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ORIGINAL ARTICLE

Pharmacological and non-pharmacological treatments for restless legs syndrome in end-stage kidney disease: a systematic review and component network meta-analysis

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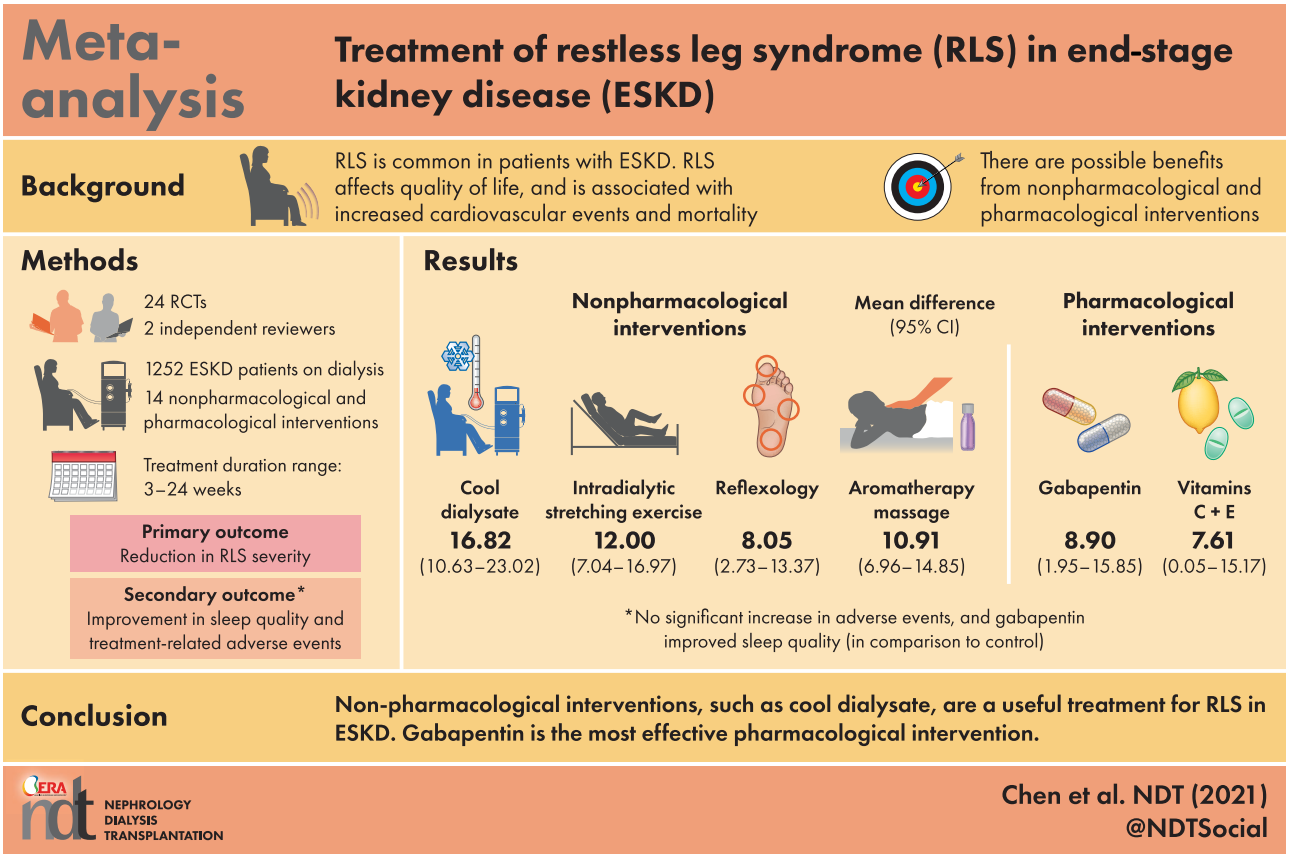
GRAPHICAL ABSTRACT



ABSTRACT

Background. Restless legs syndrome (RLS) is common among patients with end-stage kidney disease (ESKD) and is associated with poor outcomes. Several recently published studies had focused on pharmacological and non-pharmacological treatments of RLS, but an updated meta-analysis has not been conducted.

KEY LEARNING POINTS

What is already known about this subject?

- Several different pharmacological or non-pharmacological interventions were studied and applied in end-stage kidney disease (ESKD) patients with restless legs syndrome (RLS). Aromatherapy massage, cool dialysate and different types of intradialytic exercise were demonstrated to be a benefit in recent trials.

What this study adds?

- We demonstrated that cool dialysate might be the most effective intervention for RLS treatment in ESKD. Gabapentin is the most effective pharmacological intervention and could also improve sleep quality. Other potentially effective interventions include aromatherapy massage, intradialytic stretching exercises and reflexology.

What impact this may have on practice or policy?

- Non-pharmacological interventions like cool dialysate could be applied to ESKD patients with RLS. Considering other potential benefits of cool dialysate, it is appropriate to be applied in ESKD patients with RLS. A combination of effective pharmacological and non-pharmacological interventions could be considered as well.

Methods. The study population was adult ESKD patients on dialysis with RLS. Randomized controlled trials (RCTs) were selected. The primary outcome was reduction in RLS severity. The secondary outcomes were improvement in sleep quality and treatment-related adverse events. Frequentist standard network meta-analysis (NMA) and additive component NMA were performed. The evidence certainty was assessed using the Confidence in NMA (CINeMA) framework.

Results. A total of 24 RCTs with 1252 participants were enrolled and 14 interventions were compared. Cool dialysate produced the largest RLS severity score reduction {mean difference [MD] 16.82 [95% confidence interval (CI) 10.635–23.02]} and a high level of confidence. Other potential non-pharmacological interventions include intradialytic stretching exercise [MD 12.00 (95% CI 7.04–16.97)] and aromatherapy massage [MD 10.91 (95% CI 6.96–14.85)], but all with limited confidence of evidence. Among the pharmacological interventions, gabapentin was the most effective [MD 8.95 (95% CI 1.95–15.85)], which also improved sleep quality [standardized MD 2.00 (95% CI 0.47–3.53)]. No statically significant adverse events were detected.

Conclusions. The NMA supports that cool dialysate is appropriate to treat patients with ESKD and RLS. Gabapentin is the most effective pharmacological intervention and also might improve sleep quality. Further parallel RCTs with sufficient sample sizes are required to evaluate these potential interventions and long-term effects.

Keywords: cool dialysate, end-stage kidney disease, gabapentin, restless legs syndrome

INTRODUCTION

Restless legs syndrome (RLS) is a neuromuscular disorder characterized by uncomfortable sensations in the extremities accompanied by an urge to move those limbs. These uncomfortable sensations usually occur at night or at rest and can be relieved by movement. The prevalence of RLS in end-stage kidney disease (ESKD) patients ranges from 6.6% to 70% [1]. RLS is not only associated with a negative effect on quality of life, but is also associated with increased cardiovascular events and mortality [2–4].

