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CLINICAL REVIEW

Magnesium supplementation for the treatment of restless legs syndrome and periodic limb movement disorder: A systematic review

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SUMMARY

Magnesium supplementation is often suggested for restless legs syndrome (RLS) or period limb movement disorder (PLMD) based on anecdotal evidence that it relieves symptoms and because it is also commonly recommended for leg cramps. We aimed to review all articles reporting the effects of magnesium supplementation on changes in RLS and/or PLMD.

We conducted a systematic search looking for all relevant articles and then two reviewers read all article titles and abstracts to identify relevant studies. Eligible studies were scored for their quality as interventional trials.

We found 855 abstracts and 16 of these could not be definitively excluded for not addressing all aspects of our research question. Seven full-text articles were unlocatable and one was ineligible which left eight studies with relevant data. One was a randomised placebo-controlled trial, three were case series and four were case studies. The RCT did not find a significant treatment effect of magnesium but may have been underpowered. After quality appraisal and synthesis of the evidence we were unable to make a conclusion as to the effectiveness of magnesium for RLS/PLMD.

It is not clear whether magnesium helps relieve RLS or PLMD or in which patient groups any benefit might be seen.

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Introduction

Restless legs syndrome (RLS) is a common condition affecting 5–10% of European and North American adults [1,2]. The four clinical features required to diagnose RLS were defined by the International Restless Legs Study Group [3] as: 1) an urge to move the

Abbreviations: CGI, Clinical global impression; ICH/GCP, International Conference on Harmonisation/Good Clinical Practice; IRLS, International Restless Legs rating scale; NR, Not Reported; PLMD, Periodic Limb Movement Disorder; PLMs, Periodic Limb Movements during sleep; PSG, Polysomnography; RCT, Randomised Controlled Trial; RLS, Restless Legs Syndrome.

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legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs, 2) these symptoms begin or worsen during periods of rest or inactivity such as lying or sitting, 3) symptoms are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues and 4) symptoms are worse in the evening or night than during the day or only occur in the evening or night. Periodic Leg Movements in sleep (PLMs) occur in at least 80% of individuals with RLS [4]. Both genetic and environmental factors contribute to the prevalence and severity of RLS, with increased incidence in iron deficiency, pregnancy and renal failure [5], leading to the classification of RLS into primary (idiopathic) or secondary (for instance in renal failure). Although RLS has been linked to poor sleep [4] and decreased quality of life, a recent systematic review did not find an increased risk of mortality with RLS. But there was a suggestion that PLMs (in particular PLMs with arousals) may be associated with an increased risk of cardiovascular events and mortality [6]. However, other recent reviews have found evidence both for and against a cardiovascular disease association [7,8].

Periodic Limb Movement Disorder (PLMD) occurs in those with PLMs, but without the symptoms required to diagnose RLS. In PLMD, PLMs can lead to arousals during sleep and subsequent sleep disruption. Recent practice parameters [9] for RLS point out that treatment for both idiopathic RLS and PLMD are essentially similar, however to date little evidence exists regarding the treatment of PLMD as a separate entity.

Various pharmacotherapeutic options for symptomatic RLS exist, although all have notable side effect profiles that may be unsuitable or unacceptable for many patients. Agents regularly prescribed include dopamine agonists, αδ-ligands and opioid agonists [10,11]. Augmentation is a significant issue with the dopamine agents in particular [12,13] leading to clinical recommendations of how to treat augmentation and to avoid choosing them as the first-line therapy option [10]. Iron supplementation is recommended in those with iron depletion [14]. Addressing causative agents (for instance certain anti-depressants may cause or exacerbate RLS) may also be important. Many patients may prefer not to use pharmacological therapy and/or use them intermittently when symptoms require. Treatment options for milder RLS or alternatives with a more attractive side effect profile would be welcomed.

