MANAGEMENT OF RESTLESS LEG SYNDROME IN PATIENTS WITH CHRONIC KIDNEY DISEASE

BCRenal
an agency of the Provincial Health Services Authority

Assessment

- Assess and correct possible contributing factors:
  - Iron deficiency
  - Sleep deprivation
  - Neuropathic pain
  - Medication(s) that can cause/exacerbate restless legs. e.g. antipsychotics (such as haloperidol, olanzapine, risperidone), metoclopramide, antidepressants (such as SSRIs, mirtazapine, TCAs), carbamazepine, lithium.

Non-pharmacological Strategies

Preventing restless legs:

- Avoid or limit caffeine, alcohol and nicotine.
- Plan for breaks or periods of time to walk around and stretch.
- Daily physical activity. Staying active during the day can help with sleep at night.
- For RLS at night, promote sleep hygiene measures (e.g., regular and relaxing bedtime routine, regular sleep schedule, restful sleep environment).
- For RLS during the day, encourage activities that enhance mental alertness (e.g., crossword, puzzles, video games).
- Acupuncture/Acupressure may help to decrease the symptoms
- For hemodialysis patient:
- Encourage intradialytic aerobic exercise training, e.g. cycling for 45 minutes at 50 rpm during dialysis
- Consider changing dialysis schedule from late to morning sessions
- Consider longer more frequent dialysis
- In PD patients, consider altering dialysis exchange times to accommodate exercise, by reducing intra abdominal pressure and increasing patient comfort.

Easing the discomfort of restless legs:

- Stretch &/or massage the affected area.
- Take a warm or cool bath.
- Apply hot or cold packs to the affected area.
- Perform relaxation techniques or do a mentally distracting activity as listed above.

See BCPRA patient teaching tools “Restless Legs” and “Feeling Tired? Having Difficulty Sleeping?”

MANAGEMENT OF RESTLESS LEG SYNDROME IN PATIENTS WITH CHRONIC KIDNEY DISEASE

BCRenal an agency of the Provincial Health Services Authority

Pharmacologic Options (see options on the next page)

AVOID opioids and quinine for the treatment of restless leg syndrome in patients with CKD.

- For ***intermittent*** RLS, levodopa/carbidopa 100/25 mg tablet — ½ tablet PO PRN prior to anticipated RLS event, titrate Q3-7 days to effect up to 200/50 mg PO daily. If breakthrough cramps during the night, try changing to CR (controlled release) formulation.
- For ***daily*** RLS, consider dopamine agonists
  - Compared to levodopa, decreased risk of augmentation but increased incidence of hypotension and nausea. Caution re: sleep attack (driving is not recommended).
  - Ropinirole 0.25 mg PO 2 hours prior to HS; increase by 0.25 mg PO Q7-14 days (most require ≤ 2mg/day; accumulation is unlikely but dosing has not been studied in eGFR < 30mL/min).
- If ineffective with dopaminergic agent or if RLS with concomitant painful neuropathy, leg cramp or pruritus, switch to:
  - Gabapentin 100mg po HS, titrate by 100mg Q7days. Maximum dose should be adjusted based on renal function and patient tolerance — see drug monograph. Consider 50mg (compounded capsule) po HS as a starting dose in frail elderly &/or if eGFR < 15mL/min.

OR

  - Pregabalin 25 mg PO HS; titrate by 25 mg Q7days. Maximum dose should be adjusted based on renal function and patient tolerance — see drug monograph.

Go to www.bcrenalagency.ca > Health Professionals >CKD for information on costs of medications and whether coverage may be available through BCPRA, Pharmacare or Palliative Care benefit plans.

MANAGEMENT OF RESTLESS LEG SYNDROME IN PATIENTS WITH CHRONIC KIDNEY DISEASE

BCRenal an agency of the Provincial Health Services Authority

Supplemental Evidence for Treatment Options

Non-pharmacological measures should be considered for all patients. Correct iron deficiency, if applicable, as iron is a cofactor in dopamine production. Consider a trial of abstinence from alcohol, caffeine and nicotine. Rule out any offending medication(s) that may be contributing and reducing the dose or discontinuing, if feasible. Refer to the list of offending medications in algorithm. Consider a trial of mental alerting activities, such as video games or crossword puzzles, to reduce symptoms at times of boredom. Calf stretching exercises may also be helpful. Medication should be tried if patients have severe and bothersome symptoms which impair their sleep or quality of life.