Factors reported to be associated with RLS include peripheral neuropathy, dopaminergic system dysfunction and iron deficiency in specific cerebral areas [5]. Haung *et al.* [6] concluded that gabapentin is the most effective treatment for RLS in patients with ESKD. However, several randomized control trials (RCTs) have been undertaken since then. Furthermore, several recent trials have reported possible benefits from non-pharmacological interventions, including cool dialysate and aromatherapy massage [7–12]. Therefore we aimed to conduct an updated systematic review and component network meta-analysis (NMA) that included new RCTs and non-pharmacological interventions to compare the treatment efficacy and acceptability of these interventions used in the treatment of adult patients with ESKD and RLS.

MATERIALS AND METHODS

Literature search strategy

We performed this NMA in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for NMA (Supplementary data, Table S1) [13]. We registered our study protocol in PROSPERO (CRD42021252543).

Two independent reviewers (J.-J.C. and T.H.L.) searched for studies published prior to 1 May 2021 in the databases of PubMed, MEDLINE, the Cochrane Library and Embase. Search strategies targeted published clinical trials that compared the efficacy of different interventions in treating RLS among adult patients on dialysis. The detailed search strategy and results of that search process are provided in Supplementary data, Table S2. Review articles and meta-analyses were not included in our analysis, but their references were screened for relevant studies. A gray literature search was also conducted in Google Scholar and ResearchGate using the following keywords: 'restless legs syndrome' and 'dialysis' OR 'end stage renal disease'. We also examined unpublished or ongoing clinical trials.

Study eligibility criteria

The titles and abstracts of studies returned by the search were independently examined by two reviewers (J.-J.C. and T.H.L.) and the articles were excluded upon initial screening if their titles or abstracts indicated that they were clearly irrelevant to the objective of the current study. Full texts of relevant articles were reviewed to determine whether the studies were eligible to be included in the NMA. A study was included for analysis in the present study if it enrolled adults with ESKD who were under dialysis; allocated patients to at least two different intervention arms to compare the efficacy of interventions; reported outcomes on changes in RLS severity, sleep quality, treatment-related adverse events or quality of life and was an RCT. A third reviewer (G.K.) was consulted to reach an agreement through consensus in the case of any disagreement regarding a given study's eligibility.

Crossover-design trials and single-arm trials were excluded. The study population focus was on patients with ESKD and RLS, thus those studies that examined patients with idiopathic RLS or RLS preceding ESKD were excluded.

Data extraction and outcomes

Two investigators (J.-J.C. and T.H.L.) independently classified the therapies and extracted the study parameters. The primary outcome was the treatment efficacy of RLS severity. In most studies, the severity of RLS was evaluated according to the International RLS (IRLS) rating scale, which comprises an overall score that ranges from 0 to 40 [14]. If a study used more than one rating scale to assess RLS severity, we accorded priority to the IRLS scale. Secondary outcomes, including sleep quality and quality of life, were also extracted. The patients' subjective sleep quality levels were assessed by using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). The PSQI is based on a 4-point Likert scale with total scores ranging from 0 to 21 [15]. The ESS consists of eight situations with a total score ranging from 0 to 24 [16]. To assess patient quality of life we used the 36-item Short Form Survey (SF-36) [17]. Another secondary outcome was treatment acceptability, which was evaluated by the extent of treatment-related adverse events (i.e. unfavorable or unintended signs and symptoms associated with interventions) recorded in the enrolled RCTs.

Data synthesis and analysis

As for the evaluation of the effects of treatments on RLS severity, we extracted the mean difference (MD) with 95% confidence interval (CI) or standard deviation (SD) of the MD associated with each intervention arm from baseline to posttreatment stage; this was done to pool continuous outcomes. To evaluate the effects of the different treatments on sleep quality (according to the various scales), we extracted the standardized MD (SMD) with the standard error of the SMD. For treatment-related adverse events, odds ratios (ORs) were used to pool binary outcomes. Heterogeneity was examined by I^2. A two-tailed P-value <0.05 was considered statistically significant. The frequentist NMA and additive component NMA with random-effects model was performed using the statistical package netmeta in R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) [18]. All pairwise comparisons were summarized in a league table. In the frequentist standard NMA, a P-score, ranging between 0 and 1, was used to rank treatments compared within an NMA for a particular outcome (treatment effects on RLS severity, sleep quality and treatment-related adverse events) [19]. P-score has a similar interpretation to its Bayesian counterpart, surface under the cumulative ranking curve (SUCRA); a treatment with a higher P-score has a higher rank than a treatment with a lower P-score. The inconsistency was evaluated by the design-by-treatment interaction model and node-splitting model [20]. Small-study effect bias was assessed by the Egger test and a funnel plot.

Risk-of-bias and quality assessments

The study quality was assessed by two investigators (J.-J.C. and T.H.L.) using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [21] and any disagreements among the two investigators were resolved through consensus with another author (G.K.). We also assessed the confidence of evidence by using the confidence in NMA (CINeMA) framework [22].

Component NMA

Additive component NMA was conducted. Component NMA, a variant of the standard NMA, allows for decomposition of complex interventions and estimates the treatment effects of each component from composite interventions. We examined whether the effects of components are additive, i.e. the effect of a component combined with another component is equal, or is greater (synergistic) or smaller (antagonistic) than the sum of the two components by comparing the results of the standard NMA with that of the additive component NMA. In component NMA, we used the mvrnorm function in the R package MASS for running 1000 stimulations, based on the variance–covariance matrix of the component effect estimates, to obtain ranking probabilities of components.

RESULTS

Study characteristics

The flow and search strategy are detailed in Supplementary data, Figure S1 and Table S2. Through the electronic database search and after removing the duplicate articles, a total of 1047 potentially eligible studies were screened according to the abstract and the titles. After screening, 36 full-text articles were further assessed for eligibility. Finally, 24 RCTs were included (18 two-arm studies, 5 three-arm studies and 1 four-arm study) [7–12, 23–40]. A total of 1252 participants were enrolled: these participants had been randomly allocated to 1 of 14 intervention or control groups (dopamine agonist, $n = 118$; gabapentin, $n = 86$; iron, $n = 27$; vitamin C, $n = 30$; vitamin E, $n = 15$; vitamin C and vitamin E, $n = 15$; cool dialysate, $n = 52$; intradialytic stretching exercise, $n = 86$; intradialytic aerobic exercise, $n = 64$; intradialytic

aerobic exercise and dopamine agonist, $n = 7$; aromatherapy massage, $n = 186$; reflexology, $n = 65$; acupoint therapy, $n = 64$; neuromuscular electrical stimulation, $n = 30$; control group, $n = 395$). The characteristics of the selected RCTs are summarized in Table 1.

