies produced conflicting results as to whether clonazepam reduced awakening from limb movements. Both te-

mazepam and clonazepam appeared to be comparably effective; the trial was underpowered to detect a difference between them.

The CBT trial didn't describe the frequency or duration of CBT clearly.³ It isn't included in the **TABLE**.

L-Dopa decreases leg motions, effects on subjective sleep symptoms vary

Two comparison trials evaluated L-dopa (combined with carbidopa). One trial compared L-dopa with propoxyphene and placebo, and the other compared it with pergolide, a bromocriptine agonist available in Canada and Europe.^{4,5}

In both trials, L-dopa consistently reduced leg motions at night but produced a variable response in subjective sleep symptoms and nocturnal waking. Propoxyphene yielded modest improvements in subjective sleep symptoms and nocturnal waking over placebo. The L-dopa-propoxyphene comparison trial was underpowered to allow a statistical comparison between the 2 medications.

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TABLE

How well do these medications work for periodic limb movement disorder?

Study design, duration (N)	Medication (daily dose)	Improvement in subjective sleep quality vs baseline, except where indicated (P value)	Improvement in leg movements: PLM index* vs baseline, except where indicated (P value)	Improvement in waking from leg movements: PLM-arousal index† vs baseline, except where indicated (P value)
Crossover, placebo-controlled, 3 days (26) ¹	Clonazepam (1 mg PO)	Subject sleep score (Self-Assessment of Sleep and Awakening Quality Scale), 25% vs placebo (<.05)	26% vs placebo (<.05)	28% vs placebo (NS)
Double-blind crossover, placebo-controlled, 30 days (10) ²	Clonazepam (1 mg PO)	Sleep maintenance: 37% (.025)	34% (.025)	44% (.005)
	Temazepam (30 mg PO)	Sleep maintenance: 67% (.005)	26% (.05)	42% (.013)
Double-blind, crossover, placebo-controlled, 42 days (6) ⁴	L-Dopa (100-200 mg PO)	Improved sleep vs placebo: 6/6 patients	87% vs placebo (<.01)	89% vs placebo (<.01)
	Propoxyphene (100-200 mg PO)	Improved sleep vs placebo: 3/6 patients	35% vs placebo (NS)	57% vs placebo (<.05)
Double-blind, crossover, 36 days (11) ⁵	L-Dopa (250 mg PO)	Complete relief of restlessness: 1/11 patients	45% (decrease in nocturnal myoclonus syndrome disturbed cluster time) (<.025)	56% (decrease in total nocturnal awakenings) (NS)
	Pergolide‡ (0.125 mg PO)	Complete relief of restlessness: 9/11 patients	79% (decrease in nocturnal myoclonus syndrome disturbed cluster time) (<.001)	56% (decrease in total nocturnal awakenings) (NS)
Cohort, 42 days (9) ⁶	Melatonin (3 mg PO)	Resolved daytime sleepiness: 4/9 patients	60% (.004)	59% (.031)
Cohort, 3 days (9) ⁷	Apomorphine (0.5 mg subcutaneous)	Not reported	38% (<.05)	30% (NS)
Cohort, 180 days (6) ⁸	Valproate (125-600 mg PO)	Improved daytime alertness: 6/6 patients	61% (NS)	62% (NS)
Double-blind, crossover, placebo-controlled, 210 days (71) ⁹	Estrogen replacement therapy (2.5 g estradiol gel or 50 µg estradiol patch)	Not reported	0% vs placebo (NS)	23% vs placebo (NS)

NS, not significant; PLM, periodic limb movement.

*PLM Index=number of abnormal leg motions per hour.

†PLM-arousal Index=number of awakenings from abnormal leg movements per hour of sleep.

‡Pergolide is available in Canada and Europe, but not in the United States.

Melatonin and valproate produce opposite effects in small studies

Three very small trials recorded symptoms and PSG findings in patients taking melatonin, apomorphine, or valproate, and compared them with the values observed at baseline.⁶⁻⁸ Melatonin significantly improved objective measures, but most patients didn't feel less sleepy. Valproate produced the opposite effect—no clear PSG improvements, but all study patients felt better. Injected apomorphine reduced limb movements but not awakenings.

Estrogen replacement therapy doesn't help

An RCT of estrogen replacement therapy

for PLMD enrolled postmenopausal women, about half of whom were found to have PLMD.⁹ The study found estrogen replacement therapy to be ineffective for treating menopause-associated PLMD.

Recommendations

Practice parameters developed by the American Academy of Sleep Medicine state that clonazepam, pergolide, L-dopa (with a decarboxylase inhibitor), oxycodone, and propoxyphene are all reasonable choices for medical treatment of PLMD.¹⁰ The practice parameters don't specify a preference for any of these medications. **JFP**

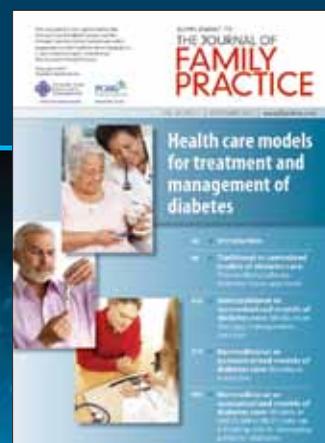
References

1. Saletu M, Anderer P, Saletu-Zyhlarz G, et al. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *Eur Neuropsychopharmacol.* 2001;11:153-161.
2. Mitler MM, Browman CP, Menn SJ, et al. Nocturnal myoclonus: treatment efficacy of clonazepam and temazepam. *Sleep.* 1986;9:385-392.
3. Edinger JD, Fins AI, Sullivan RJ, et al. Comparison of cognitive-behavioral therapy and clonazepam for treating periodic limb movement disorder. *Sleep.* 1996;19:442-444.
4. Staedt J, Wassmuth F, Ziemann U, et al. Pergolide: treatment of choice in restless legs syndrome (RLS) and nocturnal myoclonus syndrome (NMS). A double-blind randomized crossover trial of pergolide versus L-Dopa. *J Neural Transm.* 1997;104:461-468.
5. Kaplan PW, Allen RP, Buchholz DW, et al. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep.* 1993;16:717-723.
6. Kunz D, Bes F. Exogenous melatonin in periodic limb movement disorder: an open clinical trial and a hypothesis. *Sleep.* 2001;24:183-187.
7. Haba-Rubio J, Staner L, Cornette F, et al. Acute low single dose of apomorphine reduces periodic limb movements but has no significant effect on sleep arousals: a preliminary report. *Neurophysiol Clin.* 2003;33:180-184.
8. Ehrenberg BL, Eisenstein I, Corbett KE, et al. Valproate for sleep consolidation in periodic limb movement disorder. *J Clin Psychopharmacol.* 2000;20:574-578.
9. Polo-Kantola P, Rauhala E, Erkkola R, et al. Estrogen replacement therapy and nocturnal periodic limb movements: a randomized controlled trial. *Obstet Gynecol.* 2001;97:548-554.
10. Chesson AL Jr, Wise M, Davila D, et al. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine Report. *Sleep.* 1999;22:961-968.

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