Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for chronic kidney disease-associated restless legs syndrome (Review)

Gopaluni S, Sherif M, Ahmadouk NA

Gopaluni S, Sherif M, Ahmadouk NA.
Interventions for chronic kidney disease-associated restless legs syndrome.
Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010690.
DOI: 10.1002/14651858.CD010690.pub2.

www.cochranelibrary.com

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 4
OBJECTIVES 5
METHODS 5
RESULTS 7
Figure 1. 7
Figure 2. 8
Figure 3. 9
DISCUSSION 12
AUTHORS' CONCLUSIONS 13
ACKNOWLEDGEMENTS 13
REFERENCES 14
CHARACTERISTICS OF STUDIES 16
DATA AND ANALYSES 31
Analysis 1.1. Comparison 1 Exercise interventions, Outcome 1 Severity. 33
Analysis 1.2. Comparison 1 Exercise interventions, Outcome 2 QOL: physical component score. 33
Analysis 1.3. Comparison 1 Exercise interventions, Outcome 3 QOL: mental component summary score. 33
Analysis 1.4. Comparison 1 Exercise interventions, Outcome 4 Quality of sleep: subjective measure. 34
Analysis 1.5. Comparison 1 Exercise interventions, Outcome 5 Quality of sleep: Epworth Sleepiness Scale. 34
Analysis 2.1. Comparison 2 Pharmacological interventions, Outcome 1 Severity. 35
Analysis 2.2. Comparison 2 Pharmacological interventions, Outcome 2 QOL: life satisfaction. 36
Analysis 2.3. Comparison 2 Pharmacological interventions, Outcome 3 QOL: negative feelings & complaints. 36
Analysis 2.4. Comparison 2 Pharmacological interventions, Outcome 4 Quality of sleep. 36
ADDITIONAL TABLES 36
APPENDICES 37
CONTRIBUTIONS OF AUTHORS 40
DECLARATIONS OF INTEREST 40
INDEX TERMS 41

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Interventions for chronic kidney disease-associated restless legs syndrome

Seerapani Gopaluni[1,2], Mohamed Sherif[2], Naim A Ahmadouk[3]

[1]Department of Nephrology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. [2]Department of Renal Medicine, Oxford Kidney Unit, Churchill Hospital, Oxford, UK. [3]Department of Medicine, Buckinghamshire Hospitals NHS Trust, High Wycombe, UK

Contact address: Seerapani Gopaluni, Department of Nephrology, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge, CB2 0QQ, UK. pani.gopaluni@yahoo.com.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New, published in Issue 11, 2016.

Citation: Gopaluni S, Sherif M, Ahmadouk NA. Interventions for chronic kidney disease-associated restless legs syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD010690. DOI: 10.1002/14651858.CD010690.pub2.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Restless legs syndrome (RLS) is defined as the spontaneous movement of the limbs (mainly legs) associated with unpleasant, sometimes painful sensation which is relieved by moving the affected limb. Prevalence of RLS among people on dialysis has been estimated between 6.6% and 80%. RLS symptoms contribute to impaired quality of life and people with RLS are shown to have increased cardiovascular morbidity and mortality.

Various pharmacological and non-pharmacological interventions have been used to treat primary RLS. However, the evidence for use of these interventions in people with chronic kidney disease (CKD) is not well established. The agents used in the treatment of primary RLS may be limited by the side effects in people with CKD due to increased comorbidity and altered drug pharmacokinetics.

Objectives

The aim of this review was to critically look at the benefits, efficacy and safety of various treatment options used in the treatment of RLS in people with CKD and those undergoing renal replacement therapy (RRT). We aimed to define different group characteristics based on CKD stage to assess the applicability of a particular intervention to an individual patient.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 12 January 2016 through contact with the Information Specialist using search terms relevant to this review.

Selection criteria

Randomised controlled trials (RCT) and quasi-RCTs that assessed the efficacy of an intervention for RLS in adults with CKD were eligible for inclusion. Studies investigating idiopathic RLS or RLS secondary to other causes were excluded.

Data collection and analysis

Two authors independently assessed studies for eligibility and conducted risk of bias evaluation. Results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes.

Main results

We included nine studies enrolling 220 dialysis participants. Seven studies were deemed to have moderate to high risk of bias. All studies were small in size and had a short follow-up period (two to six months). Studies evaluated the effects of six different interventions against

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

placebo or standard treatment. The interventions studied included aerobic resistance exercise, gabapentin, ropinirole, levodopa, iron dextran, and vitamins C and E (individually and in combination).

Aerobic resistance exercise showed a significant reduction in severity of RLS compared to no exercise (2 studies, 48 participants: MD -7.56, 95% CI -14.20 to -0.93; I^2 = 65%), and when compared to exercise with no resistance (1 study, 24 participants: MD -11.10, 95% CI -17.11 to -5.09), however there was no significant reduction when compared to ropinirole (1 study, 22 participants): MD -0.55, 95% CI -6.41 to 5.31). There were no significant differences between aerobic resistance exercise and either no exercise or ropinirole in the physical or mental component summary scores (using the SF-36 form). Improvement in sleep quality varied. There was no significant difference in subjective sleep quality between exercise and no exercise; however one study reported a significant improvement with ropinirole compared to resistance exercise (MD 3.71, 95% CI 0.89 to 6.53). Using the Epworth Sleepiness Scale there were no significant differences between resistance exercise and no exercise, ropinirole, or exercise with no resistance. Two studies reported there were no adverse events and one study did not mention if there were any adverse events. In one study, one patient in each group dropped out but the reason for dropout was not reported. Two studies reported no adverse events and one study did not report adverse events.

Gabapentin was associated with reduced RLS severity when compared to placebo or levodopa, and there was a significant improvement in sleep quality, latency and disturbance reported in one study when compared to levodopa. Three patients dropped out due to lethargy (2 patients), and drowsiness, syncope and fatigue (1 patient).

Because of a short duration of action, rebound and augmentation were noted with levodopa treatment even though it conferred some benefit in reducing the symptoms of RLS. Reported adverse events were severe vomiting, agitation after caffeine intake, headaches, dry mouth, and gastrointestinal symptoms.

One study (25 participants) reported iron dextran reduced the severity of RLS at weeks one and two, but not at week four. Vitamins C, E and C plus E (1 study, 60 participants) helped the symptoms of RLS with minimal side effects (nausea and dyspepsia) but more evidence is needed before any conclusions can be drawn.

Authors' conclusions

Given the small size of the studies and short follow-up, it can only be concluded that pharmacological interventions and intra-dialytic exercise programs have uncertain effects on RLS in haemodialysis patients. There have been no studies performed in non-dialysis CKD, peritoneal dialysis patients, or kidney transplant recipients. Further studies are warranted before any conclusions can be drawn. Aerobic resistance exercise and ropinirole may be suitable interventions for further evaluation.

PLAIN LANGUAGE SUMMARY

Interventions for treating restless legs syndrome in patients with chronic kidney disease

What is the issue?

People with restless legs syndrome (RLS) have an irresistible urge to move their limbs to relieve themselves of unpleasant sensations. RLS is common in chronic kidney disease (CKD) patients, however the cause is unknown. Patients with RLS often have reduced quality of life and increased risk of developing heart disease.

Medications such as dopamine agonists, benzodiazepines, anti-epileptics, iron and non-pharmacological agents such as exercise that were used to treat primary RLS were also used to treat RLS in CKD patients. However, these agents may be unsuitable to CKD patients due to associated co-morbidity and altered pharmacokinetics in CKD patients.

What did we do?

We searched Cochrane Kidney and Transplant's Specialised Register to 12 January 2016. Nine studies reported enrolling 220 stable, adult haemodialysis patients of both sexes, were included in the review.

What did we find?

The quality of the studies was deemed to be moderate. Of the nine studies, one was sponsored by a pharmaceutical company and funding sources were reported for only two other studies. The included studies were heterogeneous, small in size and had short follow-up periods.

The interventions studied included exercise, gabapentin, ropinirole, levodopa, iron dextran, and vitamins C and E (individually and in combination). All interventions reduced the severity of RLS compared to a control. Intradialytic aerobic exercise reduced the severity of RLS however the safety of this intervention is unclear. Resistance exercise did not improve sleep quality but improved the mental health component on a quality of life questionnaire. This improvement in mental health component was not significant when compared to no exercise or ropinirole. Ropinirole reduced the symptoms of RLS and improved quality of sleep without any reported side effects. Gabapentin and levodopa improved the symptoms of RLS; however there were several adverse events reported included lethargy, drowsiness and fatigue for gabapentin, and vomiting, agitation, headaches, dry mouth, and gastrointestinal symptoms for levodopa. Iron dextran infusion

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

reduced the symptoms of RLS but was only significant up to two weeks after treatment. Vitamin C, E and their combination also reduced RLS symptoms with minimal side effects. Small size and short duration of follow-up were the major drawbacks of these studies.

Conclusions

The small number of studies, small sample sizes and short duration of follow up make it difficult to draw any firm conclusions. The effects of aerobic exercise and other pharmacological agents on RLS are uncertain in haemodialysis patients. There is a need to perform high quality randomised studies to establish the best treatment for RLS in patients with CKD. Aerobic exercise and ropinirole may be suitable interventions for further evaluation.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Description of the condition

The symptoms of restless legs syndrome (RLS) were first described in 1672 by Sir Thomas Willis. It is defined as the spontaneous movement of the limbs (mainly legs) associated with unpleasant, sometimes painful sensation and relieved by moving the affected limb. This definition has not been significantly modified since it was first defined in 1945 (Ekbom 1945).

Diagnostic criteria for RLS was published by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 (Walters 1995) and were subsequently revised by the National Institute of Health consensus conference in 2002 (Allen 2003) to include the following.

1. Urge to move the legs usually with unpleasant sensations in the legs; arms and other body parts are occasionally involved
2. Symptoms begin or worsen during periods of rest or inactivity
3. Symptoms partially or totally relieved by movement and as long as the activity continues
4. Symptoms are worse during the evening or night than during the day.

In addition, separate modified criteria were established for diagnosing RLS in special populations, for RLS augmentation, and for assessment of RLS in epidemiologic studies.

Prevalence of RLS in the general population is 5% to 15% whereas the prevalence in dialysis patients is 6.6% to 80% (Al-Jahdali 2009). RLS contributes to impaired quality of life (QOL) (Mucsi 2005) and patients with RLS have increased cardiovascular morbidity and mortality (La Manna 2011).

Description of the intervention

There is emerging evidence with strong recommendations advocating the use of various agents to treat primary RLS. Dopaminergic agents have been established as first line treatment options for primary RLS. Anti-epileptic drugs, benzodiazepines, opiates, alpha-adrenergic blockers, iron supplementation, aerobic exercise, and Botox have been used in the treatment of people with primary RLS (Agarwal 2011; Giannaki 2010; Hornyak 2014).

However, the evidence for use of these agents in people with chronic kidney disease (CKD) is not well established. The usual agents that have been tried in the treatment of primary RLS may be limited by the side effects in people with CKD.

Kidney impairment can alter drug pharmacokinetics and pharmacodynamics, and consequently people with kidney impairment are at risk of developing adverse effects. People with CKD need to take many drugs and are at high risk for drug interactions and drug-related problems (Manley 2003).

How the intervention might work

Advanced brain imaging techniques have implicated dysfunction of subcortical areas as causative in primary RLS.

Iron deficiency is considered to be common in primary RLS and there is an inverse relation between iron levels and the severity of RLS symptoms (Sun 1998). Abnormality of the body's ability to use and store iron may lead to the dopamine dysfunction. Iron probably works by both improving anaemia as well as being a cofactor for tyrosine hydroxylase, a rate limiting step in dopamine production pathway in the nigrostriatal area (Sloand 2004).

Evidence for the hypothesis implicating dopaminergic dysfunction as a cause for RLS came from the chance finding of symptom relief on small doses of levodopa (Akpinar 1982) and exacerbation of symptoms with dopamine antagonists (Winkelmann 2001). Dopamine agonists directly stimulate dopamine receptors and are generally superior to levodopa in treating RLS.

The pathophysiology of RLS in people with CKD is not well understood. Inadequate dialysis leading to toxin accumulation, iron deficiency, hyperparathyroidism and high calcium and phosphate levels have been implicated in the pathogenesis by various studies. Most drug interventions used for people with CKD have been extrapolated from experience in treating people with primary RLS. Some interventions specific to those with CKD have been tried based on anecdotal evidence.

- Dopamine pathways have been implicated in the pathophysiology of RLS for a long time. It is known that iron is involved in a rate-limiting step required to convert tyrosine to levodopa that is later decarboxylated to dopamine. Correcting functional iron deficiency using iron supplementation may help reduce the symptoms of RLS in haemodialysis patients.
- Gabapentin (an anticonvulsant) has been shown to help RLS in non-uraemic patients (Lee 2016). This drug is excreted by the kidney (77%) and has a long-half lifetime. Gabapentin modulates various receptor sites and alters dopamine, serotonin and norepinephrine release.
- Levodopa was shown to be beneficial in ameliorating the symptoms from RLS in non-uraemic patients. However it has adverse effects of rebound, augmentation and tolerance to beneficial effects.
- Ropinirole is a synthetic dopamine agonist with relatively large D3 and D4 affinity. Because of its short plasma half-life and liver metabolism it may be safer to use in patients with kidney failure.
- High oxidative stress has been implicated in pathogenesis of RLS and the use of anti-oxidants vitamin C and E may relieve the symptoms of RLS.

Why it is important to do this review

Abnormal limb movement disorders that affect sleep, such as periodic limb movement disorder and RLS, are reported to be common among people with CKD and those undergoing dialysis (Kavanagh 2004). These disorders, which are often both under-recognised and treated, are thought to cause significant sleep disruption and reduce QOL (Mucsi 2005). As well as experiencing poor QOL, mounting evidence suggests people with disturbed sleep patterns are also at increased risk of developing hypertension and cardiovascular diseases (Walters 2010).

