



Five Things to Know About Restless Legs Syndrome in Patients on Dialysis

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1. Restless legs syndrome is an uncontrollable impulse to move the legs while at rest

Restless legs syndrome (RLS) is a sensorimotor disorder resulting in irresistible urges to move the legs and feet.¹ Despite being termed *restless legs*, urges can occur in other locations (arms, neck, face torso, etc),² although involvement of the legs is essential for diagnosis.³ The pathophysiology of RLS in people with kidney impairment is not well understood. The diagnosis can be made if all of the following 5 criteria are met (International RLS Study Group [IRLSSG] diagnostic criteria [Table 1])⁴:

2. RLS is common in dialysis, and negatively impacts patient health, sleep, and quality of life and increases cardiovascular morbidity

In patients with kidney failure, RLS is a common, treatable condition, yet it is underdiagnosed and therefore undertreated.⁵ It has been associated with insomnia,⁶ poor quality of life,⁷ depression,⁸ and prematurely ending dialysis sessions.⁹ Patients with RLS have been associated with increased cardiovascular morbidity.¹⁰ In a prospective observational study of 100 prevalent dialysis patients with an 18-month follow-up, the incidence of new cardiovascular events in patients with RLS was 64.5% compared with 39.1% in patients without RLS ($\chi^2 = 5.53$, $P = .019$).¹⁰

3. Consider the following pharmacotherapeutic options despite published studies being quite small in size with short durations of follow-up

Most drug interventions have been extrapolated from treating patients with primary RLS.

- A. Patients with mild symptoms should be treated with $\alpha\delta$ ligand agonist—gabapentin

In a randomized, double-blind, placebo-crossover study of 13 patients receiving hemodialysis (HD) on gabapentin (200–300 mg) versus placebo ($n = 13$), 11 of 13 patients responded with reduction in RLS scores to gabapentin but not placebo ($P < .01$).¹¹

Table 1. International RLS Study Group Diagnostic Criteria.

1. A need to move the legs usually accompanied by uncomfortable, unpleasant sensations in the legs
2. Symptoms are exclusively present or worsen during times of inactivity/rest
3. Partial or total relief of symptoms by movement, such as walking or stretching, at least as long as the activity continues
4. Symptoms are generally worse or exclusively occur in the evening or during the night
5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)

In another randomized, open-label, crossover study of 15 patients receiving HD, gabapentin (200 mg/day) was compared with levodopa (125 mg/day) over a 4-week period. Gabapentin was superior to levodopa in reducing RLS scores ($P < .001$), general health, body pain, and social functions ($P < .001$). It was superior to levodopa in reducing sleep latency ($P < .001$) and sleep disturbance ($P < .001$).¹² Higher doses (>300 mg/d gabapentin and >100 mg/d pregabalin) lead to altered mental status, falls, and fractures.¹³

- B. Dopamine agonists ropinirole and pramipexole provide exceptional symptom relief and are often first-choice agents

In a 14-week, open-label, randomized, crossover study involving 11 patients receiving HD, oral ropinirole (mean dose = 1.45 mg/d) was compared with levodopa sustained-release (SR) (mean dose = 190 mg/d). The 6-item

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IRLS score (0-24) was significantly better in patients receiving ropinirole versus levodopa SR (16.6 ± 2.8 to 4.4 ± 3.8 vs 16.7 ± 3.2 to 11.1 ± 4 , $P < .001$).¹⁴

Pramipexole has been extensively studied in patients with idiopathic RLS.¹⁵ In an observational study, 10 patients on HD were initiated on pramipexole (mean dose = 0.25 mg/day) and followed for a mean duration of 8 months. The RLS severity score fell from (25.8 ± 5.75 pre-treatment to 7.7 ± 5.75 , $P < .005$) at the end of the follow-up period.¹⁶ In an 8-week randomized controlled trial (RCT) involving 45 patients on HD, 15 patients were randomized to pramipexole tablet (0.18 mg once a day), 15 received vitamin C tablet (250 mg once a day), and 15 received placebo (once a day). Restless legs syndrome scores fell significantly in the pramipexole and vitamin C arms in comparison with the placebo.¹⁷