Evidence in ND-CKD patients

Available literature in non-dialysis chronic kidney disease (ND-CKD) patients is limited to 1 small trial involving 2 patients with RLS alone. Recommendations are largely extrapolated from the hemodialysis (HD) population and most studies are of small sample size, from single centre, have significant drop-outs and short follow-up.

A single center retrospective cohort study[1] evaluates the use of gabapentin in 34 stage III-IV ND-CKD patients (mean eGFR 18.4 ± 10.8 mL/min) with uremic pruritus (n=30) and RLS (n=18) and 15 HD patients with uremic pruritus (n=13) and RLS (n=6). Only 2 ND-CKD patients had RLS alone. The most common starting daily dose of gabapentin was 50mg (44.1%) or 100mg (38.2%). Gabapentin at a median dose of 100 mg daily (range 39-455mg) significantly reduced symptoms of pruritus ($p<0.001$) and RLS ($p<0.05$) since the first visit in both groups. Side effects occurred more commonly in 47% of ND-CKD patients with 17% discontinuing medication.

Evidence in HD patients

Minimal evidence exists with regards to RLS management in dialysis patients. All studies were conducted in intermittent hemodialysis patients only. Majority of the available published studies were of short duration, small sample sizes, and inadequate power.

Intradialytic exercise training

In a single-blind controlled trial[2], 24 HD patients were randomized to the progressive exercise training (n=12) and control (n=12). Both groups undergo intradialytic cycling for 45 min at 50 rpm. Resistance was applied in the progressive exercise training at 60-65% of maximum exercise capacity. RLS symptom severity reduced by 58% in the progressive exercise training group ($p=0.003$) compared to no statistically significant reduction in the control group (17% change, $p=0.124$). Function capacity, sleep quality and depression score improved significantly in the progressive training group but not in the control group. RLS severity, depression score and daily sleepiness status were significantly better in the progressive exercise training than the control group after 6 month of intervention. No adverse effects were noted.

In a pilot study[3], 14 HD patients were assigned to 16-weeks of aerobic exercise training (n=7) or to control (n=7), based on the patient's preference. Exercise resistance was set at 65-

75% of their maximum capacity in the exercise group. Exercise training reduced IRLS score by 42% (p=0.02), improved functional ability (p=0.02), exercise capacity (p=0.01), quality of life (p=0.03) and sleep quality (p=0.01). No changes were observed in the control group.

Pharmacological Strategies

Levodopa

In a randomized, double-blind, placebo-controlled, crossover trial[4] of 5 hemodialysis patients with uremic RLS, levodopa/carbidopa 100/25 mg 1 hour before HS was compared to placebo x 1 week with 1-week washout. There was no consistent subjective improvement in sleep quality, sleep latency, the number of awakenings or RLS symptoms. The mean percentage of periodic limb movement (PLM) while asleep was 15.1 ± 4.9% with placebo and decreased to 8.6 ± 4.0% with levodopa/carbidopa (p=0.014). The mean PLM index while asleep was 101.0 ± 29.1 with placebo and was significantly decreased to 61.0 ± 28.3 with levodopa/carbidopa (p=0.006).

In another randomized, double-blind, placebo-controlled, crossover trial[5] of 11 HD patients, levodopa/benserazide 100/25 mg to 200/50 mg 1 hour before HS compared to placebo x 2 weeks without washout was shown to improve few nocturnal awakenings, sleep quality, general condition and quality of life and to decrease severity of RLS, respectively. No severe adverse effects reported.

Wetter et al[6] showed that levodopa was more effective than placebo in reducing PLM index and improve in sleep quality in a randomized, double-blind, placebo-controlled, crossover trial of 11 uremic patients with RLS.

Pramipexole

In an open label[7] of 10 hemodialysis patients with RLS with 8 month follow-up, pramipexole showed an improvement in the International Restless Leg Study Group (IRLSSG) severity scale and PLM index during sleep and while awake. Pramipexole was prescribed at an initial dose of 0.125 mg, 2 hours before sleep, with an optional upward titration according to response and tolerance to a maximum daily dose of 0.75 mg, with one dose taken at least 2 hours before dialysis. Nine patients showed a response within the first week with a mean dose of 0.25mg per day. Domperidone was prescribed to control side effects. The mean score in the severity scale fell from 25.8 ± 5.75 (in the severe range) in the pretreatment evaluation to 7.7 ± 8.36 after treatment (p< 0.005). Sleep latency, total hours of sleep, number of awakenings, and sleep efficiency showed no significant change.