In view of the coexistence of RLS with other sleep disturbances in people with kidney disease, it is difficult to identify people with RLS alone. It has only been in the last 15 years that diagnostic criteria were agreed internationally and are being used to identify participants for inclusion in therapeutic studies.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

The available evidence concerning treatment of RLS in the context of kidney impairment is limited, and the best options to treat these patients remain unclear.

OBJECTIVES

The aim of this review was to critically look at the benefits and safety of various treatment options used in the treatment of RLS in people with CKD and those undergoing RRT. We aimed to define different group characteristics based on CKD stage to assess the applicability of particular interventions to individual patients.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods), looking at the specified therapeutic interventions for people with RLS associated with CKD stages 3 to 5, including different modes of RRT were included.

Types of participants

Inclusion criteria

All RCTs that recruited adults of both sexes over the age of 18 years with CKD stages 3 to 5 with secondary RLS as diagnosed using the criteria set out by the IRLSSG were eligible for inclusion. Patients undergoing peritoneal dialysis or haemodialysis, and those who had received a kidney transplant were included.

Exclusion criteria

- Idiopathic RLS
- RLS secondary to other causes (e.g. diabetes, amyloid)
- RLS predating onset of kidney disease.

People with diagnoses of periodic limb movement disorders not specifically diagnosed as RLS were excluded from our analyses.

Types of interventions

1. Non-pharmacological interventions not related to renal replacement therapy (RRT) including exercise, smoking cessation and alcohol intake reduction
2. Pharmacological interventions (of any dose, combination, duration) versus placebo, no treatment, or other pharmacological agent. The following agents were included.
   - Iron/erythropoietic stimulating agents to adequately treat anaemia
   - Benzodiazepines: clonazepam, diazepam
   - Dopamine agonists: ropinirole, pramipexole, pergolide, cabergoline
   - Antiepileptics: gabapentin, pregabalin
   - Other medications/treatments: vitamins, minerals, nutritional supplements
3. Any other intervention that was found to be relevant such as changes to dialysis regimens, kidney transplantation, enhancing dialysis adequacy and optimising electrolyte balance.

Types of outcome measures

1. Reduction in symptoms and signs, assessed by questionnaires (International RLS Scale, Johns Hopkins RLS Severity Scale) or by objective testing (Suggested Immobilisation Test (SIT) and actigraphy)
2. Reduction in sleep disturbances related to RLS, assessed by questionnaires (RLS-6 scale, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS)) or by objective testing (actigraphy)
3. Adverse events related to interventions.

Each of the interventions described may relate to subsets of participants, depending on the stage of CKD, underlying diagnoses, RRT mode and demographic variables. Applicability was assessed by analysing studies for particular patient group characteristics and adverse events relating to specific interventions in that group.

Primary outcomes

The effects of interventions in reducing symptom severity due to RLS in people with CKD and potential complications related to the use of such interventions.

Secondary outcomes

1. Improvement in QOL
2. Improvement in quality of sleep
3. Reduction in cardiovascular mortality
4. Applicability to individual patients.

Search methods for identification of studies

Electronic searches

We searched Cochrane Kidney and Transplant Specialised Register (to 12 January 2016) through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register were identified through search strategies for CENTRAL, MEDLINE, and EMBASE, based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Searching other resources

1. Reference lists of review articles, relevant studies, and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts that were relevant to the review. Titles and abstracts were screened independently by two authors, who discarded studies that were not applicable; however studies and reviews that included relevant data or information on studies were retained initially. Two authors independently assessed the retrieved abstracts, and where necessary assessed the full text of these studies to determine which satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study existed, records were grouped together and the publication with the most complete data was included. Where relevant, outcome data that were only published in earlier versions was used. Disagreements were resolved by consultation with all authors.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Were reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Where continuous scale of measurements was used to assess the effects of treatment (improvement in the sleeping score, improvement in the international restless leg syndrome scale score, improvement in Johns Hopkins RLS Severity Scale score), the mean difference (MD) was used, or the standardised mean difference (SMD) when different scales were used.

Dealing with missing data

We attempted to contact study authors to obtain missing data.

We calculated the standard deviations when not reported and data were available either in the paper or provided by study authors.

Assessment of heterogeneity

Duration of treatment, dose and form of drugs were assessed to ensure there was no heterogeneity. Non-pharmaceutical interventions (e.g. the form and frequency of exercise) were also assessed to ensure there was no heterogeneity.

Where applicable, heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Duration of treatment, dose and form of drugs, and follow-up period were assessed to determine heterogeneity.

Non-pharmaceutical interventions (e.g. the form and frequency of exercise) and follow-up period were assessed to determine heterogeneity.

Assessment of reporting biases

We did not identify sufficient numbers of RCTs to examine for publication bias using funnel plots (Higgins 2011).

Data synthesis

Data were to be pooled using the random-effects model but the fixed-effect model was also to be used to ensure robustness of the model chosen and susceptibility to outliers. Data were not pooled due to significant heterogeneity identified in outcomes measured.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analysis to explore possible sources of heterogeneity (e.g. participants, interventions and study quality). Heterogeneity among participants could be related to age (e.g. less than 65 years versus more than 65 years old), renal pathology (for example diabetic kidney disease, glomerulonephritis, renovascular disease, polycystic kidney disease). Heterogeneity in treatments could be related to prior agent(s) used and the agent, dose and duration of therapy.

Subgroup analysis was not done due to limited number of studies investigating the effect of a particular intervention. Adverse events were tabulated and assessed with descriptive techniques, as they were different for the various agents used.

Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

We were unable to perform sensitivity analysis due to insufficient numbers of studies in each intervention category.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

RESULTS

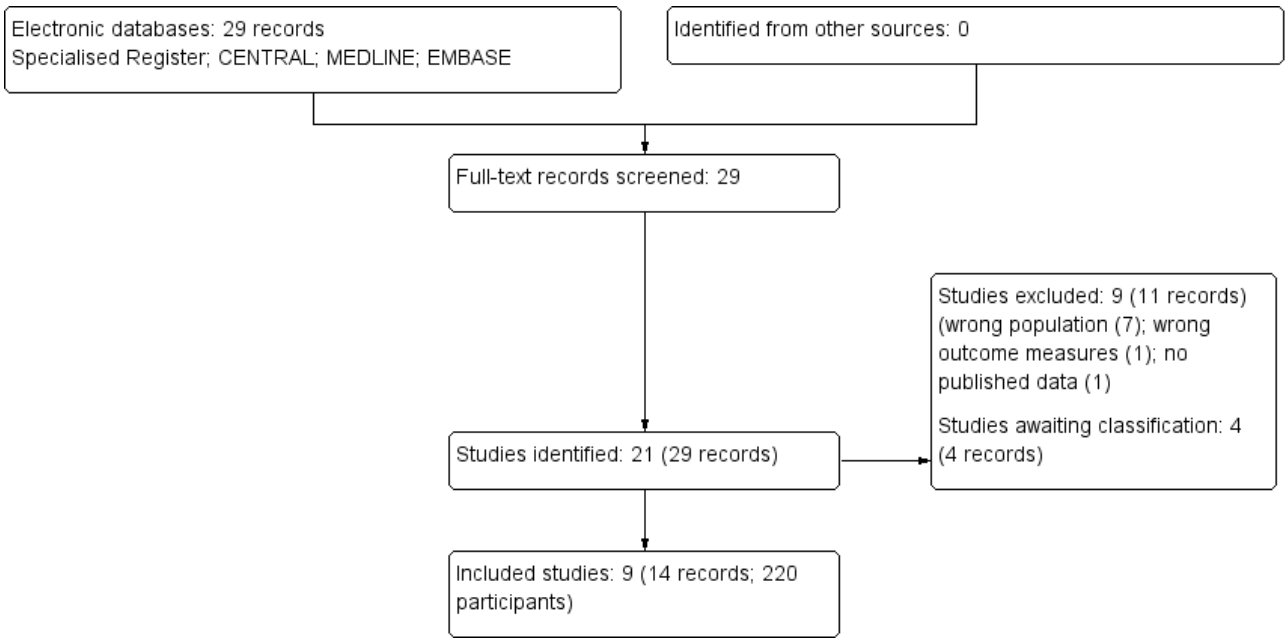
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification

Results of the search

The searches returned 29 records. After grouping these records into studies (22 studies), nine studies (11 records) were excluded after full-text review and nine studies (14 records) were included in the analyses. Four recently completed studies will be assessed in a future update of this review (NCT00996944; NCT01537042; NCT02011191; Razazian 2015) (Figure 1).

Figure 1. Study selection flow diagram



Included studies

We included nine studies that involved 220 participants undergoing RRT (Giannaki 2013; Giannaki 2013a; Micozkadioglu 2004; Mortazavi 2013; Pellecchia 2004; Sagheb 2012; Sloand 2004; Thorp 2001; Trenkwalder 1995). Eight studies only enrolled haemodialysis patients and one study enrolled haemodialysis and peritoneal dialysis patients (Sloand 2004) (Characteristics of included studies).

We contacted the authors for either missing data or clarification of the reported data; one author responded to our request.

Design

All nine studies were RCTs. Four studies were crossover studies (Micozkadioglu 2004; Pellecchia 2004; Thorp 2001; Trenkwalder 1995). Eight of the studies involved two comparisons whilst one (Sagheb 2012) included four groups for comparison. Three studies were open-labelled studies (Micozkadioglu 2004; Mortazavi 2013; Pellecchia 2004), one was single blinded (Giannaki 2013a), and the other five were double-blind (Giannaki 2013; Sagheb 2012; Sloand 2004; Thorp 2001; Trenkwalder 1995).

Sample sizes

Studies included within this review were relatively small in size, varying from 11 to 60 participants.

Setting

Studies were conducted in dialysis centres located in a number of countries and may reflect inherent variations in treatment and clinical practices. Study countries included Greece (Giannaki 2013; Giannaki 2013a); Iran (Mortazavi 2013; Sagheb 2012); USA (Sloand 2004; Thorp 2001); Germany (Trenkwalder 1995); Italy (Pellecchia 2004), and Turkey (Micozkadioglu 2004).

Participants

Participants were diagnosed with RLS based on criteria proposed by the IRLSSG. Updated IRLSSG standard criteria for RLS (Allen 2003) were used to identify participants for inclusion into the studies in all but two (Trenkwalder 1995, Thorp 2001). However criteria used by both studies were very similar to IRLSSG and were included in this review.

Interventions

Distinctly different interventions were assessed in the included studies.

- Exercise interventions
  - Aerobic exercise versus no exercise (Mortazavi 2013)
  - Resistance exercise with either ropinirole or exercise with no resistance (Giannaki 2013a).

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

- Pharmacological agents
  * Levodopa versus placebo (Trenkwalder 1995)
  * Gabapentin versus placebo (Thorp 2001)
  * Gabapentin versus levodopa (Micozkadioglu 2004)
  * Ropinirole versus levodopa (Pellecchia 2004)
  * Iron dextran versus placebo (Sloand 2004)
  * Vitamin C, vitamin E and placebo in four different combinations (Sagheb 2012).

Outcomes

The primary outcome in all studies was change in RLS severity from baseline to study end. Changes in QOL and sleep were included in the review when reported. None of the studies reported data on cardiovascular morbidity and mortality.

RLS severity was measured using different rating scales. Thorp 2001 and Trenkwalder 1995 pre-dated publication of the validated IRLSSG RLS severity scoring tool which includes 10 questions each with five options scored from 0 to 4, giving a maximum score of 40. Four studies used this as the scoring tool (Giannaki 2013; Giannaki 2013a; Mortazavi 2013; Sagheb 2012). Micozkadioglu 2004 and Pellecchia 2004 applied a six question-based IRLSSG scoring tool (introduced before the current IRLSSG tool) with a maximum score of 24. Three studies used their own non-validated scoring tools (Thorp 2001; Trenkwalder 1995; Sloand 2004).

QOL was measured using validated SF-36 questionnaire in three studies (Giannaki 2013; Micozkadioglu 2004; Mortazavi 2013). Trenkwalder 1995 used 13 visual analogue scales, each measuring different QOL components.

Sleep quality was assessed and reported in five studies using tools such as PSQI and ESS (Giannaki 2013; Giannaki 2013a; Micozkadioglu 2004; Pellecchia 2004; Trenkwalder 1995).

Adverse events were reported in all but one study (Mortazavi 2013) (Table 1).

Outcomes were measured at different time points in the studies introducing significant heterogeneity. All studies had baseline severity scores. Two studies measured outcomes at six months (Giannaki 2013; Giannaki 2013a), one study measured the outcomes at 16 weeks (Mortazavi 2013), one study at eight weeks (Sagheb 2012), two studies at six weeks (Thorp 2001; Pellecchia 2004) and three studies at four weeks (Micozkadioglu 2004; Trenkwalder 1995; Sloand 2004). There were no long-term follow-up results assessing the effects of these interventions.