The included RCTs had sample sizes ranging from 13 to 105 participants per trial. The RLS diagnoses followed the International Restless Legs Syndrome Study Group criteria in all selected studies. More than half of the participants (53.6%) were women and the average age of participants was 53.7 years. Most participants received haemodialysis, except for those in one study where 12% of participants received peritoneal dialysis [40]. The durations of interventions were 3–24 weeks. Treatment-related adverse events were extracted. Nausea, vomiting or allergic reaction were reported in patients receiving dopamine agonist treatment [36, 37]. Somnolence and lethargy were reported in patients receiving gabapentin treatment [37]. Nausea and dyspepsia were observed in patients taking vitamin C, vitamin E or a combination of the two [38]. One patient withdrew from the cool dialysate intervention group due to chills [9]. No critical adverse events were reported in the enrolled RCTs.

Figure 1 illustrates the network plot with 15 interventions (15 nodes) and 21 direct comparative arms to compare the treatment efficacy in reducing RLS symptom severity from 21 selected studies. Supplementary data, Figure S2A and B illustrate the network plots for efficacy of treatments of sleep quality and for treatment-related adverse events, respectively.

NMA outcomes

RLS severity. The pooled treatment results of 14 interventions are summarized in Figure 2A and Supplementary data, Table S3. Cool dialysate achieved the greatest reduction in RLS severity compared with the control group [MD 16.82 (95% CI 10.63–23.02)]. Intradialytic stretching exercises exhibited the second highest efficacy in reducing RLS severity [MD 12.00 (95% CI 7.04–16.97)]. Two non-pharmacological interventions also showed potential benefit in RLS treatment: aromatherapy massage [MD 10.91 (95% CI 6.96–14.85)] and reflexology [MD 8.05 (95% CI 2.73–13.27)]. Among the pharmacological interventions, gabapentin was the most effective [MD 8.95 (95% CI 1.95–15.85)]. Considerable heterogeneity across studies was noted ($I^2 = 90.8\%$). The funnel plot indicated no small-study bias and the P-value of the Egger test was 0.72 (Supplementary data, Figure S3A). The result from the current NMA mostly came from indirect evidence (Supplementary data, Figure S4A). The full design-by-treatment interaction model revealed incoherence among various study designs with $Q = 22.19$, $P = 0.001$. The node-splitting model revealed potential loop incoherence from six comparisons, but these results were not statistically significant (Supplementary data, Figure S5A and Supplementary Document).

Sleep quality. The results of the present NMA suggested that gabapentin and acupoint therapy improved the sleep quality of patients with ESKD and RLS compared with the control group (Figure 3A and Supplementary data, Table S4). Among these interventions, gabapentin achieved the greatest improvement in sleep quality compared with the control group n [SMD 2.00 (95% CI 0.47–3.53)]. Exercise, including intradialytic aerobic exercise and intradialytic stretching exercise, was not associated with a significant improvement in sleep quality compared with the control group [SMD −0.10 (95% CI −0.84–0.64)]. The heterogeneity was low ($I^2 = 0\%$) and the inconsistencies within and between groups were not significant. The funnel plot was symmetrical (Supplementary data, Figure S3B). The full design-by-treatment interaction model revealed no significant incoherence from different study designs, with $Q = 0.01$ and $P = 0.94$. More than half of the results of the pairwise comparison came from indirect evidence (Supplementary data, Figure S4B). The node no-splitting model revealed no loop incoherence (Supplementary data, Figure S5B).

Adverse events. Reflexology, intradialytic stretching exercises, vitamin C, vitamin E, cool dialysate, dopamine agonist and gabapentin were all associated with increased adverse events compared with the control, but not significantly so (Figure 3B and Supplementary data, Table S5). The Egger test and comparison-adjusted funnel plots revealed no small-study bias (Supplementary data, Figure S3C). The full design-by-treatment interaction model revealed no incoherence, with $Q = 0.99$ and $P = 0.99$. The result from the current NMA mostly came from indirect evidence (Supplementary data, Figure S4C). The node-splitting model revealed no loop incoherence from direct and indirect evidence (Supplementary data, Figure S5C).

Component NMA

We explored the individual treatment effects of different components of included composite interventions by using component NMA. As indicated in Supplementary data, Figure S6, the standard NMA and additive component NMA did not significantly differ ($P = 0.83$). The result demonstrated that a combination of two interventions might be additive rather than synergistic or antagonistic. The component NMA indicated that cool dialysate might still be the most potent component for RLS severity relief [MD 16.82 (95% CI 10.55–23.08); Figure 2B]. Regarding RLS treatment efficacy, the best and worst interventions in component NMA were cool dialysate and neuromuscular electrical stimulation, respectively (Supplementary data, Table S6 and Figure S7).

Assessing risk of bias and confidence of NMA

The results of the risk-of-bias assessment are illustrated in the Supplementary data, Figure S8 and summarized in the Supplementary Document. The degree of confidence in the evidence was assessed using the CINeMA framework. All enrolled studies were considered to warrant no concern regarding reporting bias and indirectness. To evaluate imprecision and heterogeneity, the IRLS score was defined to indicate