There is anecdotal evidence for the use of magnesium supplementation for RLS. We have observed it is often marketed as a remedy in pharmacies in Australia, New Zealand and Finland for 'restless sleep'. Magnesium is also widely utilised for nocturnal leg cramps, which has been proposed to be associated with magnesium deficiency, however a recent RCT [15] and an earlier systematic review [16] found no therapeutic effect, except possibly a mild effect in pregnant women [16]. A review in this journal on treatment of RLS in pregnancy found insufficient evidence to make any conclusion about the effectiveness of magnesium in that patient group and concluded overall that it should not be used [17]. Despite magnesium being readily available in a range of food stuffs it is possible that up to 45% of American adults may have some level of magnesium deficiency [18]. Despite this we have not found any theory about how magnesium supplementation could work to alleviate RLS/PLMD that we find biologically plausible.

We have observed RLS patients recommending magnesium to each other on the internet. In addition, one of our study team member's relatives was advised to take magnesium tablets for PLMD by his sleep physician. There have been some observational studies in patients reporting that lower magnesium levels were associated with RLS severity [19,20], however magnesium levels are to our knowledge not tested in routine clinical practice (and magnesium levels in blood may not be indicative of magnesium levels within the muscle or brain). These observations leave us asking what the evidence base is for magnesium use in RLS and how methodologically rigorous those studies are. As such, we aim to systematically review the health literature to find every study reporting the effects of magnesium supplementation on the severity of RLS or PLMD and score the methodological rigour of all identified studies using a standardised approach for interventional evidence.

Methods

This systematic review was not preregistered. Our initial scoping review (YS & NSM) of PubMed yielded only 11 total articles (The syntax we used in PubMed was: (magnesium or magmin) and ("restless leg*" or "periodic limb*" or "willis-ekbom" or "willis ekbom" or "periodic leg*") and no limits were applied. This suggested to us that we maintain a broad and open search strategy to help guarantee all pertinent evidence was collected. Because we failed to locate a single randomised controlled trial at this point we also expected that the evidence synthesis would need to be built on lower quality evidence. Our scoping review also indicated that we would be unlikely to be able to meta-analyse the results due to the paucity of combinable studies.

Two investigators (YS & NSM) developed the research question (see Appendix 1) and then designed search syntax in conjunction with the librarian team (JMC & IR) to maximise search yield across a number of databases selected specifically to attempt to find any article published on the topic at any time (see Appendix 2 for full search syntax).

We searched for clinical intervention studies testing oral or other methods of magnesium supplement administration in patients with RLS, or PLMD, or both. We included studies with patients suffering from either primary or secondary restless legs syndrome (for instance, RLS secondary to kidney disease [but not including patients receiving dialysis] or pregnancy). These patients were chosen because they are more likely to be within the clinical practice of a sleep physician. We included any dose of magnesium other than homeopathic and we included any comparator to magnesium. Any longitudinal clinical study design, including case series or case studies, was accepted. There were no restrictions on length of follow up, or publication language, or date of publication. We searched 19 different databases, including Web of Science, Medline, Scopus and CINAHL between the 28th August and the 5th October 2018 (see Appendix 2).

Every title and abstract was read by two independent reviewers (NSM RK CB JLC TL MC) who systematically assessed, in this order, whether the title and abstract did not include 1. original data, 2. a clearly delineated group of patients presenting with restless legs syndrome, or periodic limb movement disorder, or both, 3. magnesium supplementation, 4. a measure of change in the clinical severity of RLS/PLMD in conjunction with, 5. any longitudinal study design. If the abstract could not be definitively excluded (such as when there was no abstract and the title was insufficiently descriptive), a full text review was undertaken and the same criteria applied to remove articles not reporting data on the question.

Abstracts or articles written in Spanish or German were reviewed by members of our review team who were native speakers or studied those languages through to the end of high school or at a university level (RK TL RW MC JLC). Studies published in any Scandinavian language were reviewed by a team member (TL) proficient in those languages and via Google translate.

Inclusion and exclusion criteria were applied at the full text screening stage unless obviously reported in the abstract. Inclusion: Community dwelling patients rather than hospitalised

populations (such as in intensive care unit or in defined specialist clinical populations such as dialysis patients). PLMD or RLS could be diagnosed by clinical or laboratory methods, or both. There was no limit on the length of intervention (i.e., we would review a single dose study) before the outcome was measured and there was no limit on the method of measuring change in disease severity. Pregnancy was not an exclusion. We did not restrict by publication type or venue (peer-reviewed or non peer-reviewed). Exclusion: In vitro or animal studies (i.e., not biological samples taken from an RLS patient or patients and then treated with magnesium in vitro).