Excluded studies

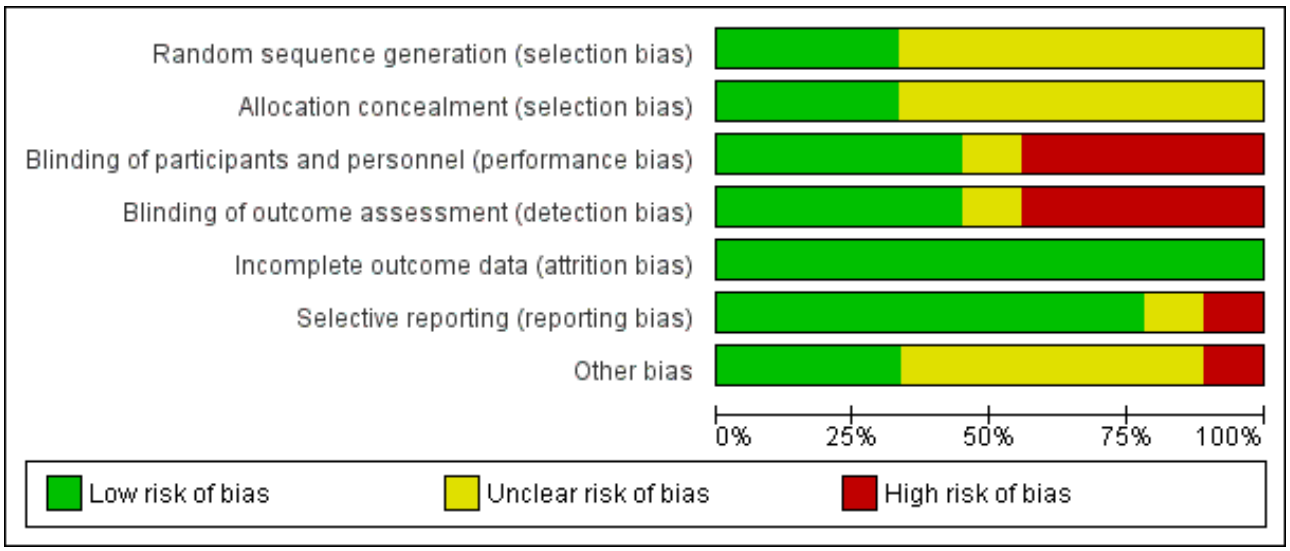
Eleven studies were excluded (Characteristics of excluded studies).

- Studies investigating uraemic neuropathy were excluded (Ausserwinkler 1989; Facchini 2004; FINESSE Study 2010; Kramer 1988; Okada 2000; Sprenger 1983; Walker 1996).
- Included polysomnographic measurements of periodic limb movements (PLM) as primary outcomes in their analyses. We excluded this from our analysis as RLS is distinctly different from PLM disorder, which is a condition that occurs during sleep and is involuntary whilst RLS is voluntary movement of the limbs in order to relieve discomfort in the limbs (Pieta 1998).
- One study registered in 2002 has never been published and the web link is no longer active (N0203077917).

Risk of bias in included studies

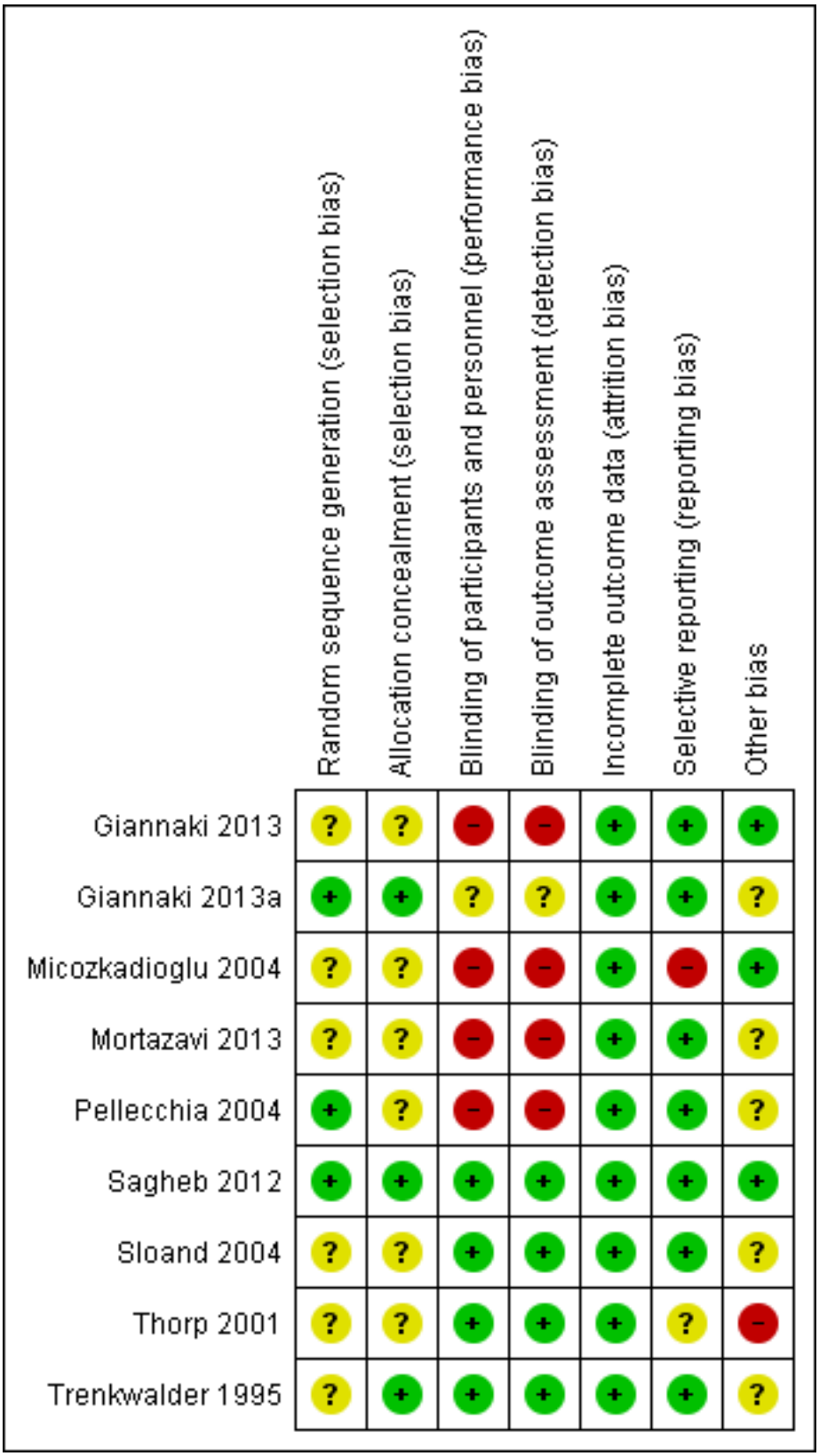
Please see Figure 2; Figure 3. Overall the risk of bias was deemed to be moderate.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Allocation

Randomisation processes were clearly described in three studies (Giannaki 2013a; Pellecchia 2004; Sagheb 2012) whilst others were deemed to have unclear risk of bias.

Allocation concealment was adequate in only three studies (Giannaki 2013a; Pellecchia 2004; Sagheb 2012). The remaining six studies were assessed as unclear due to the lack of information regarding the allocation process.

Blinding

Four studies (Giannaki 2013; Micozkadioglu 2004; Mortazavi 2013; Pellecchia 2004) had high risk of bias due to inadequate blinding. The risk of bias was unclear in Giannaki 2013a as the participants were asked to change the dialysis shifts depending on their allocation, thereby introducing some performance bias. Other studies were deemed to have unclear risk due to lack of information even though they were described as double blinded.

Incomplete outcome data

All of the studies were thought to have low risk for attrition bias as the dropouts were low and all the studies provided details related to dropouts.

Selective reporting

Selective reporting bias in general has been deemed to be low except for one study (Micozkadioglu 2004), where the data has been presented selectively in relation to SF-36 and sleep parameters.

Other potential sources of bias

One study was funded by a pharmaceutical company (Thorp 2001). Funding source was reported in only two other studies (Giannaki 2013; Sagheb 2012).

Effects of interventions

Exercise interventions

Three studies assessed the effect of exercise on the severity of RLS in haemodialysis patients: resistance exercise versus no exercise or ropinirole (Giannaki 2013), resistance exercise versus exercise with no resistance (Giannaki 2013a), and aerobic exercise to no exercise (Mortazavi 2013).

Severity of restless legs syndrome

Giannaki 2013 and Mortazavi 2013 reported a significant reduction in the scores of RLS severity between the exercise group and no exercise group (Analysis 1.1.1 (2 studies, 48 participants): MD -7.56, 95% CI -14.20 to -0.93; I^2 = 65%).

Giannaki 2013a study reported a significant reduction in the scores of severity of RLS in the resistance exercise group when compared to the exercise with no resistance group (Analysis 1.1.2 (1 study, 24 participants): MD -11.10, 95% CI -17.11 to -5.09).

Giannaki 2013 reported no evidence of reduction in the severity scores between the resistance exercise group and ropinirole group (Analysis 1.1.3 (1 study, 22 participants): MD -0.55, 95% CI -6.41 to 5.31).

Quality of Life

Two studies assessed the changes in QOL using SF-36 (Giannaki 2013; Mortazavi 2013)

Giannaki 2013 did not report overall SF-36 scores but presented physical component and mental component summary scores separately. They reported no significant difference in the physical component summary scores (Analysis 1.2.1 (1 study, 24 participants): (MD 5.40, 95% CI -4.82 to 15.62) or mental component summary scores (Analysis 1.3.1 (1 study, 24 participants); MD 6.20, 95% CI -8.54 to 20.94) between the aerobic exercise group and the no exercise group.

Similarly Giannaki 2013 reported no significant difference in the physical component summary scores (Analysis 1.2.2 (1 study, 22 participants): MD -8.60, 95% CI -18.92 to 1.72) or mental component summary scores (Analysis 1.3.2 (1 study 22 participants): MD -14.50, 95% CI -31.58 to 2.58) between the aerobic exercise group and the ropinirole group.

Mortazavi 2013 reported a non-significant improvement in the QOL, however the data presented was not in the standard format and attempts to contact the authors have not been successful.

Quality of sleep

Two studies assessed the quality of sleep (Giannaki 2013; Giannaki 2013a). Giannaki 2013 reported no significant difference in subjective sleep quality at six months for resistance exercise versus no exercise (Analysis 1.4.1 (1 study, 22 participants): MD -1.13, 95% CI -3.71 to 1.45) and resistance exercise and exercise with not resistance (Analysis 1.4.2 (1 study, 24 participants): MD -0.50, 95% CI -2.93 to 1.93). Giannaki 2013 reported a significant improvement in subjective sleep quality in the ropinirole group when compared to resistance exercise group (Analysis 1.4.3 (1 study, 22 participants): MD 3.71, 95% CI 0.89 to 6.53).

Giannaki 2013 reported no significant difference in the Epworth Sleepiness Scale scores when resistance exercise was compared with no exercise (Analysis 1.5.1 (1 study, 22 participants): (MD -0.07, 95% CI -3.47 to 3.33) or ropinirole (Analysis 1.5.3 (1 study, 22 participants): MD 2.07, 95% CI -2.15 to 6.29). Giannaki 2013a reported no significant difference in the Epworth Sleepiness Scale scores between resistance exercise and exercise with no resistance (Analysis 1.5.2 (1 study, 24 participants): MD 0.80, 95% CI -2.42 to 4.02). Mortazavi 2013 did not measure sleep parameters.

Adverse events

Giannaki 2013 and Giannaki 2013a reported there were no adverse events in the study whilst Mortazavi 2013 did not mention if there were any adverse events. In Giannaki 2013, one patient in each group dropped out but the reason for dropout was not reported.

Pharmacological interventions

Severity of restless legs syndrome

Six studies investigated pharmacological intervention for treating RLS: gabapentin versus placebo (Thorp 2001); levodopa versus placebo (Trenkwalder 1995); iron dextran versus placebo (Sloand 2004); vitamin C, vitamin E and placebo in four different combinations (Sagheb 2012); gabapentin versus levodopa (Micozkadioglu 2004); and ropinirole versus levodopa (Pellecchia 2004);

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Gabapentin versus placebo

Thorp 2001 assessed RLS severity at six weeks and at the end of a second treatment period. A non-validated self-administered RLS severity questionnaire based on the criteria developed by IRLSSG was used. The questionnaire consisted of four questions, each with a score ranging from 0 (symptoms never present) to 2 (symptoms constantly present). Eligible participants should have all four criteria with at least two present constantly giving a minimum score of six.

Thorp 2001 reported gabapentin significantly reduced the severity of RLS when compared to placebo (Analysis 2.1.1 (1 study, 26 participants): MD-2.80, 95% CI -4.53 to -1.07).

Levodopa versus placebo

Trenkwalder 1995 used their own RLS severity scoring tool. Participants scored severity of RLS from 0 (no symptoms) to 10 (very strong urge) depending on the urge to move the legs at the time of falling asleep.

Of the recruited 32 adult participants, 28 finished the study and 11 were haemodialysis patients. Results of the haemodialysis patients were reported separately. There was no significant difference in the severity of RLS between levodopa and placebo (Analysis 2.1.2 (1 study, 22 participants): MD -0.90, 95% CI -4.14 to 2.34).

Vitamins C and E versus placebo

Sagheb 2012 assessed RLS severity by IRLSSG RLS scoring tool at baseline and eight weeks. Means of RLS severity score decreased significantly in all vitamin groups compared to placebo: vitamin C (Analysis 2.1.3 (1 study, 30 participants): MD -6.90, 95% CI -9.23 to -4.57); vitamin E (Analysis 2.1.4 (1 study, 30 participants): MD -7.00, 95% CI -10.39 to -3.61); and vitamin C plus vitamin E (Analysis 2.1.5 (1 study, 30 participants): MD -7.20, 95% CI -10.28 to -4.12).

Iron dextran versus normal saline

Sloand 2004 assessed RLS severity by a locally developed (University of Rochester) scoring tool based on three questions each with a score ranging from 0 to 10 at baseline, 1, 2 and 4 weeks post infusion. Baseline median RLS severity score was 9 in the placebo group and 7 in the iron group. The placebo group did not show any difference in the scores at the end of follow-up period. In the iron dextran group, week 1 scores changed by -2 (IQR -6 to -1, P = 0.03), week 2 scores by -3 (IQR -5 to -2, P = 0.01). By week four the effects were no longer significant.

Ropinirole versus levodopa

In Pellecchia 2004 participants reported severity on a tool consisting of a 6-item questionnaire developed by IRLSSG, at the end of six weeks of treatment with each agent. Ropinirole significantly reduced the severity of RLS in the ropinirole group compared to the levodopa group (Analysis 2.1.6 (1 study, 22 participants): MD -6.70, 95% CI -9.96 to -3.44).