Table 1. Characteristics of the included studies

Study	*N*	Average age (years)	RRT modality	Average RRT vintage (months)	Treatment detail (arm)	Treatment duration (weeks)	Study design	Risk of bias	Outcome evaluation
Fauzi and Triaswati, 2021 [7]	38	45.6	HD (100%)	NR	Intradialytic stretching exercise Control	8	RCT, non-blind	High risk	RLS-3 scale, PSQI scale
Ajorpaz *et al.*, 2019 [23]	90	56.7	HD (100%)	NR	Glycerin oil message (aromatherapy massage) Lavender oil message (aromatherapy massage) Control	4	RCT, double-blind	Low risk	IRLS score
Ali *et al.*, 2020 [8]	26	45.5	HD (100%)	62.54	Levodopa, 110 mg QD Gabapentin, 200 mg TIW	4	RCT	Some concerns	IRLS score, PSQI scale
Aliabadi *et al.*, 2020 [9]	40	54.5	HD (100%)	NR	Intradialytic stretching exercise Cold dialysate, 35.5°C	6	RCT, double-blind	Low risk	IRLS score
Aliasgharpour *et al.*, 2016 [24]	33	NR	HD (100%)	NR	Intradialytic stretching exercise Control	8	RCT	Some concerns	IRLS score
Dauvilliers *et al.*, 2016 [25]	25	55.0	HD (100%)	39.6	Rotigotine, 1-3 mg QD Placebo	5*	RCT, double-blind	High risk	PLMI ratio, PLM during sleep with arousals/hour TST, IRLS score, CGI-1, RLS-6, RLS-QoL28, SF-36
Deng *et al.*, 2017 [26]	32	63.9	HD (100%)	35.34	Iron sucrose, 100 mg TIW Placebo	NR	RCT, non-blind, placebo-controlled	High risk	IRLS score
Gao *et al.*, 2016 [27]	69	45.0	HD (100%)	NR	Moxibustion (acupoint therapy) Control	16	RCT	Low risk	IRLS score, PSQI scale
Ghasemi *et al.*, 2018 [28]	70	50.5	HD (100%)	58.92	Reflexology Placebo	4	RCT, single-blind	Low risk	IRLS score
Giannaki *et al.*, 2013 [47]	29	56.3	HD (100%)	46.22	Intradialytic aerobic exercise Ropinirole, 0.25 mg QD Placebo	24	RCT, partial double-blind	High risk	Sleep diary, ESS, Zung depression scale, IRLS score, SF-36, SF-36 PCS score
Giannaki *et al.*, 2015 [30]	13	55.1	HD (100%)	45.97	Intradialytic aerobic exercise +Ropinirole, 0.25 mg QD Intradialytic aerobic exercise +Placebo	24	RCT, double-blind	Low risk	IRLS score
Hajian *et al.*, 2020 [11]	60	64.0	HD (100%)	46.20	Pramipexole, 0.18 ng QD Gabapentin, 100 mg QD	4	RCT	High risk	IRLS score
Hashemi *et al.*, 2015 [31]	59	59.3	HD (100%)	45.60	Lavender oil massage (aromatherapy massage) Control	3	RCT, single-blind	High risk	IRLS score

Table 1. Continued

Study	*N*	Average age (years)	RRT modality	Average RRT vintage (months)	Treatment detail (arm)	Treatment duration (weeks)	Study design	Risk of bias	Outcome evaluation
Kashani *et al.*, 2019 [32]	63	55.9	HD (100%)	35.92	Cool dialysate, 35.5°C Control dialysate, 37°C	4	RCT, triple-blind	Low risk	IRLS score
Mohammadi *et al.*, 2018 [33]	60	56.7	HD (100%)	36.88	Near-infrared light to acupoints (acupoint therapy) Sham therapy	4	RCT, single-blind	High risk	IRLS score
Mortazavi *et al.*, 2013 [34]	26	41.5	HD (100%)	NR	Intradialytic aerobic exercise Control	16	RCT	High risk	RLSQ questionnaire, SF-36
Nasiri *et al.*, 2019 [35]	55	52.0	HD (100%)	NR	Olive oil message (aromatherapy massage) Placebo massage	3	RCT, double-blind	Low risk	IRLS score
Oshvandi *et al.*, 2021 [10]	105	51.9	HD (100%)	>12 months	Lavender oil message (aromatherapy massage) Orange oil message (aromatherapy massage) Control	3	RCT, double-blind	Low risk	IRLS score, PSQI scale
Rafie *et al.*, 2016 [36]	44	57.4	HD (100%)	31.3	Pramipexole, 0.18 mg QD Vitamin C, 250 mg QD Placebo	8	RCT, double-blind	Low risk	IRLS score
Razazian *et al.*, 2015 [37]	82	55.3	HD (100%)	34.18	Gabapentin, 200 mg TIW Levodopa, 110 mg QD	4	RCT, double-blind	Low risk	IRLS score, PSQI scale
Sagheb *et al.*, 2012 [38]	60	52.7	HD (100%)	15.92	Vitamin C, 200 mg QD Vitamin E, 400 mg QD Vitamin C, 200 mg QD + vitamin E, 400 mg QD Placebo	8	RCT, double-blind	Low risk	IRLS score
Shahgholian *et al.*, 2016 [39]	90	55.5	HD (100%)	35.34	Reflexology Intradialytic stretching exercises Control	4	RCT	High risk	IRLS score, RLS severity questionnaires
Sloand *et al.*, 2004 [40]	23	55.2	HD (88%), PD (12%)	35.40	Iron dextran, 1000 mg TIW Placebo	4	RCT, double-blind	Low risk	RLS score
Youssef *et al.*, 2019 [12]	60	44.7	HD (100%)	23.82	Neuromuscular electrical stimulation	12	RCT	High risk	STS-5, STS-60, IRLS score
					Intradialytic aerobic exercise		RCT, non-blind		RLS-3 scale, PSQI scale

*Treatment duration including 3 weeks of treatment dosage titration and 2 weeks of maintenance.

HD, hemodialysis; *N*, number; PD, peritoneal dialysis; PSQI, Pittsburgh Sleep Quality Index; RLS-6, RLS 6-item questionnaire; RLS-QoL28, RLS quality-of-life questionnaire; RRT, renal replacement therapy; TST, total sleep time.

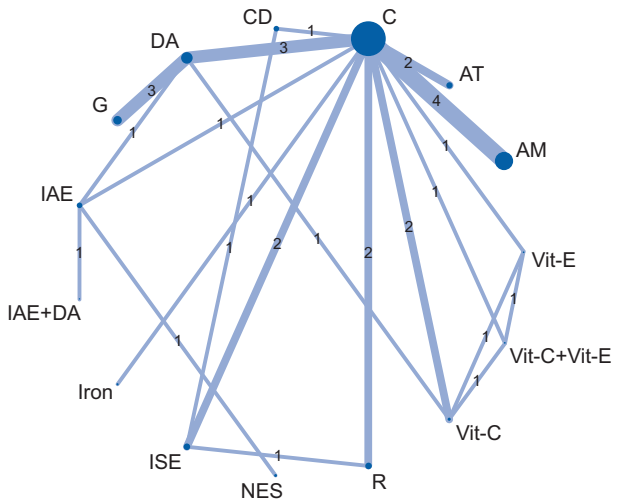


FIGURE 1: Network plot of eligible comparisons among interventions for RLS symptom relief. The size of each node indicates the number of randomized allocated participants and the width of each line indicates the number of trials of each comparison. AM, aromatherapy massage; AT, acupoint therapy; C, control; CD, cool dialysate; DA, dopamine agonist; G, gabapentin; IAE, intradialytic aerobic exercise; ISE, intradialytic stretching exercise; NES, neuromuscular electrical stimulation; Vit-C, vitamin C; Vit-E, vitamin E; R, reflexology.

clinical importance if MD was >3, in accordance with the definition used in previous studies [41]. Overall, compared with the controls, the treatment effect of cool dialysate was verified with high confidence (Supplementary Document and Supplementary data, Table S7). The treatment results of 14 interventions, their rankings by P-score and the associated levels of confidence in the evidence are summarized in Table 2. Figure 4 summarizes the results of our NMA by the scatter plot of the P-score of RLS intervention efficacy and acceptability.

