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CLINICAL REVIEW

Complementary and alternative therapies for restless legs syndrome: An evidence-based systematic review

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SUMMARY

Restless legs syndrome (RLS) is defined as an irresistible urge to move the legs, which is usually accompanied by paresthesias or dysesthesias at least twice weekly, and affects 2%–4% of adults in Europe and North America. This systematic review assesses the current complementary and alternative options for RLS and the potential benefits of those treatments on sleep quality, mood disorder, and quality of life. A systematic search of the PubMed, Embase, Cochrane, and Web of Science databases was conducted. Eighteen studies met the inclusion criterion, which included the use of the international RLS study group criteria. Complementary and alternative therapies have been found to be effective in both primary and secondary RLS. The severity of primary RLS symptoms can be significantly ameliorated by exercise training, transcutaneous spinal direct current stimulation, pneumatic compression devices, light therapy, repetitive transcranial magnetic stimulation, and acupuncture. Pneumatic compression devices and yoga also improve RLS-related disorders. Exercise training is highly efficacious in the reduction of symptom severity in uremic RLS and related effects such as poor quality of life. Endovenous laser ablation may be a good choice for patients with concurrent RLS and superficial venous insufficiency.

Introduction

Restless legs syndrome (RLS) is defined as an irresistible urge to move the legs. It is usually accompanied by paresthesia and dysesthesia, and the symptoms can be partly or totally relieved by physical activity [1–7]. Patients with RLS describe the sensory discomfort using terms such as pain, tingling, creeping, burning, bugs, electricity, or nervousness [8]. It varies in symptom frequency, severity, and duration. The effects of RLS on the ability to function range from minor annoyance to negative effects on work, social activities, and emotional well-being [9]. However, sleep disruption induced by RLS and daytime fatigue are the most common reasons for seeking medical advice [10].

Bothersome RLS affects 2%–4% of adults in Europe and North America at least twice weekly and is more common among women [11,12]. RLS is associated with female gender, pregnancy, elderly age, poor health, lower socioeconomic status, and positive family history [13–18]. It can occur in an idiopathic form or secondary to other conditions such as renal failure, iron deficiency, pregnancy, or particular medications [19]. The pathophysiology of RLS is still unclear, although it is believed to result from iron deficiency and dopamine imbalance in the central nervous system [20].

Therapies for RLS can be divided into pharmacological and non-pharmacological treatments. Three dopamine agonists (ropinirole, pramipexole, and rotigotine) and one calcium channel alpha-2delta receptor ligand (gabapentin enacarbil) are currently approved by the Food and Drug Administration for pharmacological treatment of moderate to severe RLS [9]. Various clinical trials [1–7] that have examined the efficacy of physiotherapy in the non-pharmacological treatment of RLS have demonstrated that it can alleviate the clinical symptoms. However, no systematic review has been published addressing the effectiveness and safety of non-pharmacological treatment for the relief of RLS symptoms. Hence, this systematic review was conducted to evaluate the efficacy and safety of complementary and alternative therapies for RLS, based on scientific evidence.

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Abbreviations

EECP	enhanced external counter pulsation
ELA	endovenous laser ablation
HD	hemodialysis
IRLS	International restless legs syndrome rating scale
PCDs	pneumatic compression devices
PLM	periodic limb movements
PLMI	periodic leg movements index
PLMS	periodic limb movements in sleep
PLMW	periodic limb movements in wake
PSQI	Pittsburgh sleep quality index
QoL	quality of life
RCT	randomized controlled trial
RLS	restless legs syndrome
rTMS	repetitive transcranial magnetic stimulation
SVI	superficial venous insufficiency
tDCS	transcranial direct current stimulation
tsDCS	transcutaneous spinal direct current stimulation
VAS	visual analogue scale

Methods

Data sources and search strategy

A systematic search of the PubMed, Embase, Cochrane, and Web of Science databases using the search terms 'restless leg*'or 'RLS' was conducted in August 2016 to identify available data sources for complementary and alternative therapies for RLS. Only papers in English were included in the review. Further relevant trials were obtained by manually searching the conference abstracts and reference lists of all identified related publications to avoid omitting relevant randomized controlled trials (RCTs).

Selection criteria

Studies were identified based on the following criteria. i) RCTs involving individuals with a diagnosis of RLS defined by the international restless legs syndrome study group [1]. If no such criteria were specified, the study had to present explicitly predefined diagnostic criteria for the selection of participants. ii) RCTs evaluating all complementary and alternative therapies for the treatment of primary or secondary RLS. iii) RCTs comparing complementary and alternative therapies with placebo or pharmacological treatments; we also included trials that compared a combined non-pharmacological plus pharmacological treatment with the same pharmacological treatment alone. iv) The study reported validated RLS symptom or quality of life (QoL) scale scores, visual analogue scale (VAS) scores, clinician and patient global impact scale scores, and measures of mood or sleep quality.