Gabapentin versus levodopa

In Micozkadioglu 2004 RLS severity scoring tool consisted of six questions (each with a score ranging from 0 to 4). Both drugs were shown to be effective in reducing the symptoms. Severity score decreased to a median score of 10 in participants treated with Levodopa and to 3 in gabapentin group from a baseline median score of 17 (P < 0.001). Gabapentin was effective in all treated participants whilst Levodopa was effective in 13/14 participants. Contrasting gabapentin, symptoms in levodopa group recurred in a few hours in most of the participants confirming its short duration of action.

Quality of Life

Gabapentin versus placebo

Thorp 2001 did not assess the effect of gabapentin on QOL.

Levodopa versus placebo

Trenkwalder 1995 used 13 visual analogue scales that measured various aspects of QOL. Levodopa was reported to significantly improve general well-being and few other aspects. They reported non-significant improvement in subjective QOL in relation to life satisfaction (Analysis 2.2.1, (1 study, 22 participants): MD 6.80, 95% CI -1.31 to 14.91) and reduction in scores of negative feelings and complaints (Analysis 2.3, (1 study, 22 participants): MD -2.70, 95% CI -11.06 to 5.66).

Vitamins C and E versus placebo

Sagheb 2012 did not assess the effect of vitamins C and E on QOL.

Iron dextran versus normal saline

Sloand 2004 did not assess the effect of iron dextran infusion on QOL.

Ropinirole versus levodopa

Pellecchia 2004 did not assess the effect of either ropinirole or levodopa on QOL.

Gabapentin versus levodopa

Micozkadioglu 2004 reported gabapentin was shown to significantly improve the scores in general health, body pain and social function components of SF-36. They did not report the composite scores.

Quality of sleep

Gabapentin versus placebo

Thorp 2001 did not assess the effect of gabapentin on quality of sleep.

Levodopa versus placebo

Trenkwalder 1995 reported subjective ratings of sleep quality (quality of sleep, nocturnal awakening). Subjective quality of sleep was reported to be significantly better with levodopa compared to placebo (Analysis 2.4.1, (1 study, 22 participants): MD 2.10, 95% CI 0.37 to 3.83).

Vitamins C and E versus placebo

Sagheb 2012 did not assess the effect of intervention of quality of sleep.

Iron dextran versus normal saline

Sloand 2004 did not assess effect of iron dextran infusion on quality of sleep.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Ropinirole versus levodopa

Pellecchia 2004 reported sleep time significantly increased with ropinirole when compared to levodopa (Analysis 2.4.2 (1 study, 22 participants): MD 2.10, 95% CI 0.98 to 3.22).

Gabapentin versus levodopa

Micozkadioglu 2004 reported significant improvement in sleep quality, sleep latency and sleep disturbance with gabapentin when compared with levodopa, however data were not provided.

Adverse events

Gabapentin versus placebo

Two participants in the gabapentin group dropped out due to lethargy. One participant died due to myocardial infarction in the placebo group before gabapentin was administered.

Levodopa versus placebo

Two haemodialysis patients discontinued the study due to reasons not related to the drug use (Wegener's granulomatosis and deterioration in general health).

A total of 33 adverse events were reported in 15 participants but they are not separable between idiopathic RLS group and uraemic RLS group. Nine adverse events were possibly related to levodopa whilst one event was deemed severe (agitation after caffeine intake). Most frequent events were headaches, dry mouth and GI symptoms.

Vitamins C and E versus placebo

Two participants in the vitamin C and vitamin E, one in the vitamin E and placebo, and one in the double placebo group reported nausea during the first week of treatment. One patient in the vitamins C and E, one in the vitamin C and placebo, and one in the vitamin E and placebo group reported dyspepsia during the first two weeks of the treatment.

Iron dextran versus normal saline

Nausea and vomiting occurred in 2/11 participants in the iron group and 3/14 participants in the placebo group. Headache was reported in 2/11 in the iron group.

Ropinirole versus levodopa

In the levodopa group, one participant discontinued the study due to severe vomiting related to the treatment. No adverse events noted in ropinirole group whilst morning rebound was not reported in the other group.

Gabapentin versus levodopa

One participant dropped out from gabapentin group due to symptoms of drowsiness, syncope, and fatigue, thought to be related to the use of gabapentin.

DISCUSSION

Summary of main results

This systematic review included only studies with stable haemodialysis patients as subjects as there were no studies identified in other CKD stages. Our systematic review demonstrated that in small clinical studies, aerobic exercise improved the symptoms of RLS significantly however the safety of this intervention is not clear. The effect of aerobic exercise on sleep quality was not significant.

It is worth noting that in Giannaki 2013a, patients in the exercise group had improved dialysis adequacy at the end of the study period (Kt/V improved from 1.10 ± 0.0 baseline versus 1.25 ± 0.1 post exercise, P = 0.041) when compared to the control group (1.2 ± 0.0 baseline versus 1.2 ± 0.4 post exercise, P > 0.05). As it is known that aerobic exercise improves the dialysis adequacy, and accumulation of uraemic toxins due to poor dialysis adequacy may be implicated in RLS, it is difficult to know if the benefit seen in the exercise group is related to exercise per se or better dialysis adequacy.

Ropinirole was shown to significantly improve the symptoms of RLS, sleep and mental component summary score of SF-36 without any adverse events in two small studies. Gabapentin, even though it improved the symptoms of RLS, is not well tolerated, possibly due to its accumulation in patients with kidney failure. There were more dropouts due to adverse effects in the gabapentin groups. Levodopa also reduced the symptoms of RLS but due to its short acting nature was associated with rebound and augmentation. Iron dextran led to temporary improvement in the symptoms of RLS with minimal side effects. Vitamin C, vitamin E and their combination were shown to improve the symptoms of RLS, however this is a small study and further evidence is needed before recommending these agents.

Overall completeness and applicability of evidence

We planned to find the best intervention to treat RLS in patients with CKD across stages 3 to 5. However our searches did not yield any studies that included patients with stages of CKD other than those who are on haemodialysis. This possibly reflects the ease with which this group of patients could be approached and recruited as they attend in hospital haemodialysis three times a week. Hence, these results are applicable only to haemodialysis patients and cannot be generalised to patients with other stages of CKD.

We wanted to assess the effect of treatment intervention on cardiovascular morbidity and mortality. However none of the studies included these data. Included studies were relatively small in size with a short follow-up duration, which may make it difficult to collect cardiovascular morbidity and mortality data in these studies.

Included studies were conducted in various parts of the world. It is well recognised that the clinical practices related to dialysis therapy differ significantly amongst different centres. Except for one study, there was no data available on parameters related to dialysis such as dialysis adequacy. This will be an important consideration when we try to generalise the results for haemodialysis patients.

Quality of the evidence

The quality of evidence in this review is hampered by the small size of the studies and shorter duration of follow-up and as such it should be interpreted cautiously. Although all of the studies were randomised, the process of randomisation was only described in three studies which were of low risk. Four of the included studies were open-label thereby introducing performance and detection bias.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Potential biases in the review process

We made stringent attempts to limit bias in the review process by ensuring a comprehensive search for potentially eligible studies. Searches were conducted by the Information Specialist based on a pre-defined search strategy. Our independent assessments of eligibility of studies for inclusion in this review and extraction of data minimised the potential for additional bias. We attempted to contact the authors of the studies to obtain all the relevant missing data.

Agreements and disagreements with other studies or reviews

de Oliveira 2010 published a systematic review of the pharmacological treatment for uraemic RLS. The authors opined that only a few therapeutic studies on patients with uraemia with RLS have been published, and there is insufficient scientific evidence to favour any specific therapeutic regimen for uraemia-associated RLS in keeping with our conclusions. The authors concluded that therapy using levodopa, dopaminergic agonists, anticonvulsants, and clonidine may be effective, but further studies were needed. In contrast to our review that included only studies with RLS, de Oliveira 2010 did not differentiate RLS from periodic limb movement disorder and included studies reporting periodic limb movement index.

Since the publication of de Oliveira 2010 review in 2010, four further studies were published, three studies evaluating aerobic exercise (Giannaki 2013; Giannaki 2013a; Mortazavi 2013) and one exploring vitamin C, E and their combination (Sagheb 2012). There was no further expansion of knowledge with regards to pharmacological therapy in this group of patients; however aerobic exercise has been shown to be a potential intervention to treat RLS.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review have limited clinical implications because of the small number of studies with significant heterogeneity. As only haemodialysis patients are included in the studies, these results are not applicable to other stages of CKD. Aerobic exercise appears to be effective in reducing the symptoms of RLS in haemodialysis patients. However this intervention will rely on the physical abilities and motivation of the patients along with conducive environment and resources, which may make it difficult to administer in a non-trial setting. Ropinirole seems to be effective in helping the symptoms of RLS without any side effects in one small study, and this needs to be confirmed in larger studies in the future. As dopamine agonists are used widely in clinical practice to treat RLS, there is a huge need to conduct high quality studies using these agents to establish evidence.

Implications for research

Given the high prevalence of RLS in patients with CKD and lack of high quality clinical studies, further and larger studies exploring pharmacological and non-pharmacological interventions in CKD patients are needed. In the haemodialysis group, intra-dialytic exercise program may help the symptoms of RLS without any major adverse effects and this needs to be verified by a prospective and large sized RCT. There is no evidence for using dopamine agonists to treat RLS in CKD patients, but are used routinely in clinical practice. Ropinirole may be suitable for further assessment.

ACKNOWLEDGEMENTS

We would like to acknowledge the referees for their assessments and suggestions. We would also like to thank the UK Cochrane Centre in Oxford for their support in training and provision of help over the phone or in person. We would like to thank Cochrane and Kidney Transplant's Information Specialists for their help and Sheena Deery for her invaluable advice and suggestions.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

REFERENCES

References to studies included in this review

Giannaki 2013 *{published data only}*

* 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. [MEDLINE: 24024727]

Giannaki 2013a *{published data only}*

* 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. *Nephrology Dialysis Transplantation* 2013;**28**(11):2834-40. [MEDLINE: 23929523]

Micozkadioglu 2004 *{published data only}*

* Micozkadioglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M. Gabapentin versus levodopa for the treatment of restless legs syndrome in hemodialysis patients: an open-label study. *Renal Failure* 2004;**26**(4):393-7. [MEDLINE: 15462107]

Mortazavi 2013 *{published data only}*

* Mortazavi M, Vahdatpour B, Ghasempour A, Taheri D, Shahidi S, Moeinzadeh F, et al. Aerobic exercise improves signs of restless leg syndrome in end stage renal disease patients suffering chronic hemodialysis. *Thescientificworldjournal* 2013;**2013**:628142. [MEDLINE: 24307876]

Mortazavi M, Vahdatpour B, Shahidi S, Ghasempour A, Taheri D, Dolatkhah S, et al. Aerobic exercise improves signs of restless leg syndrome in end stage renal disease patients suffering chronic hemodialysis [abstract]. *Nephrology Dialysis Transplantation* 2012;**27**(Suppl 2):ii281. [EMBASE: 70766123]

Mortazavi M, Vahdatpour B, Shahidi S, Ghasempour A, Taheri S, Ghasami M. The effect of aerobic exercise on the symptoms of restless leg syndrome and quality of life in hemodialysis patients [abstract no: P407]. *Iranian Journal of Kidney Diseases* 2011;**5**(Suppl 2):63-4. [EMBASE: 70673915]

Pellecchia 2004 *{published data only}*

* Pellecchia MT, Vitale C, Sabatini M, Longo K, Amboni M, Bonavita V, et al. Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis: an open randomized crossover trial versus levodopa sustained release. *Clinical Neuropharmacology* 2004;**27**(4):178-81. [MEDLINE: 15319704]

Sagheb 2012 *{published data only}*

Fallahzadeh MK, Akbari H, Sohrabi Nazari S, Sagheb MM. Efficacy of vitamins C, E and their combination for treatment of restless legs syndrome in hemodialysis patients; a randomized, double-blind, placebo-controlled trial [abstract no: 404]. *Iranian Journal of Kidney Diseases* 2011;**5**(Suppl 2):22-3. [EMBASE: 70673845]

* Sagheb MM, Dormanesh B, Fallahzadeh MK, Akbari H, Sohrabi NS, 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 Medicine* 2012;**13**(5):542-5. [MEDLINE: 22317944]

Sloand 2004 *{published data only}*

Halterman MW, Sloand JA. An update on the use of intravenous iron for the treatment of restless legs syndrome in end stage renal disease [Actualizacion sobre el uso de hierro intravenoso para el tratamiento del sindrome de piernas inquietas asociado a insuficiencia renal terminal]. *Salud(i)Ciencia* 2007;**15**(5):860-5. [EMBASE: 2007548364]

* Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD. A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *American Journal of Kidney Diseases* 2004;**43**(4):663-70. [MEDLINE: 15042543]

Thorp 2001 *{published data only}*

* Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *American Journal of Kidney Diseases* 2001;**38**(1):104-8. [MEDLINE: 11431189]

Trenkwalder 1995 *{published data only}*

* Trenkwalder C, Stiasny K, Pollmacher 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. [MEDLINE: 8560135]

Wetter TC, Trenkwalder C, Pollmacher T, Stiasny K, Kohnen R, Kazenwadel J, et al. Effect of levodopa therapy of idiopathic and uremic restless legs syndrome: a double blind crossover trial [abstract]. *Journal of Neurology* 1995;**242**(6 Suppl 2):S81. [CENTRAL: CN-00507525]

Wetter TC, Trenkwalder C, Stiasny K, Pollmacher T, Kazenwadel J, Kohnen R, et al. Treatment of idiopathic and uremic restless legs syndrome with L-dopa--a double-blind cross-over study [Behandlung des idiopathischen und uramischen restless-legs-syndrom mit L-Ddpa--eine doppelblinde cross-over-studie]. *Wiener Medizinische Wochenschrift* 1995;**145**(17-18):525-7. [MEDLINE: 8588396]