DISCUSSION

The present study revealed several points worth summarizing. First, cool dialysate and gabapentin were the most potent treatments for reducing RLS severity among the non-pharmacological and pharmacological interventions, respectively. Second, gabapentin and acupoint therapy may improve patients' sleep quality. Third, although several interventions produced treatment-related adverse events, none of those effects was statistically significant when comparisons were made with the control group.

Some experts have suggested attempting non-pharmacological interventions first in response to problems of sleep quality among patients with ESKD [2]. Among the non-pharmacological interventions investigated by the current meta-analysis, cool (35.5°C) dialysate had positive effects in reducing RLS severity compared with dialysate of standard temperature (37°C) [2, 9]. The efficacy of cool dialysate might originate from its capacity to reduce sensory receptor function and lower impulse input frequencies to nerve terminals while lowering body temperature [42]. Apart from reducing RLS severity, cool dialysate has been

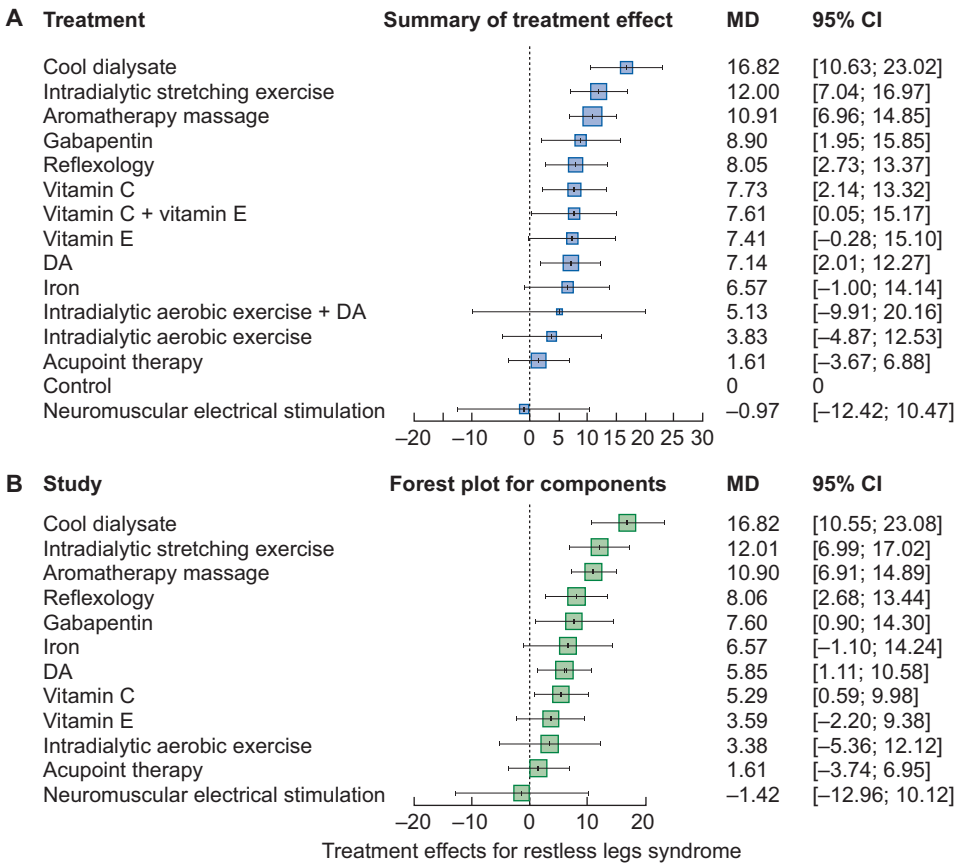


FIGURE 2: Forest plot of (**A**) NMA of RLS symptom relief and of (**B**) component NMA of RLS symptom relief.

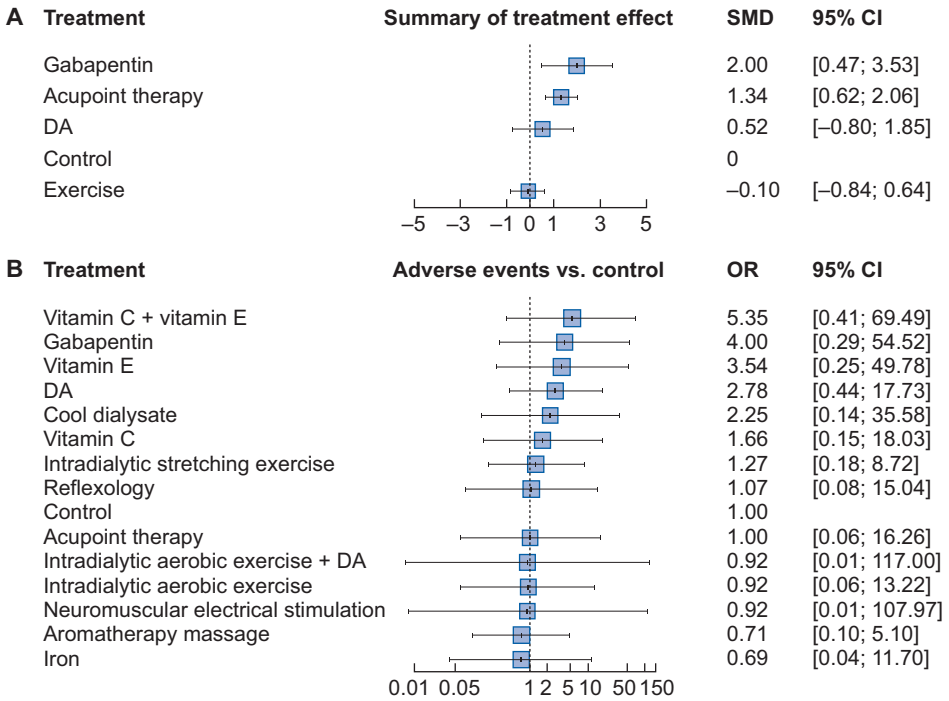


FIGURE 3: Forest plot of (**A**) NMA of sleep quality and (**B**) treatment-related adverse events.