Data were extracted and tabulated from all eligible studies by at least two investigators (NSM RW JLC). We did not contact authors for clarification of unreported data. We did contact an author of an abstract [21] reporting a pertinent randomised controlled trial when we were unable to locate the corresponding full length article in order to ascertain whether there was a full length published or unpublished report available (for instance, a clinical trial report or thesis [22]).

Quality review

We scored the quality of the studies based on a modified version of the Cochrane risk of bias tool for interventional studies [23]. We searched for evidence of randomisation via a computerised method, secure concealment of that random list from the clinical investigators enrolling patients, blinding of the investigators and patients from the intervention being received, intention to treat analyses and finally that the trial reported the outcomes it was pre-registered to collect relevant to the RLS/PLMD outcome. When this was done well and properly described, we gave a green tick (indicating a low risk of bias), when it was unclear but may have been done well, we gave an orange '?' (indicating the possibility of bias) and when not done, we gave a red X indicating a serious risk of bias (see Table 2).

Results

Our search of all databases yielded 855 abstracts after duplicates were removed. The results of our sorting algorithm can be seen in Fig. 1. 305 articles were rejected for not having original data reported in them; 495 did not have a clear group of RLS/PLMD presenting patients; 38 did not have magnesium supplementation and one did not report a change in RLS/PLMD leaving 16 articles that required full text review because we were unable to definitively exclude them based on their title and abstract alone (see Fig. 1). One article was a thesis in Spanish that was rejected at full text review because it did not contain patients with RLS/PLMD [24]. A case series described in a neurology journal was also not retrievable but appeared to have a case of RLS described in it [25]. We were unable to locate an abstract or full text to assess three articles about RLS/PLMD in natural health publications properly [26–28]. Another potentially relevant article in German had no abstract and we were unable to locate any text for it [29]. An article in Hungarian had neither an abstract or full text we could locate [30]. A final (but likely irrelevant based on its title) article was in an issue that was missing from our library [31]. This left eight articles with relevant data that are listed in Table 1. The heterogeneity in the study designs and the incompleteness of reporting meant that we were not prepared to meta-analyse the results which would create a misleading summary estimate. We included a case study in Polish based on its English abstract but were unable to review its full text completely [32].

There was one randomised placebo controlled trial [22] which we located because it was published as an abstract [21]. Neither the PSG measured severity of PLMS or the questionnaire based measures of RLS severity or clinical global impression (CGI) were significantly improved by magnesium compared to placebo.

Qualitative synthesis of the non-randomised study findings would generally indicate that RLS/PLMs tended to improve in conjunction with magnesium – however because of the biased nature of these study designs we cannot tell if this is really caused by magnesium (see Table 2). The studies were case series or case reports meaning that there are almost no high quality studies that address the effectiveness of magnesium alone for RLS or PLMD. They lack control groups and magnesium is often used in conjunction with other agents. So establishing causality is impossible.

The results of the quality appraisal are in Table 2. The RCT [22] used randomisation but it was not clear how the sequence was generated or how it was kept secret from the investigators (allocation concealment). We judged that the techniques used to maintain blinding were unlikely to have introduced bias and that there was minimal data loss after randomisation that would have damaged the assumption of intention-to-treat analyses. All other studies were case studies or case series and therefore did not employ any of the bias minimising techniques used in RCTs. None of the included studies were pre-registered, making it unclear whether reporting bias may have existed (the sole RCT was undertaken before mandatory registration came into effect).

Discussion

There is very little high quality evidence testing the hypothesis that magnesium supplementation is effective in treating RLS/PLMD. Apart from a single parallel armed randomised controlled trial