The exclusion criteria were as follows: i) reviews, animal trials, and duplicate secondary analyses; ii) case studies, dissertations, and studies that were unavailable in English; iii) unavailable or incomplete outcome data.

Outcome measures

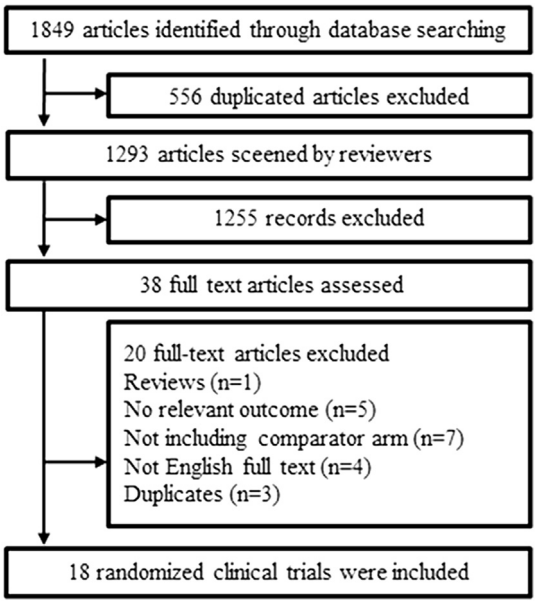
Primary outcomes included relief of restless legs symptoms measured by the International restless legs syndrome rating scale (IRLS) or other scales such as the VAS. Secondary outcomes included the relief of periodic leg movements index (PLMI), sleep disturbance, depression, and QoL scales.

Data extraction

Two reviewers independently reviewed whether trials fulfilled the inclusion criteria by assessing the titles and abstracts of each paper. Potential studies were then retrieved in full and verified for eligibility. Data extracted from the RCTs included the study designs, participants' characteristics, and outcomes. Disagreements and discrepancies were resolved via discussion or following arbitration by a third reviewer if necessary.

Results

The initial database search identified 1849 papers. Of these, only 18 studies met our inclusion criteria and were included in this systematic review. Twelve trials focused on primary RLS and the other six on secondary RLS.



Complementary and alternative therapies for primary RLS involved aerobic exercise training (n = 1), electrical stimulation (n = 3), vibratory stimulation (n = 1), enhanced external counter pulsation (EECP) (n = 1), pneumatic compression devices (PCDs) (n = 1), light therapy (n = 2), repetitive transcranial magnetic stimulation (rTMS) (n = 1), acupuncture (n = 1), and yoga (n = 1). The most common form of physiotherapy tested in uremic RLS was exercise training (n = 5), basically consisting of continuous low to medium aerobic exercise on a cycle ergometer. Only endovenous laser ablation (ELA) has been evaluated for venous-related RLS. Among the 18 trials included in our study, 16 discussed the severity of illness, four discussed motor symptoms, eight discussed sleep quality, three discussed mood disorders, and four discussed QoL.

Efficacy of complementary and alternative therapies on RLS symptom severity

Primary RLS

Our literature search for RCTs of complementary and alternative therapies for primary RLS symptom severity yielded 11 references covering eight treatment options that met our inclusion criteria (Table 1).

Exercise. RLS symptoms typically occur during periods of inactivity and are generally alleviated, at least temporarily, by movement

Table 1
The outcomes of complementary and alternative therapies for primary RLS.