- C. Levodopa/carbidopa is not as effective for chronic persistent RLS, but can be trialed for intermittent RLS

In a 2-week, double-blind, placebo-controlled, crossover study of patients receiving HD, 5 patients received single oral dose of levodopa/carbidopa (100/25 mg) and were compared with a placebo. Patients in the intervention group experienced fewer leg movements (61.0 ± 28.3 vs 101.0 ± 29.1 events/hour, $P < .006$) and far fewer arousals per hour of sleep in comparison with the placebo.¹⁸ However, the drug failed to improve other sleep measures (total sleep time, sleep latency, and efficiency) and self-reported patient assessment of symptoms in the intervention group.¹⁸ Prolonged use of levodopa/carbidopa can lead to augmentation (drug-induced worsening of RLS) as well as rebound, the recurrence of RLS in the early morning. The rate of augmentation was the highest for patients taking levodopa, followed by those on dopamine agonists, and was the lowest in patients taking either pregabalin or gabapentin.¹⁹

- D. Replenishing iron stores appears to be helpful

In an RCT involving patients receiving HD, 11 patients received 1 dose of 1000 mg of iron dextran, and in comparison, 14 patients received placebo (500 mL of normal saline). At 2 weeks, there was a decrease in the RLS score (3, interquartile range, -5 to -2), compared with no change in the placebo arm.²⁰ It is known that iron is involved in a rate-limiting step required to convert tyrosine to levodopa, which is later decarboxylated to dopamine. In the current era of protocol-driven, proactively loading patients with intravenous iron,²¹ iron deficiency is unlikely to be a therapeutic challenge.

- E. Vitamin C and vitamin E supplementation and cool dialysate appear to be safe and effective

A randomized, double-blind, placebo-controlled, 8-week trial involved (1) a combination of 200 mg vitamin C and 400 mg vitamin E ($n = 15$), (2) 200 mg vitamin C and placebo ($n = 15$), (3) 400 mg vitamin E and placebo ($n = 15$), and (4) double placebo ($n = 15$). Patients on the double vitamin combination had significantly lowered RLS scores compared with the double-placebo group ($P < .001$).²² Cool dialysate (35.5°C) in comparison with standard (37°C) dialysate led to RLS severity score reduction and represents a reasonable choice of a non-pharmacological approach for patients with RLS on dialysis.²³

4. Intradialytic exercise with resistance training is safe, effective, and should be offered more regularly

A. In a randomized trial of patients receiving HD with RLS, 24 patients were randomly assigned to 2 groups: the intervention group (progressive exercise training with resistance group, $n = 12$) versus the control group (exercise with no resistance group, $n = 12$) and were followed for 6 months. Restless legs syndrome symptom severity declined by 58% ($P = .003$), improving functional capacity ($P = .04$), sleep quality ($P = .038$), and depression score ($P = .000$) in the intervention group, whereas no significant changes were observed in the control group.²⁴

In a randomized, parallel partially double-blind, placebo-controlled trial, 32 RLS patients on HD were randomly assigned to 3 groups: (1) the exercise training group ($n = 16$), (2) the ropinirole group (0.25 mg/d) ($n = 8$), and (3) the placebo group ($n = 8$). Exercise training and ropinirole were effective in reducing RLS symptoms by 46% ($P = .009$) and 54% ($P = .001$), respectively. Both approaches significantly improved the quality of life ($P < .05$); however, ropinirole significantly improved sleep quality ($P = .009$) in comparison with exercise and placebo.²⁵

5. Intensification of dialysis and transplantation offer significant symptom relief

In a prospective cohort study, 127 patients were followed for 12 months to determine the benefits of short daily home hemodialysis (4 hours, 6 times/week). There was decline in the percentage of patients reporting RLS (35% vs 26%) and those reporting moderate-to-severe RLS (59% vs 43%) at 12 months.²⁶

In a prospective study of 40 RLS patients on HD, there was complete resolution of symptoms of RLS after undergoing renal transplantation.²⁷

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