Management of Restless Leg Syndrome in End-Stage Renal Disease

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There is a high prevalence of Restless Leg Syndrome (RLS) amongst patients with End-Stage Renal Disease (ESRD). RLS is characterized by symptoms of disagreeable discomfort in the lower extremities which manifests more prominently during periods of rest or sleep. Involuntary leg jerking during sleep results in poor sleep quality, insomnia and daytime sleepiness. The incidence of RLS is higher in ESRD patients as compared to the general population and has been associated with uremia and anemia. Incidence does not appear to differ with race, gender or type of dialysis (peritoneal or hemodialysis)[1,2,3]. RLS is diagnosed based on characteristic symptoms as described by The International Restless Legs Syndrome Study Group.[4]

Table 1. Summary of IRLSSG Essential Diagnostic Criteria for RLS

- Urge to move the extremities, usually associated with parathesias/dysparasthesias.
- Worsening of symptoms at rest or inactivity.
- Symptoms are relieved by activity as long as the activity is continued.
- Symptoms worsen in the evening or night.

RLS may be idiopathic or secondary to a predisposing medical condition such as ESRD. Due to the success in treating RLS with dopaminergic agents, the pathogenesis of RLS is hypothesized to involve dopaminergic dysfunction. However there is still very little known about the true etiology and pathogenesis of RLS in dialysis patients.

Various groups have investigated the incidence and impact of RLS in ESRD patients. There is evidence that RLS is associated with increased morbidity and mortality in this patient group. RLS has also been shown to decrease quality of life and mental well-being in dialysis patients. Such patients are more likely to be prescribed benzodiazepines, antidepressants and opioids than dialysis patients without RLS.[2]

Management of RLS in ESRD

Secondary causes of RLS should be ruled out before considering pharmacological therapy. RLS has been associated with iron deficiency anemia, therefore iron therapy and correction of hemoglobin with erythropoietin is recommended.[3] Drugs known to exacerbate RLS should be eliminated if possible.

Table 2. Factors/Drugs that may exacerbate symptoms of RLS

- TCA
- Anti-psychotics
- Dopamine antagonists
- SSRI
- Caffeine
- Lithium
- Smoking

L-dopa is a very effective treatment for the symptoms of RLS. However, development of RLS symptom augmentation (daytime symptoms and increased severity of symptoms) limits usefulness. Dopamine agonists, including pramipexole, ropinirole and pergolide are the preferred agents in treating both idiopathic and uremic RLS.[3] These agents are efficacious and have significantly less augmentation than L-dopa. Anticonvulsants including gabapentin and carbamazepine are second-line agents and are limited by their side effects. Opioids, benzodiazepines and clonidine are also used to treat RLS, however these agents are associated with less specific efficacy and also have a high incidence of adverse effects, especially in the ESRD patient population. Amantadine, baclofen and ketamine have shown some preliminary success.[3]

Drug Class	Efficacy	Dose	Disadvantages of Use/ Adverse Effects	Coverage
Iron therapy	• Correction of anemia with iron and erythropoietin has improved symptoms in hemodialysis patients.[5] • High dose iron dextran infusion has been associated with a significant but transient reduction in symptoms in ESRD patients.[6] • More recently, other studies show conflicting results.[7]	1000 mg Iron Dextran	• Abdominal pain, nausesa/vomiting, diarrhea • Arthralgias, arthritis • Urticaria, pruritus, rash • Risk of anaphylactic reactions	Usually provided in hospital
Levodopa (with carbidopa)	• efficacious • 2 small randomized studies and 1 small cohort study supported the use of L-dopa in uremic patients suffering from RLS. • These studies showed improved quality of life and sleep, decreased movements and symptoms of RLS.[8,9,10]	Sinemet 25/100 50-200 mg 1-2 hrs before bedtime	• Initially effective but eventually patient will develop augmentation • Morning rebound • Nausea/vomiting, orthostatic hypotension, insomnia	Covered by ODB (LU needed for CR dosage form)

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Drug Class	Efficacy	Dose	Disadvantages of Use/ Adverse Effects	Coverage
Non-Ergotamine dopamine agonists	• Dramatically reduces symptoms in idiopathic RLS.[11] • one small non-randomized trial showed pramipexole to be an effective treatment for RLS in uremic patients without important adverse effects.[12] • No augmentation.	Pramipexole (Mirapex) 0.25-0.75 mg QHS Ropinirole (Requip) 0.5 mg QHS	• Nausea, constipation, anorexia, dizziness	Covered by ODB Covered by ODB
Ergotamine dopamine agonists	• efficacious • Pergolide was shown to be effective in a small, double-blind, placebo-controlled trial of patients with uremic RLS.[13]	Pergolide (permax) 0.5 mg 2 hrs prior to bedtime (starting dose = 0.05 mg QHS)	• Mild augmentation (less than L-dopa) • Nausea/vomiting, nasal stuffiness, edema, blurred vision • Pleuropulmonary fibrosis (rare)	Covered by ODB
Benzo-diazepines	• Conflicting results. • Positive results with clonazepam in an open study of 15 patients with uremic RLS.[14] • May be beneficial in young patients with mild symptoms. • Benefits of BNZ non-specific and likely due to effect on sleep.	Clonazepam 0.5-2 mg QHS Others agents are also used.	• Long term use is limited by tolerance • Sedation • Daytime sleepiness • Cognitive impairment	Covered by ODB
Antiepileptics	• A crossover study of gabapentin versus placebo found gabapentin to be a safe effective treatment for RLS in hemodialysis patients.[15] • Carbamazepine also shown to be effective in idiopathic RLS however limited evidence in ESRD patients.	Gabapentin 300-1200 mg Starting dose 300 mg	Sedation, dizziness, fatigue, somnolence, ataxia	Not covered by ODB for this indication. Section 8 approval required.
Opioids	• Subjectively improves leg sensations, motor restlessness and daytime alertness. • Only used for patients with severe resistant symptoms.	Numerous agents	Considered a last resort due to adverse effects.	Many agents covered by ODB.

Current evidence is limited because no large-scale, long-term, multi-centre trials exist for any particular agent for the treatment of RLS in ESRD. In addition, prior to 2002, there weren't standard diagnostic criteria for RLS. Further comparative studies are needed to substantiate current evidence and to investigate the use of novel agents.

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