Study	Study design	Intervention	Duration	Treatment groups	Intervention vs. placebo(n)	Primary outcomes	Secondary outcomes	adverse effects
Altunrende 2014 [32]	Randomized, double-blind, sham-controlled trial	rTMS	Four weeks	rTMS vs. sham stimulation	11 vs. 8	Parallel:58% improvement in IRLS score Crossover:78% improvement in IRLS score	NR	No side effects
Aukerman 2006 [2]	Randomized controlled trial	Aerobic and resistance exercise/three times per week	12 wk	Exercise vs. control	11 vs. 17	39% improvement in IRLS score	NR	Knee pain (9%)
Heid 2014 [23]	Double-blind, placebo-controlled study	tsDCS	15 min	Anodal vs. cathodal vs. Sham	20 vs. 20 vs. 20	t1: anodal:42% improvement in VAS score cathodal:26% improvement in VAS score t2: anodal:32% improvement in VAS score cathodal: no significant effects	NR	No side effects
Innes 2012 [51]	Randomized, controlled study	Yoga	Eight weeks	Yoga vs. educational film	8 vs. 10	NR	59 %improvement in PSQI; 75% reductions in prevalence of insomnia; 78% reductions in depression	Mild, temporary muscle soreness (38%)
Koo 2015 [24]	Double-blind, randomized, sham-controlled trial	tDCS	Two week	Cathode vs. anodal vs. Sham	10 vs. 10 vs. 11	No significant difference among the groups	No significant difference in PSQI and BDI-II among the groups	Itching sensation (22%), pain (13%), fatigue (9%), tingling sensation (6%), burning sensation (6%), headache (6%)
Lettieri 2009 [3]	Randomized, double-blind, sham-controlled trial	PCDs	Four weeks	PCDs vs. sham PCDs	21 vs. 14	59% improvement in IRLS score and 48% improvement in JHRLSS score	26% improvement in RLS-QLI; 42% improvement in ESS; 47% improvement in fatigue	NR
Mitchell 2011 [30]	Randomized controlled trial	Near-infrared light	Four weeks	Near-infrared light vs. sham treatment	17 vs. 17	52% improvement in IRLS score	NR	NR
Mitchell 2011 [31]	Randomized controlled trial	Two near-infrared light	Four weeks	Anodyne vs. health light	11 vs. 13	44% vs. 52% improvement in IRLS score	NR	NR
Montagna 1984 [27]	Randomized, controlled, crossover trial	Vibratory stimulation	One week	Vibratory stimulation vs. placebo	6 vs. 6	No significant improvement in severity of RLS	No significant effect in leg jerking and leg dysaesthesia	NR
Pan 2015 [35]	Randomized, single-blind sham-controlled study	Acupuncture	Six weeks	Standard acupuncture vs. randomized acupuncture	15 vs. 16	25% vs. 6% improvement in IRLS score	25% improvement in nocturnal activity; 22% improvement in early sleep activity; 16% improvement in ESS	No side effects
Rajaram 2006 [29]	Randomized, double-blind placebo-controlled study	EECP	Seven weeks	EECP vs. placebo EECP	4 vs. 2	No significant improvement in IRLSS score between the groups	No significant improvement in sleep efficiency and PLMI between the groups	NR

Rozeman 2014 [26]	Randomized crossover study	External sensory stimulation	30 min	No electrical stimulation vs. tactile and provocative sensory stimulation vs. tactile sensory stimulation only	18 vs. 18 vs. 18	No significant differences in VAS scores between the different conditions	No significant differences in PLMI between the different conditions	NR

Abbreviations: BDI-II, Beck depression inventory version II; EECP, Enhanced external counter pulsation; ESS, Epworth sleepiness scale; IRLS, International restless legs syndrome rating scale; NR, Not reported; PCDs, Pneumatic compression devices; PLMI, Periodic limb movements index; PSQI, Pittsburgh sleep quality index; RLS, Restless legs syndrome; RLS-QLI, Restless legs syndrome quality of life instrument; rTMS, Repetitive transcranial magnetic stimulation; tDCS, Transcranial direct current stimulation; tsDCS, Transcutaneous spinal direct current stimulation; t1, Directly after tsDCS; t2, 30 min after tsDCS; VAS, Visual analogue scale.

[21]. Some websites advocate light to moderate exercise to alleviate RLS symptoms, although there is only Class III evidence to support this recommendation in the clinical guidelines [2,22]. To date, only one study has examined the effectiveness of aerobic and resistance exercise on the symptoms of primary RLS [2]. The intervention with exercise lasted for 12 wk and resulted in a 39% improvement in RLS severity assessed by the IRLS. The improvement in RLS symptoms appeared to show a ceiling effect at six weeks, with no further significant improvement thereafter. However, as these conclusions were based on only one study, future studies are necessary to further address the effects of exercise on the symptoms of RLS.

Electrical stimulation. Heide et al. were the first to use transcutaneous spinal direct current stimulation (tsDCS) to reduce pathologically enhanced spinal excitability to ameliorate the clinical symptoms of RLS [23]. In this study, 20 patients with idiopathic RLS received one session of cathodal, anodal, or sham stimulation of the thoracic spinal cord for 15 min (2.5 mA) in a randomized order. The application of anodal and cathodal stimulation led to a short-lasting improvement in VAS scores for restless legs symptoms compared with sham stimulation, and no side effects were reported except for a slight sensation beneath the electrodes.

Based on the pathophysiology of a hyperexcitable somatosensory cortex in people with RLS, a two-week, double-blind, randomized, sham-controlled trial was carried out in 2015 [24]. However, transcranial direct current stimulation (tDCS) with electrodes on the sensorimotor areas showed no significant effect in people with drug-naïve RLS, and an itching sensation was the most common adverse effect. Notably, the negative results might have been caused by the strong placebo effect of tDCS stimulation, which is known to activate both dopamine and endogenous opioid peptides, which are related to the treatment of RLS, in the nucleus accumbens [25].