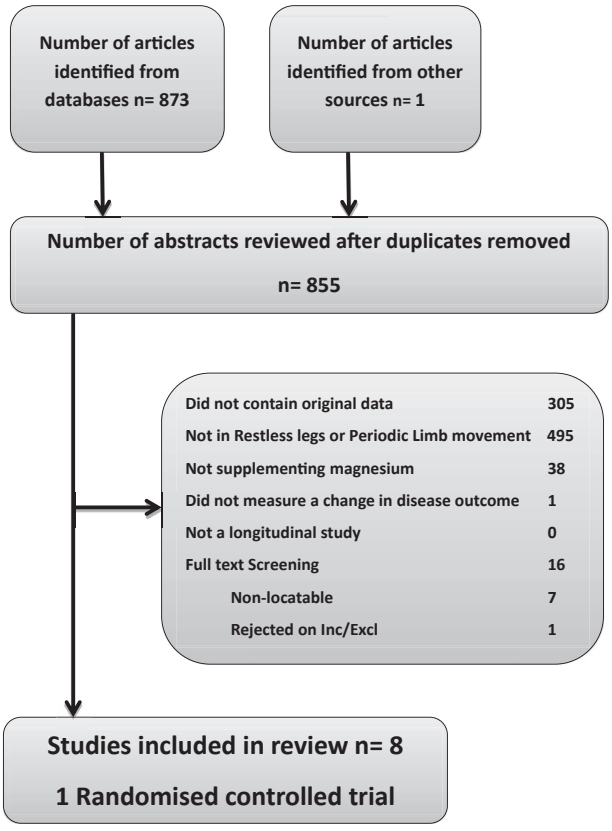


Fig. 1. Flow chart of the study selection procedure.

Table 1
Characteristics of selected studies.

Author Year	Publication type	Primary or Secondary (cause)	Diagnostic method	Dose, Timing, Route	Comparator	Outcome measure	Study Design	Sample size	Gender ratio	Age	RLS or PLMD severity	Concomitant medications
Mendelski 2005 [22]	Thesis	Primary RLS	clinical + PSG	three tablets in the morning and four tablets in the evening by mouth for 28 d. Daily dose 364.8 mg magnesium/ day	Placebo	PSG & IRLS	Parallel RCT	30 (15 in each group)	3:2 ♀:♂	59 & 56 Treatment & placebo	63 & 43 plm/hr Treatment & placebo	nil
Hornyak 1998 [35]	Journal article	RLS or PLMD	clinical + PSG	oral 12.4 mmol 305 mg evening 4–6 wk	Nil	PSG	Case series	10	2:3 ♀:♂	57	17.7 h	nil
Neykov 2015 [33]	Abstract	Symptomatic and Idiopathic RLS	Clinical	NR	nil	IRLS	Case Series	70	NR	NR	32 in idiopathic and 26 in symptomatic	dopamine agonists
Metta 2015 [34]	Abstract	Type II Diabetes	Clinical (International RLS rating scale)	Magnesium *dicitrate* (600 mg) for 12 wk	nil	IRLS rating scale	Case series	17	NR	52	IRLS = 12.7	Co enzyme Q10 (100 mg)
Bartell 2006 [19]	Short article	Pregnancy	Clinical	IV MgSO4 2 g per hour for 2 d.	nil	IRLS rating scale	Case study	1	1♀	33	Not established at baseline	Terbutaline before Mg
Filseth 2004 [39]	Letter	Unclear	NR	NR	nil	Personal report of symptoms	Case Study	1	1♀?	NR	Not reported	B Vitamin
Jonczak 2004 [32]	Journal article (Polish)	PLMS + Sleep apnea	PSG	Oral administration probably but timing and dose NR	nil	Clinical impression or possibly PSG	Case Study	1	1♀	?	13.6/hr at baseline	Iron supplementation & clonazepam
Pujol 2001 reported in Ferrándiz 2002 [40]	Abstract	Primary RLS	Seems to be clinical + PSG	NR	nil	Clinical impression only	Case Study	1	1♀	29	NR	pramipexole

Studies are ordered on study type and then alphabetically by first authors name within study type. NR = Not Reported; PSG =Polysomnography; IRLS International Restless Legs rating scale [41]; RLS Restless Legs Syndrome; PLMD Periodic Limb Movement Disorder; RCT Randomised Controlled Trial.

Table 2
Risk of bias assessment for interventional studies.

Study	Randomisation	Allocation Conceal	Blinding	Intention to treat	Reporting bias
Mendelski 2005[22]	?	?	√	√	?
Hornyak 1998[35]	X	X	X	X	?
Neykov 2015[33]	X	X	X	X	?
Metta 2015[34]	X	X	X	?	?
Bartell 2006[19]	X	X	X	?	?
Filseth 2004[39]	X	X	X	?	?
Jonczak 2004[32]	X	X	X	?	?
Pujol 2001 reported in Ferrándiz 2002[40]	X	X	X	?	?