Table 2. Summary of treatment effects, treatment-related adverse events, the rank by P-score and the level of confidence from 14 interventions

	RLS severity			Sleep quality			Adverse events			
Intervention	MD (95% CI)	P-score (%)	Rank	SMD (95% CI)	P-score (%)	Rank	OR (95% CI)	P-scores (%)	Rank	Confidence of evidence[b]
Cool dialysate	16.82 (10.63–23.02)	97.24	1	–	–	–	2.25 (0.14–35.58)	41.30	9	High
ISE	12.00 (7.04–16.97)	81.46	2	−0.10 (−0.84–0.64)	0.1418	4[a]	1.27 (0.18–8.72)	28.98	12	Low
Aromatherapy massage	10.91 (6.96–14.85)	76.22	3	–	–	–	0.71 (0.10–5.10)	67.57	1	Low
Gabapentin	8.90 (1.95–15.85)	63.06	4	2.00 (0.47–3.53)	0.9426	1	4.00 (0.29–54.52)	28.98	13	Very low
Reflexology	8.05 (2.73–13.37)	56.37	5	–	–	–	1.07 (0.08–15.04)	57.26	7	Very low
Vitamin C	7.73 (2.14–13.32)	54.62	6	–	–	–	1.66 (0.15–18.03)	49.59	8	Moderate
Vitamin C + vitamin E	7.61 (0.05–15.17)	53.82	7	–	–	–	5.35 (0.41–69.49)	22.59	14	Low
Vitamin E	7.41 (−0.28–15.10)	52.50	8	–	–	–	3.54 (0.25–49.78)	32.07	11	Moderate
Dopamine agonist	7.14 (2.01–12.27)	49.86	9	0.52 (−0.80–1.85)	0.4400	3	2.78 (0.44–17.73)	35.14	10	Very low
Iron	6.57 (−1.00–14.14)	47.43	10	–	–	–	0.69 (0.04–11.70)	65.74	2	Very low
IAE + dopamine agonist	5.13 (−9.91–20.16)	42.66	11	–	–	–	0.92 (0.01–117.00)	57.32	6	Low
IAE	3.83 (−4.87–12.53)	32.93	12	−0.10 (−0.84–0.64)	0.1418	4[a]	0,92 (0.06–13.22)	60.73	3	Very low
Acupoint therapy	1.61 (−3.67–6.88)	18.83	13	1.34 (0.62–2.06)	0.7684	2	1.00 (0.06–16.26)	58.38	4	Low
NES	−0.97 (−12.42–10.47)	12.99	14	–	–	–	0.92 (0.01–107.97)	57.41	5	Very low

[a]Intradialytic stretching exercise and intradialytic aerobic exercise were merged as one group when analysing sleep quality.
P-scores (as percentages) and rank for each intervention were obtained from standard network meta-analysis.
[b]Confidence of evidence was assessed according to the results of NMA regarding RLS severity treatment effect by CINeMA.
IAE, intradialytic aerobic exercise; ISE, intradialytic stretching exercise; NES, neuromuscular electrical stimulation.

demonstrated to reduce intradialytic hypotension, fatigue, brain ischaemia [43, 44] and cardiovascular mortality [45]. With no associated critical adverse events and only symptoms of chills during dialysis, cool dialysate represents a reasonable choice of a non-pharmacological approach for patients with RLS on dialysis. Intradialytic exercise has demonstrated mixed results in previous studies [46, 47]. In the current study, we analysed two types of intradialytic exercise separately regarding their effects on relieving RLS severity. Intradialytic stretching was the second most effective non-pharmacological intervention for reducing RLS severity; the mechanism underlying this reduction is potentially associated with elevated cardiac output, dilation of blood vessels and increased lower limb circulation [7, 48]. Several types of oil massage were investigated to identify their capacities to reduce RLS severity and all of them were merged into the aromatherapy massage group in the present study. Gupta *et al.* [49] observed that 76.9% of patients with RLS preferred to massage their legs to alleviate unpleasant sensations. Our study revealed that aromatherapy massage might play a role in reducing RLS severity. However, among the included studies, only the study of Nasiri *et al.* [35] compared the effects of aromatherapy massage with those of a placebo massage (in which paraffin was used). Because the evidence was limited, distinguishing

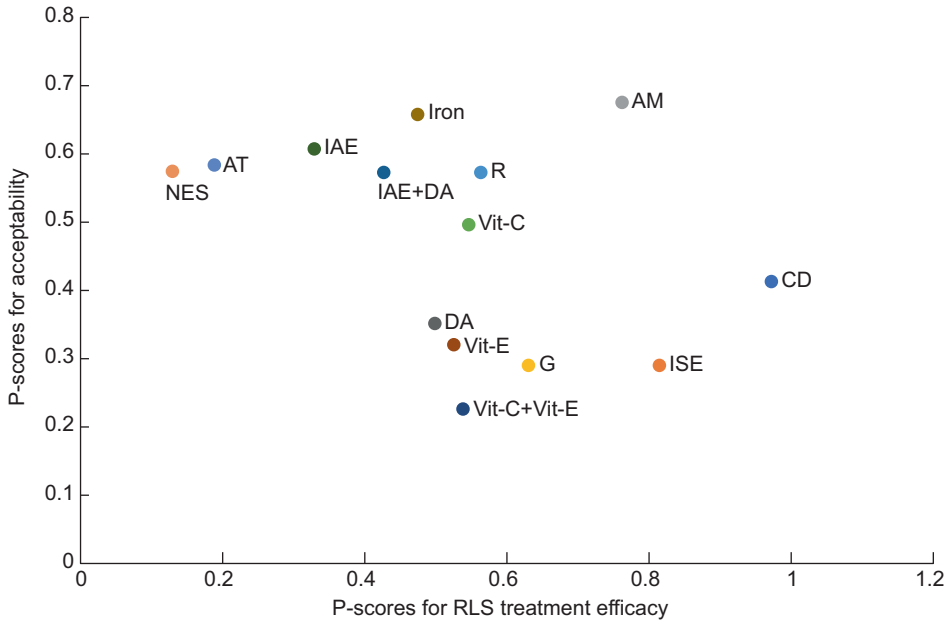


FIGURE 4: Scatter plot of P-score of efficacy and acceptability in the indicated treatments for ESRD patients with RLS. *x*-axis: efficacy; *y*-axis: acceptability. AM, aromatherapy massage; AT, acupoint therapy; C, control; CD, cool dialysate; DA, dopamine agonist; G, gabapentin; IAE, intradialytic aerobic exercise; ISE, intradialytic stretching exercise; NES, neuromuscular electrical stimulation; Vit-C, vitamin C; Vit-E, vitamin E; R, reflexology.

whether these treatment effects were the result of massage therapy generally or oil-based aromatherapy massage is difficult.