A randomized crossover study measured the effect of external sensory stimulation on RLS severity [26]. By coincidence, Rozeman et al. were not able to show a significant improvement in RLS symptoms on VAS scores after the appliance of an external tactile and/or proprioceptive electrical stimulus. However, they did find a small trend toward lower VAS scores in conditions with external sensory stimulus and recommended further investigation.

Vibratory stimulation. In a 1984 study [27], patients applied a small electrically driven battery-operated mechanical vibrator (4.5 V, 120 Hz) to one sural region for at least 15 min each night before going to sleep. The vibratory stimulation of the lower limbs, which mainly activates muscle spindle afferent discharges, failed to exert a pronounced and significant effect. However, we should stress that the stimulation was only applied for one week, and thus its long-term efficacy remains to be assessed.

Enhanced external counter pulsation. EECP is an adjunctive means of improving coronary blood flow by increasing the venous return to the heart during diastole, and was reported to improve RLS symptoms significantly in an open-label study [28]. However, a subsequent small short-term RCT ($n = 6$) conducted by Rajaram et al. found that EECP treatment did not show a short- or long-term improvement in RLS symptoms compared with placebo [29].

Pneumatic compression devices. In addition to EECP, PCDs for enhancing venous and lymphatic drainage have also been assessed in the treatment of RLS. Lettieri and colleagues [3] enrolled 21 treatment subjects and 14 sham subjects in their study of therapeutic PCDs applied for four weeks. Therapeutic subjects reported a significant reduction of 58.62% in RLS severity and one third reported complete relief, compared with none of the subjects using

sham devices. Potential explanations for the effect were that vascular compression from PCDs stimulates the release of endothelial mediators, or improves local perfusion to relieve subclinical ischemia. Regardless, it seems that PCDs are a promising therapeutic option for RLS that deserves further research.

Light therapy. Near-infrared light treatment to the lower legs significantly improved RLS symptoms in an RCT conducted in 2006 [30]. Four weeks of treatment resulted in a mean decrease of 12.7 (±7.7) in IRLS scores in the treatment group compared with a decline of 4.4 (±3.6) in the control group. There was also a steady improvement in RLS symptoms. The purported mechanism for this response could be the vasodilatory effect of nitric oxide. Subsequently, Lettieri et al. initiated a clinical study to assess whether different wavelengths and frequencies influenced the effectiveness of the treatment [31]. It is interesting that the wavelengths and frequencies had no effect on the outcome, and the two near-infrared light devices both produced a considerable improvement in RLS symptoms after four weeks of treatment, confirming the previous findings by Rajaram et al.

Repetitive transcranial magnetic stimulation. RTMS is a non-invasive technique that is used to alter brain functions by improving cortical plasticity, and can be used in various neurological disorders [32,33]. A randomized double-blinded study evaluated the effect of high-frequency (5 Hz) rTMS over the supplementary motor area on RLS symptoms in idiopathic RLS patients [32]. This small trial reported a statistically significant improvement in IRLS scores in the real stimulation group ($n = 11$) but not the sham stimulation group ($n = 8$) after the fifth and tenth sessions. In addition, the IRLS scores of five patients who received both sham and real stimulation did not change with the sham stimulation, whereas a significant improvement was seen with the real stimulation. This study is still ongoing and there are plans to include a larger sample size and extend the time between sessions to determine the best interval for rTMS administration. We look forward to the results.

Acupuncture. Acupuncture is an ancient healing art that has been an integral part of traditional Chinese medicine for over 2000 y [34,35]. In recent years, acupuncture has been shown to be a remarkably effective and well-tolerated agent for the treatment of serious neurological and psychiatric diseases [34,36–40]. The efficacy of acupuncture on primary RLS symptoms was investigated in a prospective single-blind sham-controlled trial [35]. The results were very promising, as standard acupuncture significantly improved IRLS scores (−5.5 vs. −1.4) in RLS patient without any side effects. The acupoints used in patients of the standard group were *Shenshu, Mingmen, Xuehai, Chenshan, Taichun, Zusanli, Sanyinjiao*, and *Taixi*.

Uremic RLS

The prevalence of RLS in hemodialysis (HD) patients is almost 30%, which is significantly higher than in the general population [41]. Despite the high prevalence and the great impact of the syndrome on HD patients, limited data are available regarding physiotherapy treatment options to reduce RLS symptoms. The literature to date only includes studies that used exercise training as an intervention. The silver lining is that the effect of exercise training in HD patients has been studied more thoroughly than in idiopathic patients, and has been found to be a safe and effective approach for uremic RLS (Table 2).