References to studies excluded from this review

Ausserwinkler 1989 *{published data only}*

Ausserwinkler M, Schmidt P. Clonidine is effective in the treatment of 'restless leg' syndrome in chronic uraemic patients [abstract]. *Nephrology Dialysis Transplantation* 1988;**3**(4):530. [CENTRAL: CN-00260393]

Ausserwinkler M, Schmidt P. Successful clonidine treatment of restless leg syndrome in chronic kidney insufficiency [Erfolgreiche behandlung des "restless legs"-syndroms bei chronischer Niereninsuffizienz mit clonidin]. *Schweizerische*

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Medizinische Wochenschrift [Journal Suisse de Medicine] 1989;**119**(6):184-6. [MEDLINE: 2928741]

Facchini 2004 *{published data only}*

Facchini MG, Mambelli E, Checchia G, Balboni M, Bainotti S, Santoro A. Lorenz therapy™ a new treatment of uremic neuropathy [abstract no: SU-PO379]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):616A. [CENTRAL: CN-00583895]

Facchini MG, Mambelli E, Checchia G, Gaggi R, Santoro A. The Lorenz™ therapy: a new tool in the treatment of uremic neuropathy [abstract]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon, Portugal. 2004:375. [CENTRAL: CN-00509181]

FINESSE Study 2010 *{published data only}*

Jardine M, Krishnan A, Gallagher M, Snelling P, Hawley C, Pussell B, et al. Uraemic neuropathy remains ubiquitious: rationale and feasibility of the FINESSE (Filtration in the Neuropathy of End Stage kidney disease Symptom Evolution) trial [abstract no: 235]. *Nephrology* 2010;**15**(Suppl 4):88. [EMBASE: 70467239]

Kramer 1988 *{published data only}*

Kramer G, Suss W, Kohler H, Schneider B, Hopf HC. Ganglioside therapy in uremic polyneuropathy [Gangliosid-therapie der uramischen polyneuropathie]. *Medizinische Klinik* 1988;**83**(1):7-11. [MEDLINE: 3352557]

N0203077917 *{published data only}*

Bingham C. Pergolide for restless legs in uraemia. www.nihr.ac.uk/Profile/Pages/NRRResults.aspx?publication_id=N0203077917 (link no longer active) 2002.

Okada 2000 *{published data only}*

Okada H, Moriwaki K, Kanno Y, Sugahara S, Nakamoto H, Yoshizawa M, et al. Vitamin B6 supplementation can improve peripheral polyneuropathy in patients with chronic renal failure on high-flux haemodialysis and human recombinant erythropoietin. *Nephrology Dialysis Transplantation* 2000;**15**(9):1410-3. [MEDLINE: 10978399]

Pieta 1998 *{published data only}*

Pieta J, Millar T, Zacharias J, Fine A, Kryger M. Effect of pergolide on restless legs and leg movements in sleep in uremic patients. *Sleep* 1998;**21**(6):617-22. [MEDLINE: 9779521]

Sprenger 1983 *{published data only}*

Sprenger KB, Bundschu D, Lewis K, Spohn B, Schmitz J, Franz HE. Improvement of uremic neuropathy and hypogeusia by dialysate zinc supplementation: a double-blind study. *Kidney International - Supplement* 1983;**16**:S315-8. [MEDLINE: 6330425]

Walker 1996 *{published data only}*

Walker SL, Fine A, Kryger MH. L-DOPA/carbidopa for nocturnal movement disorders in uremia. *Sleep* 1996;**19**(3):214-8. [MEDLINE: 8723378]

References to studies awaiting assessment

NCT00996944 *{published data only}*

NCT00996944. Clinical evaluation of ropinirole IR (immediate release) tablets in patients who are diagnosed with symptomatic restless legs syndrome (RLS) associated with chronic kidney disease (CKD) managed with haemodialysis (including haemofiltration and haemodiafiltration). www.clinicaltrials.gov/ct2/show/study/NCT00996944 (accessed 21 July 2016).

NCT01537042 *{published data only}*

NCT01537042. A sleep laboratory study to investigate the safety and efficacy of the rotigotine skin patch in subjects with restless legs syndrome and end-stage renal disease requiring hemodialysis. www.clinicaltrials.gov/ct2/show/NCT01537042 (accessed 21 July 2016).

NCT02011191 *{published data only}*

Moretti H. Biotin deficiency and restless legs syndrome: evidence for a causal relationship from randomized, double-blind, placebo-controlled trial. www.clinicaltrials.gov/ct2/show/NCT02011191 (accessed 21 July 2016).

Razazian 2015 *{published data only}*

Razazian N, Azimi H, Heidarnejadian J, Afshari D, Ghadami MR. Gabapentin versus levodopa-c for the treatment of restless legs syndrome in hemodialysis patients: a randomized clinical trial. *Saudi Journal of Kidney Diseases & Transplantation* 2015;**26**(2):271-8. [MEDLINE: 25758874]

Additional references

Agarwal 2011

Agarwal P, Sia C, Vaish N, Roy-Faderman I. Pilot trial of onabotulinumtoxina (Botox) in moderate to severe restless legs syndrome. *International Journal of Neuroscience* 2011;**121**(11):622-5. [MEDLINE: 21740308]

Akpinar 1982

Akpinar S. Treatment of restless legs syndrome with levodopa plus benserazide. *Archives of Neurology* 1982;**39**(11):739. [MEDLINE: 7126008]

Al-Jahdali 2009

Al-Jahdali HH, Al-Qadhi WA, Khogeer HA, Al-Hejaili FF, Al-Ghamdi SM, Al Sayyari AA. Restless legs syndrome in patients on dialysis. *Saudi Journal of Kidney Diseases & Transplantation* 2009;**20**(3):378-85. [MEDLINE: 19414938]

Allen 2003

Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Medicine* 2003;**4**(2):101-19. [MEDLINE: 14592341]

de Oliveira 2010

de Oliveira MM, Conti CF, Valbuza JS, de Carvalho LB, do Prado GF. The pharmacological treatment for uremic restless

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

legs syndrome: evidence-based review. *Movement Disorders* 2010;**25**(10):1335-42. [MEDLINE: 20544816]

Ekbom 1945

Ekbom K. Restless legs. *Acta Medica Scandinavica* 1945;**121**(S158):7-123.

Giannaki 2010

Giannaki CD, Sakkas GK, Hadjigeorgiou GM, Karatzaferi C, Patramani G, Lavdas E, et al. Non-pharmacological management of periodic limb movements during hemodialysis session in patients with uremic restless legs syndrome. *ASAIO Journal* 2010;**56**(6):538-42. [MEDLINE: 21245801]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hornyak 2014

Hornyak M, Scholz H, Kohnen R, Bengel J, Kassubek J, Trenkwalder C. What treatment works best for restless legs syndrome? Meta-analyses of dopaminergic and non-dopaminergic medications.[Erratum appears in Sleep Med Rev. 2014 Aug;18(4):367-8]. *Sleep Medicine Reviews* 2014;**18**(2):153-64. [MEDLINE: 23746768]

Kavanagh 2004

Kavanagh D, Siddiqui S, Geddes CC. Restless legs syndrome in patients on dialysis. *American Journal of Kidney Diseases* 2004;**43**(5):763-71. [MEDLINE: 15112166]

La Manna 2011

La Manna G, Pizza F, Persici E, Baraldi O, Comai G, Cappuccilli ML, et al. Restless legs syndrome enhances cardiovascular risk and mortality in patients with end-stage kidney disease undergoing long-term haemodialysis treatment. *Nephrology Dialysis Transplantation* 2011;**26**(6):1976-83. [MEDLINE: 21056943]

Lee 2016

Lee DO, Buchfuhrer MJ, Garcia-Borreguero D, Avidan AY, Ahmed M, Hays R, et al. Efficacy of gabapentin enacarbil in adult patients with severe primary restless legs syndrome. *Sleep Medicine* 2016;**19**:50-6. [MEDLINE: 27198947]

Manley 2003

Manley HJ, McClaran ML, Overbay DK, Wright MA, Reid GM, Bender WL, et al. Factors associated with medication-related problems in ambulatory hemodialysis patients. *American Journal of Kidney Diseases* 2003;**41**(2):386-93. [MEDLINE: 12552501]

Mucsi 2005

Mucsi I, Molnar MZ, Ambrus C, Szeifert L, Kovacs AZ, Zoller R, et al. Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. *Nephrology Dialysis Transplantation* 2005;**20**(3):571-7. [MEDLINE: 15671074]

Sun 1998

Sun ER, Chen CA, Ho G, Earley CJ, Allen RP. Iron and the restless legs syndrome. *Sleep* 1998;**21**(4):371-7. [MEDLINE: 9646381]

Walters 1995

Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Movement Disorders* 1995;**10**(5):634-42. [MEDLINE: 8552117]

Walters 2010

Walters A, Rye D. Evidence continues to mount on the relationship of restless legs syndrome/periodic limb movements in sleep to hypertension, cardiovascular disease, and stroke. *Sleep* 2010;**33**(3):287. [MEDLINE: 20337185]

Winkelmann 2001

Winkelmann J, Schadrack J, Wetter TC, Zieglgansberger W, Trenkwalder C. Opioid and dopamine antagonist drug challenges in untreated restless legs syndrome patients. *Sleep Medicine* 2001;**2**(1):57-61. [EMBASE: 2001086037]

References to other published versions of this review

Gopaluni 2013

Gopaluni S, Sherif M, Ahmadouk NA. Interventions for chronic kidney disease-associated restless legs syndrome. *Cochrane Database of Systematic Reviews* 2013, Issue 9. [DOI: 10.1002/14651858.CD010690]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Giannaki 2013

Methods	• Study design: parallel placebo-controlled RCT • Study duration: September 2007 to October 2009 • Study follow-up period: 6 months
Participants	• Country: Greece

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Giannaki 2013 *(Continued)*

- Setting: single centre
- Health status: stable adult HD patients; specialist neurologist diagnosed patients with RLS using IRLSSG criteria
- Number: 32; treatment group 1 (16); treatment group 2 (8), control group (8)
- Mean age ± SD (years): treatment group 1 (56.4 ± 12.5); treatment group 2 (55.7 ± 10.4); control group (56.8 ±16.5)
- Sex (M/F): treatment group 1 (11/4); treatment group 2 (4/3); control group (5/2)
- Exclusion criteria: diagnosed neuropathies (3, clinically examined by a neurologist); catabolic state (2, opportunistic infections and active inflammation); within 3 months prior to the start of the study CRP > 3.0 mg/L (1); unable to exercise (3); refusal to participate for personal reasons (4)

Interventions	Treatment group 1 • Progressive aerobic exercise training (recumbent cycling) at an intensity of 60% to 65% of patient's maximal exercise capacity for 45 minutes during HD session 3 times/wk for a 6 month period Treatment group 2 • Ropinirole 0.25 mg in an identical capsule to that of placebo, 2 hours before bed daily for 6 months Control group • Placebo (plain flour) in a similar capsule, to be taken 2 hours before bed daily for 6 months. Co-interventions • None
Outcomes	• RLS severity using IRLSSG severity rating scale • Sleep quality: weekly sleep diary (adapted from University of Massachusetts Medical School) • QOL - SF36 • Lean body mass • Physical performance • Depression score using self rated Zung questionnaire
Notes	• Funding source: Supported by the National and Community Funds of the Greek Ministry of Development - General Secretariat of Research and Technology and by the European Social Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised 2:1:1 but no details of how the randomisation was done
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Physical intervention versus drug (double blinded in the placebo versus ropinirole arms)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients aware of the intervention in physical versus drug groups
Incomplete outcome data (attrition bias)	Low risk	One patient withdrew from each group (transplantation (2); chronic infection (1)

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Giannaki 2013 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	All results of parameters assessed were clearly detailed. However, the reasons for dropouts were not specified; stated only that it was for reasons unrelated to the study
Other bias	Low risk	Government funding

Giannaki 2013a

Methods	• Study design: single blinded (participant) parallel RCT • Study duration: September 2006 to July 2010 • Study follow-up period: 6 months
Participants	• Country: Greece • Setting: 2 outpatient HD centres • Health status: stable adult HD patients with RLS diagnosed by IRLSSG questionnaire; participants on dialysis for ≥ 3 months with adequate dialysis delivery (Kt/V) and with stable clinical condition; none of the recruited patients were engaged in any systematic exercise training program prior to recruitment • Number: treatment group (12); control group (12) • Mean age ± SD (years): treatment group (59.2 ± 11.8); control group (58.0 ± 10.7) • Sex (M/F): treatment group: (9/3); control group (8/4) • Exclusion criteria: diagnosed neuropathies; reasons for being in a catabolic state within 3 months prior to the start of the study; unable to exercise
Interventions	Treatment group • Progressive aerobic exercise training (pedalling cycle ergometer at 50 revolutions/min) at an intensity of 60% to 65% of patient's maximal exercise capacity for 45 minutes during HD session 3 times/wk for a 6 month period • Participated under the supervision of a trained exercise physiotherapist Control group • Exercise with no resistance (pedalling cycle ergometer at 50 revolutions/min) for 45 minutes during HD session 3 times/wk for a 6 month period • Participated under the supervision of a trained exercise physiotherapist Co-interventions • None of the participants received any medication for RLS prior to the study
Outcomes	• Change in IRLS severity score • Sleep quality • Daily sleepiness • Depression score
Notes	• Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using customised randomisation software

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Giannaki 2013a *(Continued)*

Allocation concealment (selection bias)	Low risk	Used randomisation software
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Even though patients belonging to different groups dialysed on different days, the nature of the intervention (resistance vs exercise with no resistance) would make it easy for the participants to know which arm they have been randomised to
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Patients may have been influenced by the knowledge of their intervention when reporting the outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals in the study
Selective reporting (reporting bias)	Low risk	A number of exercise sessions were reported as incomplete (patients were unable to complete the full 45 min cycling). Reasons for this were stated as personal reasons. Those instances were not systematically recorded and, hence, authors were unable to indicate the level of compliance clearly. The authors gauged compliance as very high
Other bias	Unclear risk	Funding source not reported