Note: Pramipexole is not recommended in patients with CKD because of the risk of possible accumulation.

Ropinirole

In an open label, prospective, randomized, controlled crossover trial[8] of 10 hemodialysis patients, ropinirole was shown to be superior to levodopa SR in reducing 6-item IRLS score, 16.6±2.8 to 4.4±3.8 vs 16.7±3.2 to 11.1±4,respectively (p<0.0001) and increasing sleep time. Four patients reported a complete reversion of RLS symptoms. Ropinirole dose was 0.25 mg PO daily, doubling Q5days for the first 2 weeks until symptom relief, then up to a maximum of 2 mg/day (mean dose was 1.45 mg/day). Levodopa SR dose was 100/25 mg PO daily, then doubling after 2 weeks until symptom relief (mean levodopa dose 190 mg/day). Vomiting reported in one levodopa patient resulting in study discontinuation.

In a randomized, partially double blind, placebo controlled trial[9], 32 HD patients were randomized assigned to exercise training (n=16), ropinirole 0.25 mg po daily (n=8) and placebo (n=8) x 6 months. Both exercise training

and ropinirole were effective in reducing RLS symptoms by 46% and 54%, respectively. Both were effective in improving quality of life but only ropinirole improved sleep quality (p=0.009). No side effects were noted.

Gabapentin

The previously described single center retrospective cohort study[1] evaluates the use of gabapentin in 34 stage III-IV ND-CKD patients (mean eGFR 18.4 ± 10.8 mL/min) with uremic pruritus (n=30) and RLS (n=18) as well as 15 HD patients with uremic pruritus (n=13) and RLS (n=6). Only HD 4 patients had RLS alone. The most common starting daily dose of gabapentin was 50mg (44.1%) or 100mg (38.2%). Gabapentin at a median dose of 100 mg daily (range 39-455mg) significantly reduced symptoms of pruritus (p<0.001) and RLS (p<0.05) since the first visit in both groups. Side effects occurred more commonly in 47% of ND-CKD patients. Only 13.3% of HD patients reported adverse drug reactions: 1 patient with unsteadiness and 2 patients with confusion.

In an open label controlled trial[10] of 15 hemodialysis patients, gabapentin 200 mg PO post-HD x 4 weeks was significantly more effective than levodopa 125 mg PO daily. The median RLS score decreased from baseline of 17 to 10 and 3 after treatment with levodopa and gabapentin, respectively. In SF-36 assessment, gabapentin improved general health, body pain and social function (P<0.001) while levodopa significantly improved body pain only (p<0.002). Gabapentin was significantly superior to levodopa for sleep quality, sleep latency (p<0.001) and sleep disturbance (p<0.000).

In a randomized double-blind, controlled, crossover trial[11] of 13 patients, gabapentin 300 mg PO 3 times weekly at the end of HD x 6 week was more effective than placebo. IRLSSG rating score decreased from a mean of 5.8 ± 2.3 with placebo to 3.0 ± 2.2 with gabapentin (p<0.01). Eleven of 13 patients responded to gabapentin but not to placebo, one responded to placebo but not gabapentin while one responded to neither drug. Lethargy was reported.

Clonidine

In a randomized, double-blind, placebo-controlled, parallel study[12], clonidine 0.075 mg PO BID was compared to placebo x 3 days in 20 patients. Complete relief of symptoms was noted in 8/10 pts, marked alleviation in 1/10 patients and unchanged symptoms in 1/10 patients treated with clonidine, compared with placebo (p<0.001).

Vitamins

In a randomized, double-blind, placebo-controlled trial involving 60 hemodialysis patients[13], vitamin C 200mg + placebo, vitamin E 400mg + placebo, vitamin C 200mg + vitamin E 400mg, and double placebo daily x 8 weeks were randomized to 4 parallel groups. Vitamins C, E, and the combination were found to improve the IRLS score by approximately 45, 53 and 50%, respectively, as compared to a non-significant 3% reduction with placebo. No oxalosis was reported. Two combinations, 1 vitamin E and 1 double placebo patients reported nausea. One combination, 1 vitamin E and 1 vitamin C patients reported dyspepsia. Further studies are needed to confirm these results, especially safety data in non-dialysis CKD patients.

Evidence in PD patients

Gabapentin

In a case series, 4 PD patients experienced relief from their RLS within a few days of gabapentin initiation. The doses used were 100-300mg per day. No side effects were reported.