Exercise. The first study to investigate the influence of exercise training on RLS in HD patients was conducted by Sakkas et al., in 2008 [4]. The exercise training regime consisted of 45 min of continuous cycling using a bedside cycle ergometer at 45–50 rpm during the HD session. The exercise resistance was set between 65% and 75% of the patient's maximum power capacity (watts). The results showed that 16 wk of aerobic exercise training was safe and efficacious in reducing uremic RLS symptoms, and IRLS scores improved by up to 42%. A similar RCT was subsequently conducted [5], and the 16-wk exercise training in uremic RLS patients again reduced the RLS symptom severity by 28%, confirming the previous findings.

As exercise training has been shown to improve RLS symptoms in uremic RLS patients, Giannaki and colleagues conducted a trial to investigate whether the improvement is due to the expected adaptation to systemic exercise or to the relief that leg movements confer while exercising on a cycle ergometer [6]. Their data showed that RLS symptom severity declined by 58% in the progressive aerobic exercise training group, while 17% in the control group performed the exercise with no added resistance. This result indicates that chronic exercise-induced adaptations ameliorate the symptoms rather than the acute relief conferred by leg movements. Hence, to achieve substantial improvements in RLS symptoms with exercise training, uremic patients should preferably exercise with a certain amount of resistance applied.

Another study compared the effectiveness of exercise training with dopamine agonist treatment for reducing the severity of uremic RLS [7]. A six-month exercise training regime (46% improvement) was as effective as a six-month low dose dopamine agonist treatment (54% improvement) in reducing RLS symptoms, whereas there was no significant change in IRLS scores in the placebo group (6% improvement).

RLS with superficial venous insufficiency

Endovenous laser ablation. As venous disease has been proposed as a cause of RLS [42], Hayes et al. [43] conducted a randomized, unblinded, controlled trial to examine the effect of ELA in patients with concurrent RLS and duplex-proven superficial venous insufficiency (SVI). Their results showed that ELA of the refluxing superficial axial veins and sclerotherapy of the associated varicosities alleviated or eliminated RLS symptoms in patients with moderate to very severe RLS and SVI, which suggests that venous disease plays some role in RLS. Therefore, all RLS patients should be evaluated for venous insufficiency and those that are diagnosed with SVI should be referred for ELA before initiation or continuation of drug therapy.

Effects of complementary and alternative therapies on aspects of motor symptoms

Between 80% and 90% of RLS patients also present with increased stereotypic repetitive movements called periodic limb movements (PLM) [1,44,45]. These movements may occur during waking (PLMW) or sleeping (PLMS), and have been used for assessing the severity of RLS [46]. In addition, PLMS is reported to be an independent predictor of mortality in hemodialysis patients [47].

Primary RLS

The first study that used the periodic limb movement index (PLMI) as a measure of severity in the physiotherapy treatment of RLS was published in 2006 [29]. In this study, EECP treatment failed to show a marked effect upon PLMS and its associated arousals in RLS patients. Subsequently, the next few articles were also attention to use the PLMI or activity levels to assess the severity of RLS.

Table 2
The outcomes of complementary and alternative therapies for secondary RLS.

Study	Type of RLS	Study design	Intervention	Duration	Treatment groups	Intervention vs. placebo(n)	Primary outcomes	Secondary outcomes	adverse effects
Hayes 2008 [43]	RLS with SVI	randomized, unblinded, controlled trial	ELA	Six weeks	ELA vs. non-operative	19 vs. 16	80% improvement in IRLS score	NR	Transient postoperative discomfort in the region of the treated veins, and mild bruising at the access sites.
Giannaki 2010 [48]	Uraemic RLS	Randomized, crossover, study	Exercise	45 min	light exercise vs. heavy exercise vs. no exercise	8 vs. 8 vs. 8	NR	Light exercise: 34% improvement in PLM/h_{HD} heavy exercise: 29% improvement in PLM/h_{HD}	NR
Giannaki 2013 [6]	Uraemic RLS	Single-blind randomized controlled trial	Aerobic exercise/three times per week	six months	Progressive exercise training vs. exercise with no resistance	12 vs. 12	58% improvement in IRLS score	20% improvement in sleep quality, 24% in Zung depression scale	Without adverse effects
Giannaki 2013 [7]	Uraemic RLS	Randomized, partially double blind, controlled trial	Aerobic exercise/three times per week	six months	Exercise training vs. dopamine agonists vs. placebo	16 vs. 8 vs. 8	46% improvement in IRLS score	9% improvement in Sleep Diary, 18% in depressive symptoms, 18% improvement in SF-36 questionnaire	Without adverse effects
Mortazavi 2013 [5]	Uraemic RLS	Randomized controlled trial	Aerobic exercise/three times per week	16 wk	Exercise vs. control	13 vs. 13	28% improvement in IRLS score	No significant difference in SF-63 among the groups	NR
Sakkas 2008 [4]	Uraemic RLS	Randomized controlled trial	Aerobic exercise/three times per week	16 wk	Exercise vs. control	7 vs. 7	42% improvement in IRLS score	25% improvement in QoL, 50% in sleep quality, 50% in exercise capacity	NR