Micozkadioglu 2004

Methods	• Study design: open-label crossover RCT • Study duration: not reported • Study follow-up period: 10 weeks (4 weeks of first drug, 2 weeks wash out period and 4 weeks of second drug)
Participants	• Country: Turkey • Setting: outpatient dialysis centre • Health status: stable adult HD patients identified as having RLS according to IRLSSG criteria; patients agreed not to take any psychotropic drugs at least 2 weeks before baseline and during the study • Number: 15 • Mean age ± SD: 45.8 ± 15.3 years • Sex (M/F): 10/5 • Exclusion criteria: not reported
Interventions	Treatment group • Gabapentin 200 mg orally after dialysis (3 times/wk) for 4 weeks Control group • Levodopa 125 mg/d, 2 hours before sleep for 4 weeks Co-interventions • None
Outcomes	• RLS severity at 0, 4, 10 weeks using a six point severity scale (unclear if the questionnaire is validated or not) • QOL (SF-36)

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Micozkadioglu 2004 *(Continued)*

	• Adverse events reported
Notes	• Funding source unclear but no pharmaceutical support • Waiting for email reply regarding randomisation and allocation methods • Severity scores given in median and range

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Patients and study personnel were aware of the type of intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 patient excluded (due to medication side effect)
Selective reporting (reporting bias)	High risk	Selectively reported three domains of SF-36; data not provided to support conclusions reached with regard to sleep parameters
Other bias	Low risk	Funding source: "There was no pharmaceutical industry support of this study"

Mortazavi 2013

Methods	• Study design: open-label parallel RCT • Study duration: not reported • Study follow-up period: 16 weeks
Participants	• Country: Iran • Setting: 2 HD centres • Health status: stable adult HD patients receiving 3 times/wk with a diagnosis of RLS according to IRLSSG criteria; participants on HD for at least 3 months; sufficient dialysis for at least 3 times/wk; ferritin > 100 ng/mL; TSAT > 20% • Number: treatment group (13) control group (13) • Mean age ± SD (years): treatment group (32.3 ± 6.7); control group (47.1 ± 13.1) • Sex (M/F): 18/8; no split data between the groups provided • Exclusion criteria: musculoskeletal disorders causing physical disability; history of ischaemic heart disease (recent myocardial infarction or unstable angina); any catabolic process such as malignancies, opportunistic infections, and infections needing antibiotic therapy during the last 3 months
Interventions	Treatment group

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Mortazavi 2013 *(Continued)*

	• Aerobic exercise: pedalling Medi-Bike continuously for 30 min between 2nd and 3rd hours during dialysis, 3 times/wk for 16 weeks * First 5 min after starting, participants had warm-up time and last 5 min they had cool-down time Control group • No treatment Co-interventions • None
Outcomes	• Severity of RLS using RLS questionnaire performed at 0 and 16 weeks • QOL questionnaire (SF-36) performed at 0 and 16 weeks • No information on adverse effects
Notes	• Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available
Selective reporting (reporting bias)	Low risk	Outcome in question was reported (severity of RLS)
Other bias	Unclear risk	Funding source not mentioned

Pellecchia 2004

Methods	• Study design: open-label crossover RCT • Study duration: not reported • Study follow-up period: 14 weeks including 1 week screening and 1 week washout period
Participants	• Country: Italy • Setting: outpatient HD centre • Health status: stable adult HD patients receiving 3 times/wk dialysis with a diagnosis of RLS established according to IRLSSG criteria; patients agreed not to take any psychotropic drug (e.g. levodopa

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Pellecchia 2004 *(Continued)*

	SR, dopamine agonists, antidepressants, and neuroleptics) at least 1 month before baseline evaluation • Number: 11 • Mean age ± SD: 56.2 ± 8.7 years • Sex (M/F): 7/4 • Exclusion criteria: patients with clinically significant orthostatic hypotension; unstable medical condition including serious cardiovascular, pulmonary, hepatic, or psychiatric disease; concurrent or past diagnosis of malignant melanoma
Interventions	Treatment group • Ropinirole, 0.25 mg/d orally doubled every 5 days to a maximum dose of 2 mg/d for a period of 6 weeks • 1 week washout period before switch to alternate therapy Control group • Levodopa SR 25/100 mg once/d orally, doubled to a maximum of 50/200 mg once/d after 2 weeks, for a period of 6 weeks Co-interventions • None
Outcomes	• Reduction in severity of RLS scores (IRLSSG: 0 to 24) at baseline, 6 weeks and at end of study • Adverse events
Notes	• Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	Unclear risk	Open label
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adverse events were clearly stated
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Unclear risk	Funding source not reported

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sagheb 2012

Methods	• Study design: 4-arm parallel RCT • Study duration: March 2008 to February 2009 • Study follow-up period: 8 weeks
Participants	• Country: Iran • Setting: HD centre • Health status: chronic stable adult HD patients with RLS diagnosed using IRLSSG questionnaire • Number: treatment group 1 (15); treatment group 2 (15); treatment group 3 (15); control group (15) • Mean age ± SD (years): treatment group 1 (47.4 ± 14.2); treatment group 2 (54.6 ± 15.2); treatment group 3 (49.3 ± 12.9); control group (59.5 ± 17.9) • Sex (M/F): treatment group 1 (6/9); treatment group 2 (6/9); treatment group 3 (4/11); control group (9/6) • Exclusion criteria: participants receiving medications known to aggravate RLS such as tricyclic antidepressants, selective serotonin reuptake inhibitors, dopamine antagonists, dopamine blocking antiemetics, lithium, and sedative antihistamines; history of kidney stones were excluded due to concerns over increased risk of oxalosis and its joint and vascular complications in HD patients who consume vitamin C
Interventions	Treatment group 1 • Vitamin C 200 mg + Vitamin E 400 mg for 8 weeks Treatment group 2 • Vitamin C 200 mg + placebo for 8 weeks Treatment group 3 • Vitamin E 400 mg + placebo for 8 weeks Control group • Placebo for 8 weeks Co-interventions • None
Outcomes	• Severity of RLS at 0 and 8 weeks and the change in the score using IRLSG scoring system (0 to 40 max) • Adverse events
Notes	• Funding source: grant from the Shiraz University of Medical Sciences, Shiraz, Iran

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation with a fixed block size of four by randomisation sequence generator
Allocation concealment (selection bias)	Low risk	1:1:1:1 random assignment to the 4 groups; this was done by an investigator who had no clinical involvement in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sagheb 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Used random sequence generating software
Selective reporting (reporting bias)	Low risk	Clear reporting of side effects. Study protocol clear enough from the methods section
Other bias	Low risk	Funded by a Grant from the Shiraz University of Medical Sciences, Shiraz, Iran

Sloand 2004

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up period: 4 weeks
Participants	• Country: USA • Setting: dialysis centre in Rochester, USA • Health status: stable adult HD and PD (3 in placebo group) diagnosed with RLS; concurrent medications used to treat RLS were not discontinued or tapered, but new medications, including oral iron, could not be added within 1 month before entry into this study and the dosage of medications used to treat RLS could not be changed within this period or during the study • Number: treatment group (11); control group (14) • Mean age ± SD (years): treatment group (55.8 ± 11); control group (54.3 ± 3.7) • Sex (M/F): treatment group (6/5); control group (10/4) • Exclusion criteria: childbearing potential; severe liver disease; polycythaemia or evidence for haemochromatosis; a history of 10 or more blood transfusions during the 2 years before the study; history of hypersensitivity to IV iron; receipt of any IV iron within 1 month of enrolment; weight < 50 kg; URR < 65% (unless kinetic modelling using Kt/V was > 1.2); a change in dialysis prescription within 3 months of entry; fistula recirculation > 12%; active inflammatory or rheumatologic disease
Interventions	Treatment group • IV iron dextran 1000 mg IV diluted in 500 mL on dialysis (administered only once during the study period) Control group • 500 mL of normal saline infused during dialysis (administered only once during the study period) Both placebo and drug were infused during dialysis by infusion pump with the medication (or placebo) and tubing covered with an opaque obscuring sleeve so that neither the patient, investigator, nor study nurse could detect which was being administered
Outcomes	• RLS severity assessed by a non-validated questionnaire at 0, 1, 2, 4 weeks (scores range from 0 to 10) • Multiple other lab parameters such as haemoglobin, iron stores were measured • Adverse events
Notes	• Funding source not reported
Risk of bias	

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Sloand 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear mention of the randomisation process
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both placebo and drug were infused during dialysis by infusion pump with the medication (or placebo) and tubing covered with an opaque obscuring sleeve so that neither the patient, investigator, nor study nurse could detect which was being administered
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients were blinded to the treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available
Selective reporting (reporting bias)	Low risk	Protocol not available but published report contained expected outcome (Improvement in RLS severity) Side effects were also reported
Other bias	Unclear risk	Funding source not reported

Thorp 2001

Methods	• Study design: double blind crossover RCT • Study duration: not reported • Study follow-up period: 13 weeks (6 weeks of treatment with first agent, 1 week washout period and 6 weeks of treatment with second agent)
Participants	• Country: USA • Setting: HD centre in Portland Veterans Affairs Medical centre, Portland, USA • Health status: stable chronic adult HD patients with RLS diagnosed according to criteria similar to the current IRLSSG criteria • Number: 16 • Mean age ± SD: 64.1 ± 5.9 years • Sex (M/F): 15/1 • Exclusion criteria: participants with other cause of leg discomfort on neurological examination
Interventions	Treatment group • Gabapentin 300 mg orally at the end of dialysis (3 times/wk) for 6 weeks Control group • Placebo similar to gabapentin administered orally at the end of dialysis (3 times/wk) for 6 weeks Treatment administered under the direct supervision on nurse at the end of dialysis treatment. One week washout period between 2 treatments

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Thorp 2001 *(Continued)*

Outcomes	• RLS severity assessed by non-validated Questionnaire at 0, 6, 13 weeks
Notes	• Funding source: Drug was supplied by Pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear mention how randomised
Allocation concealment (selection bias)	Unclear risk	Method of concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, nurses, and physicians were blinded to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessments (questionnaires) were carried out while subjects and staff were still blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clearly mention drop outs and withdrawals with specified reasons
Selective reporting (reporting bias)	Unclear risk	No study protocol but expected outcome (improvement in severity of RLS) is clearly discussed
Other bias	High risk	"Gabapentin was supplied by Parke-Davis Pharmaceuticals"

Trenkwalder 1995

Methods	• Study design: crossover RCT • Study duration: not reported • Study follow-up period: 8 weeks (unclear if there was a washout period)
Participants	• Country: Germany • Setting: Department of Neurology in the Klinikum Grosshadern • Health status: participants both with idiopathic RLS and with uraemic RLS were included (criteria for RLS similar to IRLSSG criteria); more than 5 PLM related -arousals/h of sleep; sleep latency of more than 25 min; sleep efficiency index < 85% in addition to symptoms of RLS • Number: 11 (patients with uraemic RLS out of a total of 32 patients in the study) • Mean age ± SD: 49 ± 11 years • Sex (M/F): 6/5 • Exclusion criteria: patients with signs of any other sleep disorder on polysomnography, especially narcolepsy and sleep apnoea syndrome; receiving neuroleptic or antidepressant medications; any severe additional illness or history of drug abuse; pregnant or lactating women and women without safe contraceptive methods
Interventions	Treatment group • Madopar (L-dopa 100 mg + benserazide 25 mg) given orally 1 hour before bedtime for 4 weeks; dose could be doubled after 2 weeks

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Trenkwalder 1995 *(Continued)*

	Control group • Placebo given orally 1 hour before bedtime for 4 weeks Co-interventions • None
Outcomes	• Polysomnographic studies • Actigraphy • Subjective rating (using modified 50-mm Hamburger VAS) • Physician's rating (CGI) • Safety evaluation for rate of side effects of medications
Notes	• Funding source not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on the randomisation procedure
Allocation concealment (selection bias)	Low risk	Double blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No clear statement of blinding of outcome assessment, but assessments of outcome (polysomnographic studies, Actigraphy, subjective rating and physician's rating) were carried out at different points of the study while participants and investigators were still blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data regarding different assessment methods were clearly shown and data regarding both groups (idiopathic versus uraemic RLS) were clearly shown
Selective reporting (reporting bias)	Low risk	No protocol but outcomes (improvement in RLS) assessment clearly outlined
Other bias	Unclear risk	Funding source not reported

CGI - clinical global impression; CRP - C-reactive protein; HD - haemodialysis; IRLSSG - International RLS Study group; M/F - male/female; PD - peritoneal dialysis; QOL - quality of life; RCT - randomised controlled trial; RLS - restless legs syndrome; SD - standard deviation; SF-36 - short form 36 question survey; TSAT - transferrin saturation; URR - urea reduction ratio; VAS - visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ausserwinkler 1989	Wrong population: participants with uraemic polyneuropathy which is a sensorimotor polyneuropathy caused by uraemic toxins

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Facchini 2004	Wrong population: participants with uraemic polyneuropathy which is a sensorimotor polyneuropathy caused by uraemic toxins
FINESSE Study 2010	Wrong population: participants with uraemic polyneuropathy which is a sensorimotor polyneuropathy caused by uraemic toxins
Kramer 1988	It was a study of uraemic neuropathy, which is a sensorimotor polyneuropathy caused by uraemic toxins and it can be a cause for secondary RLS which is one of our exclusion criteria
N0203077917	No data has been published since the study was first registered in the UK in 2002
Okada 2000	It was a study of uraemic neuropathy, which is a sensorimotor polyneuropathy caused by uraemic toxins and it can be a cause for secondary RLS which is one of our exclusion criteria
Pieta 1998	It was a study of periodic limb movement disorder and not RLS, so excluded
Sprenger 1983	Wrong population: participants with uraemic polyneuropathy which is a sensorimotor polyneuropathy caused by uraemic toxins
Walker 1996	The primary outcome was measured objectively using polysomnography and there were no data on subjective improvement