References

1. Hassan HIC, Brennan F, Collett G, Josland EA, Brown MA. Efficacy and safety of gabapentin for uremic pruritus and restless Legs syndrome in conservatively managed patients with chronic kidney disease. J Pain Sympt Manage 2015;49: 782-9.
2. Giannaki CD, Hadjigeorgiou GM, Karatzaferi C, Maridaki MD, Koutedakis Y, Founta P, et al. A single-blind randomized controlled trial to evaluate the effect of 6 months of progressive aerobic exercise training in patients with uraemic restless legs syndrome. Nephrol Dial Transplant 2013; 28: 2834-40.
3. Sakkas GK, Hadjigeorgious GM, Karatzaferi C, Maridaki MD, Giannaki CD, Mertens PR, et al. Intradialytic Aerobic Exercise Training Ameliorates Symptoms of Restless Legs Syndrome and Improves Functional Capacity in Patients on Hemodialysis. A Pilot Study. ASAIO J 2008; 54: 185-90.
4. Walker SL, Fine A, Kryger MH. L-DOPA/ carbidopa for nocturnal movement disorders in uremia. Sleep 1996; 3: 214-8.
5. Trenkwalder C, Stiasny K, Pollmacher T, et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a doubel-blind, crossover trial. Sleep 1995; 18: 681-8.
6. Wetter TC, Trenkwalder C, Stiasny K, et al. Treatment of idiopathic and uremic restless legs syndrome with L-dopa: a double-blind cross-over study [in German]. Wien Med Wochenschr 1995; 145: 525-7.
7. Miranda M, Kagi M, Fabres L, et al. Pramipexole for the treatment of uremic restless legs in patients undergoing hemodilaysis. Neurology 2004; 62: 831-2.
8. Pellecchia MT, Vitale C, Sabatini M, et al. Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis: an open randomized crossover trial versus levodopa sustained release. Clin Neuropharmacol 2004; 4: 178-81.
9. Giannaki CD, Sakkas GK, Karatzaferi C, Hadjigeorgiou GM, Lavdas E, Kyriakides T, et al. Effect of exercise training and dopamine agonists in patients with uremic restless legs syndrome: a six-month randomized, partially double-blind, placebo-controlled comparative study. BMC Nephrology 2013, 14: 194-205.
10. Micozkadioglu H, Ozdemir FN, Kut A, et al. Gabapentin versus levodopa for the treatment of restless legs syndrome in hemodialysis patient: an open-label study. Ren Fail 2004; 26: 393-7.
11. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless leg syndrome among hemodialysis patients. Am J Kidney Dis 2001; 38: 104-8.
12. Ausserwinkler M, Schmidt P. Successful clonidine treatment of restless leg syndrome in chronic kidney insufficiency. Schweiz Med Wochenschr 1989; 199: 184-6.
13. Sagheb MM, Dormanesh B, Fallahzadeh MK, Akbari H, Nazari SS, Heydari ST, et al. Efficacy of vitamins C, E, and their combination for treatment of restless legs syndrome in hemodialysis patients: a randomized, double-blind, placebo-controlled trial. Sleep Med 2012; 13: 542-5.
14. Tan J, Derwa A, Sanu V, Rahman N, Woodrow G. Gabapentin in treatment of restless legs syndrome in peritoneal dialysis patients. Perit Dial Int 2006; 26: 276-8.

General References

a) Giannaki CD, Hadjigeorgiou GM, Karatzaferi C, Pantzaris MC, Stefanidis I, Sakkas GK. Epidemiology, impact, and treatment options of restless legs syndrome in end-stage renal disease patients: an evidence-based review. Kid Int 2013; 85: 1275-82.

b) Sakkas GK, Giannaki CD, Karatzaferi C, Maridaki M, Koutedakis Y, Hadjigeorgiou GM, et al. Current trends in the management of uremic restless legs syndrome. A systematic review on aspects related to quality of life, cardiovascular mortality and survival. Sleep Med Rev 2015; 21: 39-49.
c) de Oliveira MM, Conti CF, Valbuza JS, de Carvalho LBC, do Prado GF. The pharmacological treatment for uremic restless legs syndrome: evidence-based review. Mov Disord 2010; 25: 1335-42.
d) Molnar MZ, Novak M, Mucsi I. Management of restless legs syndrome in patients on dialysis. Drugs 2006; 66: 607-24.
e) Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA, et al. An algorithm for the management of restless legs syndrome. Mayo Clin Proc 2004; 79: 916-22.