Abbreviations: ELA, Endovenous laser ablation; IRLS, International restless legs syndrome rating scale; NR, Not reported; PLM, Periodic limb movements; QoL, Quality of life; RLS, Restless legs syndrome; SVI, Superficial venous insufficiency.

In a randomized crossover study that evaluated the effect of external sensory stimulation on RLS [26], patients who suffered from PLMW underwent three consecutive immobilization tests in a random order: no electrical stimulation, tactile and provocative sensory stimulation, and tactile sensory stimulation only. However, the PLMI did not detect any significant differences between the different immobilization tests.

Fortunately, in a 2015 study by Pan et al. [35], standard acupuncture significantly improved patients' scores on the IRLS and significantly decreased their scores for nocturnal activity (31.34 vs. 10.18) and early sleep activity (36.07 vs. 8.57) compared with randomized acupuncture. It seems that acupuncture could serve as an effective approach in the treatment of RLS movement symptoms; however, the mechanism of its effect on RLS symptoms remains unknown.

Uremic RLS

The only study to date that has examined the potential beneficial effects of complementary and alternative therapies on the motor symptoms of uremic patients with RLS focused on aerobic exercise [48]. A single bout of either light or heavy exercise was shown to be equally effective in significantly reducing PLM/h_{HD} in hemodialysis patients with RLS, by 34% and 29%, respectively, and was well tolerated. This was the first study to show that acute intradialytic aerobic exercise, independent of intensity, could effectively reduce the motor symptoms during hemodialysis in patients with uremic RLS.

Effects of complementary and alternative therapies on aspects of sleep quality

According to the literature, sleep loss is the most common presenting complaint of patients seeking medical care for RLS [49,50], and is considered the greatest contributor to the negative effects on patients' QoL [11]. Therefore, the effects of complementary and alternative therapies on sleep aspects of RLS are discussed below.

Primary RLS

A trial investigating the efficacy of TDCS in people with drug-naïve RLS reported a significant decrease in the Pittsburgh sleep quality index (PSQI), but there was no significant difference between TDCS and sham stimulation [24]. Similarly, vibratory stimulation, another physical approach, also failed to show a significant effect on the subjective quality of sleep in a randomized trial published in 1984 [27]. The first study to use polysomnography to assess the quality of sleep unfortunately reported that EECP did not improve RLS patients' rapid eye movement sleep and slow wave sleep compared with a placebo [29]. These negative results seem to argue against the role of physiotherapy treatments in RLS-related sleep disorders, but it should be noted that the sample size of these studies were too small to draw a firm conclusion and further studies should be encouraged.

Fortunately, two complementary and alternative approaches did show a positive effect on the quality of sleep in RLS patients. PCDs are convenient devices for patients to operate, and a trial performed by Lettieri et al. [3] showed that they improved sleep quality more than sham devices (16% versus 8%, respectively) with no adverse reactions. Yoga, a popular ancient mind-body discipline, has also been shown to be effective in improving RLS-related sleep disorders [51]. It was proposed as a particularly promising non-pharmacological therapy for older women with RLS based on the results of the trial with 20 postmenopausal women randomized to receive either an eight-week yoga or educational film program. The yoga group demonstrated

significantly greater improvement than controls on several domains of the PSQI (−5.14 vs. −1.25), a greater reduction in the prevalence of insomnia (75% vs. 30%), and a greater increase in average sleep duration (1.61 vs. −0.12 h). However, the mechanisms underlying the improvements observed in this study remain speculative, and larger controlled trials are needed to confirm the benefits of yoga in this and other adult populations with RLS and to evaluate the potential underlying mechanisms.