RLS - restless legs syndrome

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00996944

Methods	• Parallel RCT • Subjects completing the screening period will be randomised (1:1) to receive ropinirole immediate release (IR) or placebo for 12 weeks.
Participants	• Male and female patients aged 18 to 79 years • Inclusion criteria at week -1 (at the screening visit): patients who are diagnosed with symptomatic restless legs syndrome associated with CKD managed with haemodialysis. RLS are diagnosed based on the IRLSSG diagnostic criteria.QTc criteria. Patients with QTc < 450 msec or < 480 msec for patients with bundle branch block • Exclusion criteria at week -1 (at the screening visit): signs of primary RLS; sleep disorder not associated with RLS (narcolepsy, sleep terror disorder, sleepwalking disorder, breathing related sleep disorder; complication of movement disorder; severe hepatic/cardiac/pulmonary disorder or haematopoietic disorder other than those on haemodialysis (including haemofiltration and haemodiafiltration); history of malignancies within the past 5 years, with the exception of basal cell carcinoma or carcinoma in situ of cervix; medical history or complication of substance abuse; supine systolic blood pressure(SBP) < 100 mm Hg or >190 mm Hg or supine diastolic blood pressure (DBP) ≥ 120 mm Hg before the dialysis; intolerant to ropinirole hydrochloride (HCl) or other dopamine agonists or ropinirole HCl or other dopamine agonists are considered to be of safety concern by the investigator/sub-investigator; history of augmentation or end-of-dose-rebound in the early morning after medications of dopamine agonists (including ropinirole HCl) and/or L-dopa; without night time sleeping habit (e.g. night-shift worker) and those who must drastically change the habitual bedtime during the study duration; participated in another clinical study of an investigational product or medical device within the last 12 weeks prior to the start of the screening period; pregnant or lactating, who may be pregnant, or who plan for pregnancy during the study; current or chronic history of liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones); presence of HBsAG, positive hepatitis C test result within 3 months of screening; medical conditions which could affect efficacy and safety assessment; unable to discontinue prohibited medications during the screening peri-

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

NCT00996944 *(Continued)*

	od; will imminently receive a transplant; changed the dose or administration method of anxiolytics or hypnotics and sedatives within the last 4 weeks prior to the start of the screening period, and/or patients who used more than two drugs; others whom the investigator/sub-investigator considers ineligible for the study. • Exclusion criteria at week 0 (start of the treatment period): supine SBP of < 100 mm Hg or > 190 mm Hg or supine DBP of ≥120 mm Hg before the dialysis at Week 0; started treatment with medications including an oestrogen drug product, anxiolytics, hypnotics and sedatives or who have changed the dose or administration method of such medications between week -1 (start of the screening period) and week 0 (start of the treatment period); serum ferritin level is < 10 µg/L (ng/mL) at the screening visit
Interventions	Treatment group • The treatment with IR will be started at the initial dose of 0.25 mg/d within 1 to 3 hours before bedtime. The maximum available dose is 3 mg/d. For all subjects completing short-term period and entering the long-term treatment period, the open-label treatment will be started from IR 0.25 mg/d regardless of dose levels during short-term period. The dose will be upward titrated from 0.25 mg/d to 0.5 mg/d and after that in increments of 0.5 mg/d until sufficient efficacy is obtained (targeting "much improved" or "very much improved" in the CGI-Improvement scores without safety/tolerability problem Control group • Matching placebo to IR in the double-blind treatment period. All participants completing the double-blind treatment period were eligible to continue in the open-label long-term treatment period. In the open-label period, participants received ropinirole IR tablets in the same way as in the ropinirole IR-ropinirole IR group.
Outcomes	• IRLS rating scale at week 0 and week 12 • Number with the indicated CGI-improvement scores at week 12 • RLS-QOL • PSQI • Mean daily number of hours of RLS symptoms • Drug clearance rate on-dialysis and off-dialysis
Notes	• This study was prematurely terminated after 5 months had passed since its initiation, because GlaxoSmithKline concluded that it was impossible to recruit sufficient participants within a reasonable timeframe. In this study, no participants had completed. The maximum duration was 24 weeks plus follow-up (up to week 64) • Some data available on ClinicalTrials.gov

NCT01537042

Methods	• Study design: parallel multicentre RCT
Participants	• Male and female patients aged 18 to 85 years • Inclusion criteria: ESKD requiring haemodialysis. Diagnosis of RLS based on the 4 cardinal diagnostic clinical features according to the IRLSSG. Initial response to previous dopaminergic treatment for RLS, or has had no previous dopaminergic treatment (ie, de novo). Score of ≥ 15 points on the IRLS (indicating moderate to severe RLS) at baseline score of ≥ 11 points on the RLS-Diagnostic Index at baseline score of ≥ 4 points on the CGI Item 1 assessment (indicating moderately ill) at baseline. Scores ≥ 15 PLM/h on the PLMI based on polysomnography (recorded during the second night) as assessed by the investigator at Baseline. • Exclusion criteria: clinically relevant polyneuropathy or varicosis which cannot be clearly differentiated from RLS symptoms in the opinion of the investigator; clinically relevant concomitant diseases; other central nervous system diseases; evidence of an impulse control disorder according to the modified Minnesota Impulsive Disorders Interview; lifetime history of suicide attempt, or

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

NCT01537042 *(Continued)*

	has suicidal ideation in the past 6 months; prior history of psychotic episodes; history of symptomatic (not asymptomatic) orthostatic hypotension; clinically relevant CVD; clinically relevant venous or arterial peripheral vascular disease malignant neoplastic disease requiring therapy within 12 months of visit 1; treatment with any of the following drug classes: neuroleptics, norepinephrine and dopamine reuptake inhibitors, gabapentin, budipine, dopamine antagonist antiemetics (except domperidone), opioids, monoamine oxidase (MAO) inhibitors, `catechol-O-methyltransferase` inhibitors, or psychostimulants; pregnancy, nursing, childbearing potential who is not surgically sterile, 2 years postmenopausal, or does not use 2 combined effective methods of contraception; previous treatment with dopamine agonists within a period of 14 days prior to baseline, or L-dopa within 7 days prior to baseline; medical history indicating intolerability to dopaminergic therapy (if pretreated) or has experienced augmentation when previously treated with any dopaminergic agent; subject has received previous treatment with rotigotine; known hypersensitivity to any of the components of the study medication, such as a history of significant skin hypersensitivity to adhesives, known hypersensitivity to other transdermal medications, or unresolved contact dermatitis
Interventions	Treatment group • Rotigotine: transdermal patch, 1 mg/24 h, 2 mg/24 h or 3 mg/24 h once daily depending on optimal dose; maximal dose is 3 mg/24 h Control group • Placebo: transdermal patch; patches matching to active treatment patches in size and appearance
Outcomes	Ratio from baseline in PLMI Change from baseline • PLMI • IRLSSG • CGI • RLS-6 (rating scales 1 to 6) • PLMSAI • Sleep efficiency • RLS-QOL • SF-36 mental component summary • SF-36 physical component summary
Notes	• The recruitment for the SP0934 study began in April 2012. It concluded in October 2013. This was a multicentre study with subjects enrolled by 9 sites across Europe and 6 sites across the United States. • Some data available on ClinicalTrials.gov

NCT02011191

Methods	• Study design: parallel RCT
Participants	• Inclusion criteria: adults and children with ESKD requiring HD or PD for a duration of at least 3 months • Exclusion criteria: history of consumption > 300 µg/d of biotin; oral contraceptive therapy containing high amounts of oestrogen; women of childbearing age
Interventions	Treatment group • Biotin: 10,000 µg biotin daily for 8 weeks

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

NCT02011191 *(Continued)*	Control group • Placebo: sugar pill
Outcomes	• Biotin status • Change in RLS symptoms
Notes	• ClinicalTrials.gov last updated: 12 December 2013 • No data available

Razazian 2015

Methods	• Study design: crossover RCT
Participants	• Aged > 15 years
Interventions	Treatment group 1 • Capsules of gabapentin 200 mg after every HD for 4 weeks, 2 hours before sleep Treatment group 2 • Tablet of levodopa-C 110 mg nightly 2 hours before sleep for 4 weeks
Outcomes	• Severity of RLS • Severity of sleep disorder • QOL • Day time sleepiness • Drug adverse reaction
Notes	• Some study data no longer accessible (figures and tables)

CGI - Clinical Global Impressions; CKD - chronic kidney disease; CVD - cardiovascular disease; DBP - diastolic blood pressure; ESKD - end-stage kidney disease; HD - haemodialysis; IRLSSG - International Restless Legs Syndrome Study Group Rating Scale; PD - peritoneal dialysis; PLMI - periodic limb movements index; PLMSAI - Periodic Limb Movement During Sleep Arousal Index; PSQI - Pittsburgh Sleep Quality Index; QOL - quality of life; RCT - randomised controlled trial; RLS - restless legs syndrome; RLS-6 - Restless Legs-6 Rating Scale; RLS-QOL - Restless Legs-Quality of Life SBP - systolic blood pressure

DATA AND ANALYSES

Comparison 1. Exercise interventions

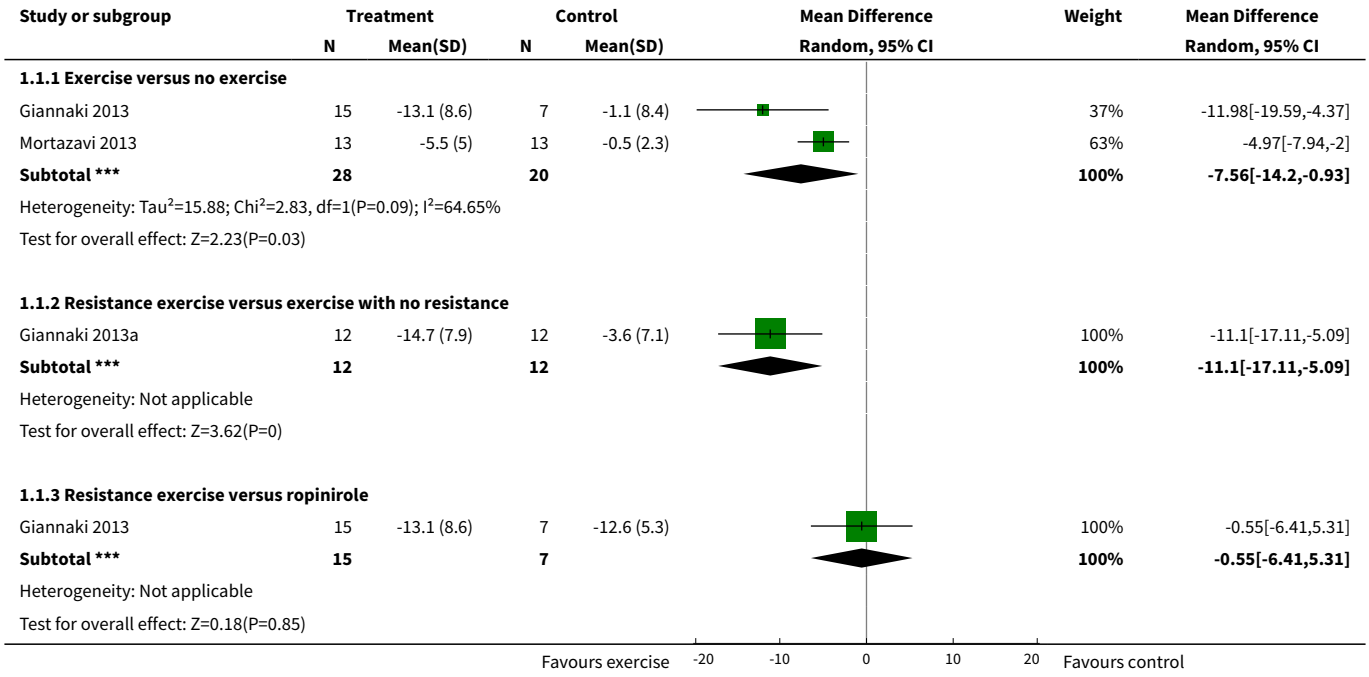
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severity	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Exercise versus no exercise	2	48	Mean Difference (IV, Random, 95% CI)	-7.56 [-14.20, -0.93]

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

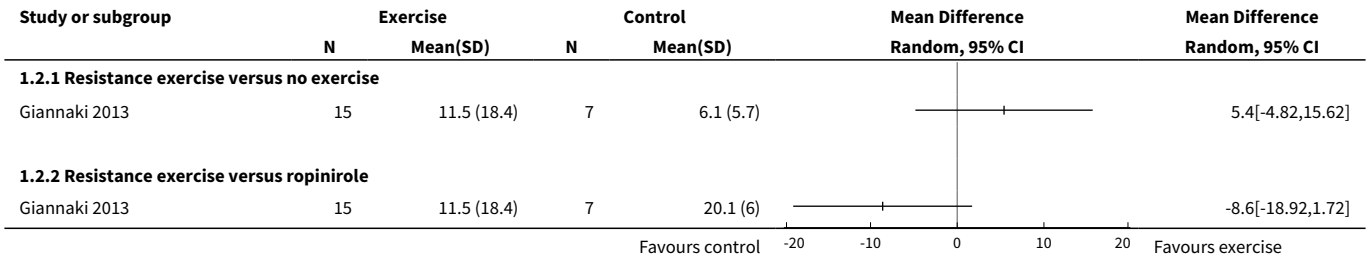
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Resistance exercise versus exercise with no resistance	1	24	Mean Difference (IV, Random, 95% CI)	-11.1 [-17.11, -5.09]
1.3 Resistance exercise versus ropinirole	1	22	Mean Difference (IV, Random, 95% CI)	-0.55 [-6.41, 5.31]
2 QOL: physical component score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Resistance exercise versus no exercise	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Resistance exercise versus ropinirole	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 QOL: mental component summary score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Resistance exercise versus no exercise	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Resistance exercise versus ropinirole	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Quality of sleep: subjective measure	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Resistance exercise versus no exercise	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Resistance exercise versus exercise with no resistance	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Resistance exercise versus ropinirole	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Quality of sleep: Epworth Sleepiness Scale	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Resistance exercise versus no exercise	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Resistance exercise versus exercise with no resistance	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Resistance exercise versus ropinirole	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

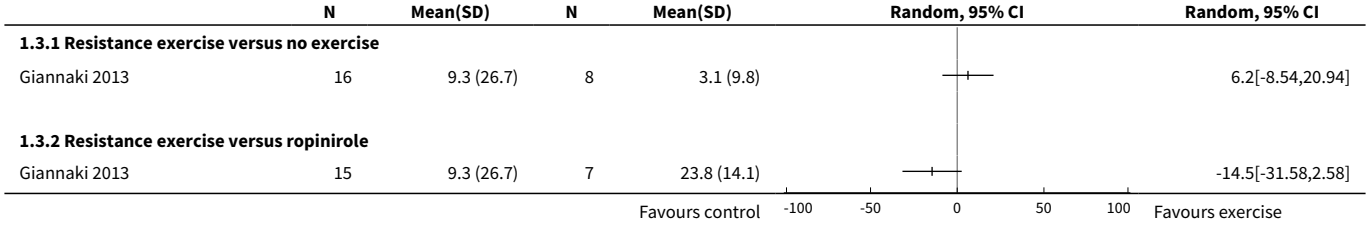
Analysis 1.1. Comparison 1 Exercise interventions, Outcome 1 Severity.