In the present study, gabapentin was the most effective pharmacological intervention in reducing RLS symptoms. The gabapentin dosage in the included studies was 100–300 mg after dialysis sessions [8, 11, 37]. Although the treatment dosage was within the recommended range, gabapentin-related adverse events and patient dropouts were still reported [37]. Dopaminergic dysfunction has been implicated in the pathogenesis of RLS, and L-dopa therapy has proven its efficacy in previous studies [50]. In the current study, dopamine agonists reduced RLS severity when comparisons were made with a control group.

Only Giannaki *et al.* [30] addressed the effects of a combination of pharmacological (dopamine agonist) and non-pharmacological (intradialytic aerobic exercise) treatments. No antagonist effect was detected according to the current component NMA, therefore this combination might be a reasonable approach.

In addition to reductions in RLS severity and improvements in sleep quality, we had planned to evaluate the enhancements in patients' quality of life associated with various interventions. However, only three RCTs—those of Dauvilliers *et al.* [25], Giannaki *et al.* [29] and Mortazavi *et al.* [34]—reported outcomes about patients' quality of life. No newer RCTs investigating quality of life have emerged, thus the conclusion on improving patient quality of life is expected to be the same as that in a previous report [6].

Our study has several strengths. First, we conducted a component NMA to evaluate the treatment effect of each component in composite interventions. Second, we performed an updated NMA including several non-pharmacological interventions that had not been reviewed before. Third, we demonstrated that different types of intradialytic exercise induce different effects in the reduction of RLS severity. Fourth, we assessed the degree of confidence in the evidence associated with our work using CINeMA.

The present study had several limitations. First, we grouped different dopamine agonists into one group and aromatherapy massage treatments with different oils into one group when comparing their effects on reducing RLS severity. However, the treatment response might be different. Second, to enroll the maximum number of participants, three studies exhibiting different RLS severity scores were excluded [7, 34, 40]. Third, the short duration of interventions in enrolled studies limits the validity of extrapolations to the long-term outcomes of the interventions. Fourth, most of the enrolled studies were based on haemodialysis patients, with only one study with mixed haemodialysis patients and peritoneal dialysis patients [40]. This mixed population could be a source of heterogeneity. Furthermore, the protocols of non-pharmacological interventions used in enrolled studies were based on haemodialysis sessions. Therefore, the effectiveness of current mentioned non-pharmacological interventions and their clinical applications in peritoneal dialysis patients need further discussion. Fourth, most of the comparisons came from indirect evidence. Moreover, most of the comparisons were considered to have low to very low confidence of evidence according to CiNeMA. The reason for low confidence is that most of the comparisons were judged as having major concerns regarding imprecision and incoherence.

CONCLUSION

Cool dialysate was concluded with high confidence to be the most effective treatment in reducing RLS severity and gabapentin was the most potent pharmacological treatment. Because cool dialysate is effective and has other potential benefits, it is appropriate to apply it to treat patients with ESKD and RLS. Other potential interventions include aromatherapy massage, intradialytic stretching exercises and reflexology, but all have limited confidence of evidence. More effectively designed parallel RCTs with sufficient sample sizes are required to evaluate these potential interventions and their long-term outcomes.

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SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