Uremic RLS

In the first trial that investigated the effect of exercise training on uremic RLS [4], in line with the improvement in IRLS scores, aerobic training for 16 wk also had a positive effect on the quality of sleep, with a 50% decrease in sleep diary scores in the exercise group. The outcomes of that study were confirmed by a more recent study by Giannaki et al. [6], which showed that a six-month intradialytic progressive aerobic exercise training regime was safe and beneficial in improving sleep quality compared with a no-resistance exercise (control) group (−1.8 vs. −1.3). Meanwhile, the changes in sleep quality in the progressive exercise group correlated strongly with the respective changes in Kt/V (dialysis efficiency), indicating a possible association of HD adequacy with sleep, possibly mediated by the known favorable systemic effects of exercise. Whereas exercise training, also at an intensity of 60%–65% of the patient's maximal exercise capacity, failed to improve subjective sleep quality in the comparative study by Giannaki et al., in 2013 [7].

Effects of complementary and alternative therapies on aspects of mood disorders

Apart from damaged sleep quality, RLS has been linked to substantial impairment in mood and health and is associated with significant societal and economic burdens [52–54]. Mood disorders are also considered an important contributor to the poor QoL of patients with RLS [52].

Primary RLS

In an eight-week RCT published in 2012 [51], a yoga program was proposed as a safe and effective intervention for improving depression (decrease 78%) and anxiety (decrease 85%) in postmenopausal women with RLS. The mechanisms underlying the improvements with yoga remain speculative, and it may improve mood by reducing the activity of the sympathetic nervous system and hypothalamic–pituitary–adrenal axis, or by increasing the inhibitory neurotransmitter GABA. In another trial performed by Koo et al. [24], tDCS with electrodes on the sensorimotor areas failed to show a significant effect on depression because of the strong placebo effect.

Uremic RLS

Three articles investigated the effect of exercise training on aspects of mood disorders in patients with uremic RLS. In all of these trials, patients' depression levels were assessed using the self-report scale developed by Zung. The first study conducted by Sakkas et al. showed that aerobic training for 16 wk failed to improve the depression symptoms of uremic RLS patients [4]. In the following studies, exercise training showed a positive role in mood disorders related to uremic RLS. In one six-month trial [6], an intradialytic progressive aerobic exercise training regime improved depression scores by 24% compared with 2% in the no-resistance exercise training group. In another six-month trial [7], an aerobic exercise training treatment was proven to be equal to a low dosage dopamine agonist treatment in improving depression scores in uremic patients (19.06% vs. 15.84%). In contrast, a significant deterioration in depression symptoms was detected in the placebo group, clearly showing the negative effect that RLS can have if left untreated.

Effects of complementary and alternative therapies on QoL

Primary RLS

It is well known that moderate to severe RLS can greatly reduce a patient's QoL and has a significant social cost, with a 20%–50% loss of work productivity [55,56]. Meanwhile, considering that augmentation, which has a considerable impact on patients, often occurs during pharmacological treatment, complementary and alternative therapy may be a good substitute for improving RLS patients' QoL. However, only one RCT investigated the role of complementary and alternative treatment on the QoL in individuals with primary RLS. In that trial [3], PCDs produced greater improvements in all QoL domains and in the severity of illness than sham devices. PCDs seem to be an effective adjunctive or alternative therapy for primary RLS that deserves further research. Unfortunately, no data exist regarding the effect of other complementary and alternative treatments such as yoga on the QoL of RLS patients.

Uremic RLS

It is known that the end-stage renal disease population is characterized by a very low QoL and it is suggested that the accompanying uremic RLS symptoms have an additional detrimental effect [57–59]. Suitable ways to alleviate their RLS symptoms and improve their QoL are urgently needed.

In a study published in 2008 [4], a 16-wk aerobic exercise training regimen significantly improved the QoL of patients with RLS undergoing dialysis using the SF-36 QOL questionnaire. Furthermore, the data showed a 25% improvement in patients' QoL, which mainly because of their poor quality of sleep and inadequate rest. Similarly, the study performed by Giannaki et al. showed a statistically significant improvement in the physical component of QoL, while the changes in the mental component did not reach statistically significant levels [7]. However, a 16-wk RCT that enrolled 26 hemodialysis patients did not find a significant effect of aerobic exercise on the QoL of RLS patients compared with those in control group [5].

In general, aerobic exercise training is suggested as an effective intervention for improving the QoL of patients with end-stage renal disease and future studies with more patients are recommended to confirm this conclusion. Meanwhile, as both the symptom severity and the effects of RLS on various health and QoL parameters are significantly worse in the uremic form than the idiopathic form of the syndrome [60,61], studies investigating other physiotherapy approaches are also needed.

Discussion and conclusion

The results of this systematic review revealed that the severity of primary RLS symptoms can be significantly ameliorated by complementary and alternative options such as exercise training, tsDCS, PCDs, light therapy, rTMS, and acupuncture. With regard to secondary RLS, the application of intradialytic exercise training has consistently been shown to be highly efficacious in the reduction of uremic RLS symptom severity, and ELA has been proven to alleviate or relieve RLS symptoms in patients with RLS and SVI. As for the motor symptoms of RLS, ancient acupuncture was observed to significantly decrease nocturnal activity and early sleep activity in primary RLS patients; and aerobic exercise, independent of

intensity, was suggested to effectively reduce the PLM/h_{HD} in uremic RLS patients.