Analysis 1.2. Comparison 1 Exercise interventions, Outcome 2 QOL: physical component score.



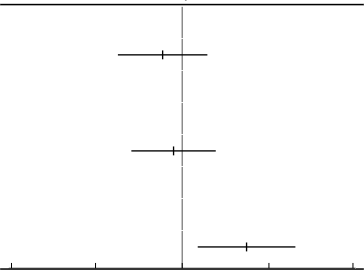
Analysis 1.3. Comparison 1 Exercise interventions, Outcome 3 QOL: mental component summary score.



Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

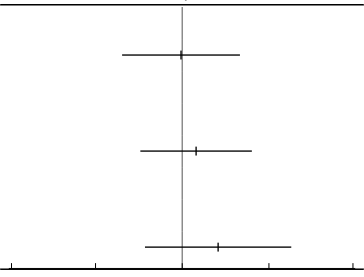
Analysis 1.4. Comparison 1 Exercise interventions, Outcome 4 Quality of sleep: subjective measure.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.4.1 Resistance exercise versus no exercise						
Giannaki 2013	15	-0.7 (3.2)	7	0.4 (2.7)		-1.13[-3.71,1.45]
1.4.2 Resistance exercise versus exercise with no resistance						
Giannaki 2013a	12	-1.8 (2.5)	12	-1.3 (3.5)		-0.5[-2.93,1.93]
1.4.3 Resistance exercise versus ropinirole						
Giannaki 2013	15	-0.7 (3.2)	7	-4.4 (3.1)		3.71[0.89,6.53]



Analysis 1.5. Comparison 1 Exercise interventions, Outcome 5 Quality of sleep: Epworth Sleepiness Scale.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.5.1 Resistance exercise versus no exercise						
Giannaki 2013	15	-0.3 (2.7)	7	-0.3 (4.2)		-0.07[-3.47,3.33]
1.5.2 Resistance exercise versus exercise with no resistance						
Giannaki 2013a	12	-0.1 (2.7)	12	-0.9 (5)		0.8[-2.42,4.02]
1.5.3 Resistance exercise versus ropinirole						
Giannaki 2013	15	-0.3 (2.7)	7	-2.4 (5.4)		2.07[-2.15,6.29]



Comparison 2. Pharmacological interventions

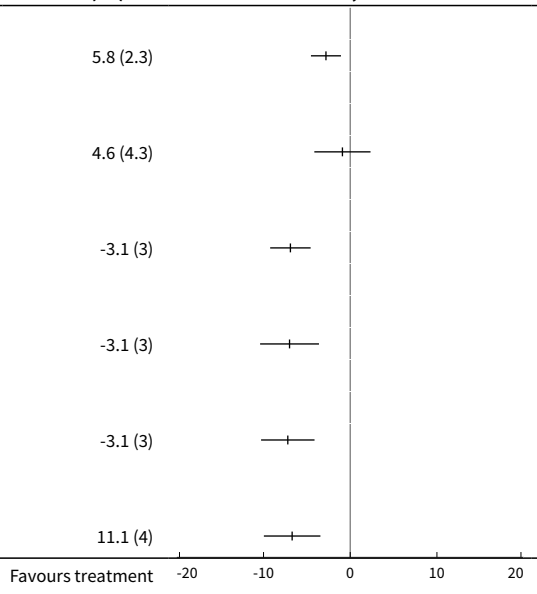
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severity	4		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Gabapentin versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Levodopa versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Vitamin C versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Vitamin E versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Vitamin C & E versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Ropinirole versus levodopa	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 QOL: life satisfaction	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Levodopa versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 QOL: negative feelings & complaints	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Levodopa versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Quality of sleep	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Levodopa versus placebo	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Ropinirole versus levodopa	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Pharmacological interventions, Outcome 1 Severity.

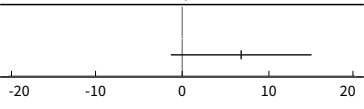
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.1.1 Gabapentin versus placebo						
Thorp 2001	13	3 (2.2)	13	5.8 (2.3)		-2.8[-4.53,-1.07]
2.1.2 Levodopa versus placebo						
Trenkwalder 1995	11	3.7 (3.4)	11	4.6 (4.3)		-0.9[-4.14,2.34]
2.1.3 Vitamin C versus placebo						
Sagheb 2012	15	-10 (3.5)	15	-3.1 (3)		-6.9[-9.23,-4.57]
2.1.4 Vitamin E versus placebo						
Sagheb 2012	15	-10.1 (6)	15	-3.1 (3)		-7[-10.39,-3.61]
2.1.5 Vitamin C & E versus placebo						
Sagheb 2012	15	-10.3 (5.3)	15	-3.1 (3)		-7.2[-10.28,-4.12]
2.1.6 Ropinirole versus levodopa						
Pellecchia 2004	11	4.4 (3.8)	11	11.1 (4)		-6.7[-9.96,-3.44]



Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

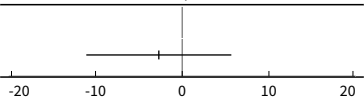
Analysis 2.2. Comparison 2 Pharmacological interventions, Outcome 2 QOL: life satisfaction.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.2.1 Levodopa versus placebo						
Trenkwalder 1995	11	24.2 (10.1)	11	17.4 (9.3)		6.8[-1.31,14.91]



Analysis 2.3. Comparison 2 Pharmacological interventions, Outcome 3 QOL: negative feelings & complaints.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.3.1 Levodopa versus placebo						
Trenkwalder 1995	11	21.6 (9.6)	11	24.3 (10.4)		-2.7[-11.06,5.66]



Analysis 2.4. Comparison 2 Pharmacological interventions, Outcome 4 Quality of sleep.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.4.1 Levodopa versus placebo						
Trenkwalder 1995	11	5 (1.8)	11	2.9 (2.3)		2.1[0.37,3.83]
2.4.2 Ropinirole versus levodopa						
Pellecchia 2004	11	7.9 (1)	11	5.8 (1.6)		2.1[0.98,3.22]

ADDITIONAL TABLES

Table 1. Adverse events

Study	Intervention: number of events	Comments	Control: number of events	Comments
Giannaki 2013	Resistance exercise: 0/16	No adverse events	No exercise: 0/16	No adverse events
Giannaki 2013a	Exercise with no resistance: 0/12	No adverse events	Exercise with no resistance: 0/12	No adverse events
Mortazavi 2013	Exercise: not reported	Not reported	No exercise: not reported	Not reported
Thorp 2001	Gabapentin: 2/15	Withdrawal due to lethargy in gabapentin group.	Placebo: 1/16	Myocardial infarction in placebo group prior to receiving gabapentin

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Adverse events *(Continued)*

Micozkadioglu 2004	Gabapentin: 1/15	Withdrawal due to fatigue, syncope in gabapentin group	Levodopa: not reported	Not reported
Trenkwalder 1995	Levodopa: adverse effects were pooled and not reported separately for dialysis patients	Adverse effects were pooled and not reported separately for dialysis patients	Placebo: adverse effects were pooled and not reported separately for dialysis patients.	Adverse effects were pooled and not reported separately for dialysis patients.
Pellecchia 2004	Ropinirole: 0/13	No adverse events	Levodopa: 1/13	Withdrawal due to vomiting in levodopa group
Sloand 2004	Iron dextran: 2/11 had nausea/vomiting & 2/11 had headaches	Nausea/vomiting Headache	IV saline: 3/14 had nausea	Nausea
Sagheb 2012	Vitamin C & E, vitamin C & placebo, vitamin E & placebo: 3/45 had nausea 3/45 had dyspepsia	Nausea Dyspepsia	Placebo: 1/15 had nausea	Nausea

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. (restless next leg*):ti,ab,kw 2. (ekbom* next syndrome):ti,ab,kw 3. (periodic next leg next movement*):ti,ab,kw 4. (periodic next limb next movement*):ti,ab,kw 5. (PLM or PLMS):ti,ab,kw 6. ((ur*emic next polyneuropath*) or (ur*emic next neuropath*) or (peripheral next polyneuropath*)):ti,ab,kw 7. ((nocturnal next movement*) or (nocturnal next leg next movement*) or (nocturnal next limb next movement*)):ti,ab,kw 8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) 9. (renal next replacement next therapy):ti,ab,kw 10.dialysis:ti,ab,kw 11.(h*emodialysis or h*emodiafiltration or h*emofiltration):ti,ab,kw 12.(CAPD or CCPD or APD):ti,ab,kw 13.((kidney or renal) next disease*):ti,ab,kw 14.((kidney or renal) next failure):ti,ab,kw 15.(CKF or CKD or CRF or CRD):ti,ab,kw 16.(ESRF or ESKF or ESRD or ESKD):ti,ab,kw 17.ur*emi*:ti,ab,kw 18.(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(Continued)

	19.(#8 AND #18)
MEDLINE	1. Restless Legs Syndrome/ 2. restless leg$.tw. 3. Ekbom$ syndrome.tw. 4. periodic leg movement$.tw. 5. periodic limb movement$.tw. 6. (PLM or PLMS).tw. 7. (ur?emic polyneuropath$ or ur?emic neuropath$).tw. 8. peripheral polyneuropath$.tw. 9. (nocturnal movement$ or nocturnal leg movement$ or nocturnal limb movement$).tw. 10.or/1-9 11.exp Renal Dialysis/ 12.(hemodialysis or haemodialysis or hemodiafiltration or haemodiafiltration or hemofiltration or haemofiltration).tw. 13.dialysis.tw. 14.(PD or CAPD or CCPD or APD).tw. 15.Renal Insufficiency/ 16.exp Renal Insufficiency, Chronic/ 17.Kidney Diseases/ 18.Uremia/ 19.(kidney disease or kidney failure or renal disease or renal failure).tw. 20.(ESRF or ESKF or ESRD or ESKD).tw. 21.(CKF or CKD or CRF or CRD).tw. 22.ur?emi$.tw. 23.or/11-22 24.and/10,23
EMBASE	1. Restless Legs Syndrome/ 2. restless leg$.tw. 3. Ekbom$ syndrome.tw. 4. periodic leg movement$.tw. 5. periodic limb movement$.tw. 6. (PLM or PLMS).tw. 7. (ur?emic polyneuropath$ or ur?emic neuropath$).tw. 8. peripheral polyneuropath$.tw. 9. (nocturnal movement$ or nocturnal leg movement$ or nocturnal limb movement$).tw. 10.or/1-9 11.exp Renal Replacement Therapy/ 12.(hemodialysis or haemodialysis or hemodiafiltration or haemodiafiltration or hemofiltration or haemofiltration).tw. 13.dialysis.tw. 14.(PD or CAPD or CCPD or APD).tw. 15.Kidney Disease/ 16.Chronic Kidney Disease/ 17.Kidney Failure/ 18.Chronic Kidney Failure/ 19.Uremia/ 20.(kidney disease or kidney failure or renal disease or renal failure).tw. 21.(CKF or CKD or CRF or CRD).tw. 22.(ESRF or ESKF or ESRD or ESKD).tw. 23.ur?emi$.tw.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(Continued)

	24.or/11-23 25.and/10,24

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with ob-

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(Continued)

Attrition bias due to amount, nature or handling of incomplete outcome data.	served event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: MS, SG
2. Study selection: MS, SG
3. Extract data from studies: MS, SG
4. Enter data into RevMan: MS, SG
5. Carry out the analysis: MS, SG
6. Interpret the analysis: MS, NA, SG
7. Draft the final review: MS, NA, SG
8. Disagreement resolution: MS, NA, SG
9. Update the review: MS, NA, SG

DECLARATIONS OF INTEREST

- Seerapani Gopaluni: none known
- Mohamed Sheriff: none known

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

- Naim A Ahmadouk: none known

INDEX TERMS

Medical Subject Headings (MeSH)

*Renal Replacement Therapy; Amines [therapeutic use]; Anticonvulsants [*therapeutic use]; Ascorbic Acid [therapeutic use]; Cyclohexanecarboxylic Acids [therapeutic use]; Dopamine Agonists [*therapeutic use]; Exercise Therapy [*methods]; Gabapentin; Indoles [therapeutic use]; Iron-Dextran Complex [therapeutic use]; Levodopa [therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [complications] [*therapy]; Resistance Training; Restless Legs Syndrome [complications] [*therapy]; Vitamin E [therapeutic use]; Vitamins [therapeutic use]; gamma-Aminobutyric Acid [therapeutic use]

MeSH check words

Humans

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.