AUTHORS' CONTRIBUTIONS

C.-H.C., T.H.L. and J.-J.C. participated in conceptualization (create ideas and overarching research goal). T.H.L., J.-J.C. and G.K. participated in methodology, validation and writing the original draft. J.-J.C. carried out the software programing and supporting algorithms. G.K. and J.-J.C. carried out the formal analysis. T.H.L., J.-J.C. and G.K. carried out the investigation and data curation. P.-C.F. and H.-Y.Y. were responsible for resources and visualization. C.-L.Y. and H.-Y.Y. reviewed and edited the manuscript. C.-H.C. and Y.-K. were responsible for the supervision and project administration. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Lin CH, Wu VC, Li WY *et al.* Restless legs syndrome in end-stage renal disease: a multicenter study in Taiwan. *Eur J Neurol* 2013; **20**: 1025–1031
2. Scherer JS, Combs SA, Brennan F. Sleep disorders, restless legs syndrome, and uremic pruritus: diagnosis and treatment of common symptoms in dialysis patients. *Am J Kidney Dis* 2017; **69**: 117–128
3. Lin XW, Zhang JF, Qiu MY *et al.* Restless legs syndrome in end stage renal disease patients undergoing hemodialysis. *BMC Neurol* 2019; **19**: 47
4. Winkelman JW, Chertow GM, Lazarus JM Restless legs syndrome in end-stage renal disease. *Am J Kidney Dis* 1996; **28**: 372–378
5. Massey TH, Robertson NP. Restless legs syndrome: causes and consequences. *J Neurol* 2020; **267**: 575–577
6. Huang CW, Lee MJ, Wang LJ *et al.* Comparative efficacy and acceptability of treatments for restless legs syndrome in end-stage renal disease: a systematic review and network meta-analysis. *Nephrol Dial Transplant* 2020; **35**: 1609–1618
7. Fauzi A, Triaswati R. The effect of intradialytic stretching training on restless legs syndrome and sleep quality in hemodialysis patients. *Korean J Adult Nurs* 2021; **33**: 37–43
8. Ali M, Iram H, Nasim F *et al.* Comparison of the efficacy of gabapentin versus levodopa-C for the treatment of restless legs syndrome in end-stage renal disease on hemodialysis patients. *Cureus* 2020; **12**: e12034
9. Zirak Aliabadi A, Mirhosseini Z, Rastaghi S *et al.* Comparison of the effect of cold dialysate versus stretching exercises on severity of restless legs syndrome in patients undergoing hemodialysis: a randomized controlled trial. *Evidence Based Care* 2020; **10**: 15–22
10. Oshvandi K, Mirzajani Letomi F, Soltanian AR *et al.* The effects of foot massage on hemodialysis patients' sleep quality and restless leg syndrome: a comparison of lavender and sweet orange essential oil topical application. *J Complement Integr Med* 2021; doi: 10.1515/jcim-2020-0121
11. Hajian S, Rajabpoor Nikfam MR, Esmayeilzad Z. Comparison of the effects of pramipexole and gabapentin on the treatment of restless leg syndrome in end-stage chronic renal failure patients undergoing hemodialysis. *J Nephropathol* 2020; **9**: e25
12. Youssef MK. Efficacy of neuromuscular electric stimulation versus aerobic exercise on uraemic restless legs syndrome. *Int Ther Rehabil* 2019; **26**: 1–12
13. Moher D, Liberati A, Tetzlaff J *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; **151**: 264–269, W264
14. Geraint M. Withdrawal of 0.6% glauline (metipranolol). *Br J Ophthalmol* 1991; **75**: 64
15. Buysse DJ, Reynolds CF 3rd, Monk TH *et al.* The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; **28**: 193–213
16. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; **14**: 540–545
17. Kalantar-Zadeh K, Kopple JD, Block G *et al.* Association among SF36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. *J Am Soc Nephrol* 2001; **12**: 2797–2806
18. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019; **22**: 153–160
19. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Method* 2015; **15**: 58
20. Higgins JP, Jackson D, Barrett JK *et al.* Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012; **3**: 98–110
21. Sterne JAC, Savović J, Page MJ *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898
22. Nikolakopoulou A, Higgins JPT, Papakonstantinou T *et al.* CINeMA: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020; **17**: e1003082
23. Mirbagher Ajorpaz N, Rahemi Z, Aghajani M *et al.* Effects of glycerin oil and lavender oil massages on hemodialysis patients' restless legs syndrome. *J Bodyw Mov Ther* 2020; **24**: 88–92
24. Aliasgharpour M, Abbasi Z, Pedram Razi S *et al.* The effect of stretching exercises on severity of restless legs syndrome in patients on hemodialysis. *Asian J Sports Med* 2016; **7**: e31001
25. Dauvilliers Y, Benes H, Partinen M *et al.* Rotigotine in hemodialysis-associated restless legs syndrome: a randomized controlled trial. *Am J Kidney Dis* 2016; **68**: 434–443
26. Deng Y, Wu J, Jia Q. Efficacy of intravenous iron sucrose in hemodialysis patients with restless legs syndrome (RLS): a randomized, placebo-controlled study. *Med Sci Monit* 2017; **23**: 1254–1260
27. Gao Y, Zhao J, Guo C. Effect of governor moxibustion for restless legs syndrome of maintenance hemodialysis:a randomized controlled trial. *Zhongguo Zhen Jiu* 2016; **36**: 597–600
28. Ghasemi M, Rejeh N, Heravi-Karimooi M *et al.* The effectiveness of foot reflexology in the severity of restless legs syndrome in female patients undergoing dialysis: a randomized controlled trial. *Crit Care Nurs J* 2018; **11**: e68945
29. Giannaki CD, Sakkas GK, Karatzaferi C *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 Nephrol* 2013; **14**: 194
30. Giannaki CD, Sakkas GK, Karatzaferi C *et al.* Combination of exercise training and dopamine agonists in patients with RLS on dialysis: a randomized, double-blind placebo-controlled study. *ASAIO J* 2015; **61**: 738–741
31. Hashemi SH, Hajbagheri A, Aghajani M. The effect of massage with lavender oil on restless leg syndrome in hemodialysis patients: a randomized controlled trial. *Nurs Midwifery Stud* 2015; **4**: e29617
32. Kashani E, Mirhosseini Z, Rastaghi S *et al.* The effect of the cool dialysate on the restless leg syndrome in hemodialysis patients: randomized triple-blind clinical trial. *Iran J Nurs Midwifery Res* 2019; **24**: 200–205
33. Mohammadi MM, Raygani AAV, Ghobadi A *et al.* Effect of near-infrared light therapy based on acupoints on the severity of restless legs syndrome in patients undergoing hemodialysis: a single-blind, randomized controlled trial. *Clin Med Res* 2018; **16**: 1–8
34. Mortazavi M, Vahdatpour B, Ghasempour A *et al.* Aerobic exercise improves signs of restless leg syndrome in end stage renal disease patients suffering chronic hemodialysis. *Sci World J* 2013; **2013**: 628142
35. Nasiri M, Abbasi M, Khosroabadi ZY *et al.* Short-term effects of massage with olive oil on the severity of uremic restless legs syndrome: a double-blind placebo-controlled trial. *Complement Ther Med* 2019; **44**: 261–268
36. Rafie S, Jafari M, Azizi M *et al.* Restless legs syndrome in hemodialysis patients. *Saudi J Kidney Dis Transpl* 2016; **27**: 326–330
37. Razazian N, Azimi H, Heidarnejadian J *et al.* Gabapentin versus levodopa-C for the treatment of restless legs syndrome in hemodialysis patients: a randomized clinical trial. *Saudi J Kidney Dis Transpl* 2015; **26**: 271–278
38. Sagheb MM, Dormanesh B, Fallahzadeh MK *et al.* Efficacy of vitamins C, E, and their combination for treatment of restless legs syndrome in hemodialysis patients: a randomized, double-blind, placebo-controlled trial. *Sleep Med* 2012; **13**: 542–545
39. Shahgholian N, Jazi SK, Karimian J *et al.* The effects of two methods of reflexology and stretching exercises on the severity of restless leg syndrome among hemodialysis patients. *Iran J Nurs Midwifery Res* 2016; **21**: 219–224
40. Sloand JA, Shelly MA, Feigin A *et al.* A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *Am J Kidney Dis* 2004; **43**: 663–670
41. Allen RP. Minimal clinically significant change for the International Restless Legs Syndrome Study Group rating scale in clinical trials is a score of 3. *Sleep Med* 2013; **14**: 1229
42. Palmieri-Smith RM, Leonard-Frye JL, Garrison CJ *et al.* Peripheral joint cooling increases spinal reflex excitability and serum norepinephrine. *Int J Neurosci* 2007; **117**: 229–242
43. Larkin JW, Reviriego-Mendoza MM, Usvyat LA *et al.* To cool, or too cool: is reducing dialysate temperature the optimal approach to preventing intradialytic hypotension? *Semin Dial* 2017; **30**: 501–508
44. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol* 2015; **26**: 957–965
45. Dasgupta I, Thomas GN, Clarke J *et al.* Associations between hemodialysis facility practices to manage fluid volume and intradialytic hypotension and patient outcomes. *Clin J Am Soc Nephrol* 2019; **14**: 385–393
46. Song YY, Hu RJ, Diao YS *et al.* Effects of exercise training on restless legs syndrome, depression, sleep quality, and fatigue among hemodialysis patients: a systematic review and meta-analysis. *J Pain Symptom Manage* 2018; **55**: 1184–1195
47. Giannaki CD, Hadjigeorgiou GM, Karatzaferi C *et al.* A single-blind randomized controlled trial to evaluate the effect of 6 months of progressive aerobic exercise training in patients with uraemic restless legs syndrome. *Nephrol Dial Transplant* 2013; **28**: 2834–2840
48. van Vilsteren MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. *Nephrol Dial Transplant* 2005; **20**: 141–146
49. Gupta R, Goel D, Ahmed S *et al.* What patients do to counteract the symptoms of Willis-Ekbom disease (RLS/WED): effect of gender and severity of illness. *Ann Indian Acad Neurol* 2014; **17**: 405–408
50. Trenkwalder C, Stiasny K, Pollmacher T *et al.* L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. *Sleep* 1995; **18**: 681–688

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