We also reviewed the complementary and alternative treatment options for improving aspects of sleep quality, mood disorder, and QoL. Interestingly, the application of PCDs and yoga were suggested to improve the sleep quality of primary RLS. Yoga was also proposed as an effective intervention for improving mood in postmenopausal women with RLS, and PCDs seemed to improve all QoL domains. Unfortunately, as no further data exist regarding the effect of other complementary and alternative treatments on the QoL of RLS patients, it was not possible to provide a comprehensive review of this important domain, which is closely related to RLS.

Notably, apart from the effect of exercise training on symptom severity, it is well known that this type of non-pharmacological approach can also confer many beneficial effects on RLS-related PLM, poor sleep, depression, and low QoL, underlining the potential value of this type of intervention on uremic patients' overall mental and physical health. The mechanism(s) by which exercise training could ameliorate RLS symptomatology is still unclear. A possible explanation might lie in the recognized effect of exercise on the β-endorphin system [62]. β-endorphins are opioids that promote a sense of well-being and pain relief. The pathophysiology of RLS is related to a defective opioid system in the brain in this type of patient [63], while treatment with opioids resulted in a successful improvement of RLS symptom severity [64]. Interestingly, in a recent study, β-endorphin levels were found to be reduced in the thalamus of patients with idiopathic RLS [65], supporting the hypothesis of endogenous opioid system involvement in the pathogenesis of the syndrome. In addition, independently from the transmitter system involved, the benefits of RLS symptom severity observed with aerobic exercise may arise through improvements in brain blood flow [66] and HD efficiency [7].

Medicines, especially dopamine agonists, are the most commonly used treatment for RLS [67–69]. However, long-term therapy with a constantly increasing dosage of drugs is associated with the “augmentation phenomenon” and often requires interruption of the therapy [67,70]. On the contrary, no augmentation phenomena or serious adverse effects were observed with complementary and alternative treatment in either idiopathic or secondary RLS patients based on the previous data. It is plausible to incorporate physical therapy such as exercise into current practice in addition to pharmacological treatment as a monotherapy or a complementary measure in the management of RLS disorders.

Based on the currently available evidence, we would recommend exercise training, tsDCS, PCDs, light therapy, rTMS, or acupuncture in the treatment of primary RLS, exercise training in uremic RLS, and ELA in RLS with SVI. Yoga and PCDs should be considered as options to improve the quality of sleep in primary RLS patients with insomnia. For postmenopausal women with RLS, yoga may be a good choice as it is reported to significantly reduce both sleep and mood disturbance without adverse effects. Moreover, as PCDs are convenient and seem to be effective in improving RLS symptom severity and all QoL domains, they represent a very promising adjunctive or alternative therapy for RLS.

It should be noted that insufficient research has been conducted on many of the complementary and alternative approaches reviewed here to verify their treatment effects on RLS, and hence the level of evidence is weak. The preliminary data on complementary and alternative medicines are very promising, but larger and longer-term therapy studies are necessary before these approaches are routinely prescribed for RLS.

Practice points

1) Significant reductions in primary RLS symptom severity were observed in studies using exercise training, transcutaneous spinal direct current stimulation (tsDCS), pneumatic compression devices (PCDs), light therapy, repetitive transcranial magnetic stimulation (rTMS), and acupuncture.
2) PCDs and yoga were found to improve RLS-related disorders.
3) Intradialytic exercise training has been shown to be highly efficacious in the reduction of uremic RLS symptom severity and RLS-related disorders such as poor QoL.
4) Endovenous laser ablation (ELA) may alleviate or relieve RLS symptoms in patients with RLS and superficial venous insufficiency (SVI).

Research agenda

1) Large, long-term complementary and alternative studies are encouraged to further confirm the effects on RLS symptoms.
2) The effects of each complementary and alternative approach on various QoL related parameters such as depression and sleep should be investigated.
3) Other complementary and alternative approaches used for the treatment of primary RLS should be investigated in uremic RLS patients because the condition is significantly worse in these patients than in idiopathic RLS patients, and the preliminary data on complementary and alternative therapies for primary RLS are very promising.
4) RCTs comparing complementary and alternative treatments with pharmacological treatments, and comparing non-pharmacological therapy plus pharmacological treatment with the same pharmacological treatment alone are also needed to help instruct the clinical choice suitable treatment plan.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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