√ with green background = Scored as a low risk of bias. ? with orange background = scored as a potential risk of bias. X with red background = scored as a high risk of bias. Studies are ordered on study type (see Table 1) and then alphabetically by first authors name within study type.

(n = 30) [22], we found only three case series (n = 70,[33] 17[34] & 10[35]) and four case reports (see Table 1). The uncontrolled studies did not have control arms and frequently reported magnesium use in conjunction with other agents, meaning that causality cannot be reliably ascertained in a condition where placebo effects are known to be large [36]. They also suffer from a number of well-known biases that preclude making strong interventional conclusions (see Table 2). However, this absence of evidence does not rule out the possibility that magnesium supplementation does have a meaningful therapeutic effect on RLS or PLMS.

The single RCT we found [22] did not find that oral magnesium (364.8 mg daily) relieved RLS. But this could be a false negative due to underpowering and some inequality in the severity of the condition in the two treatment groups at baseline. The baseline median serum magnesium levels in the trial patients (0.79 mmol/l in treatment group and 0.81 mmol/l in the placebo group) were close to a recently reported German general population average (0.82 mmol/l) [20]. In addition serum magnesium did not significantly increase in the intervention group and the groups did not differ significantly after treatment [22]. Together these factors may have inhibited the detection of a true beneficial effect of magnesium. Diarrhea was the major reported side-effect of magnesium supplementation in this trial with seven reported incidents in patients in the active arm (5 mild and two severe) versus none in the placebo treated patients [22].

Readers of this field may also be interested in an RCT protocol we found that may report data in the future [IRCT2017070134806N1]. It compares the effects of magnesium to vitamin B6 supplementation in patients also receiving pramipexole. However, this single-blinded trial is only enrolling 25 patients in each of three arms and was due to complete recruitment by March 2018 (https://en.irct.ir/trial/26502).

Our search was not designed to detect studies exploring the association between restless legs syndrome and magnesium levels. However, we did locate observational studies reporting inconsistent associations between magnesium levels and RLS [37,38]. Immediately after our search date Szentkiralyi and colleagues [20] published a much larger population-based study of PLMS (n = 1107). They report a very small univariate difference in serum magnesium levels between people with and without PLMS (PLM Index >15/hr; 0.81 vs 0.82 mmol/L, p = 0.01). However, this difference is too small to present a viable clinical trial target in a broad spectrum of patients. This observational study also brings into doubt the likelihood that magnesium could be an effective treatment in a broad spectrum of RLS/PLMS patients because the afflicted cases do not have magnesium deficiency. It remains possible that in susceptible patients with low magnesium and RLS, supplementation with magnesium might be effective, but such an approach must be tested in a properly powered trial with robust design.

Magnesium supplementation potentially represents a cheap and relatively safe therapeutic option for sufferers of RLS. However, our systematic review located no studies that definitely demonstrate whether magnesium is efficacious or not and the observational studies have not demonstrated that a treatable magnesium deficiency exists.

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Authors contribution

Marshall: Conception and design, acquisition of data, analysis and interpretation of data, drafting and revising article, and final approval of article.

Serinel: Conception and design, abstract review, analysis and interpretation, drafting and final approval of article.

Killick: Abstract reviewing, interpretation, drafting, editing, and final approval of the article.

Child & Raisin: Design of study and design of and undertaking of the database search, editing and final approval of the article.

Killick, Berry, Lallukka, Wassing, Comas, Chapman: Abstract reviewing editing, and final approval of the article.

Lee, Ratnavadivel, Vedam, Grunstein, Wong, Hoyos, Cayanan: Conception and final approval of the article.

Yee: Conception and design, interpretation, editing, and final approval of the article.

Practice Points

- There is no evidence supporting the use of magnesium supplementation in RLS, despite its anecdotal use. We don't know whether any formulation at any dose may or may not be effective.
- Patients may report significant clinical benefit from taking magnesium. Given the current evidence base we would not tell patients that the supplement is in fact not working for them.
- Dietary supplements are generally safe but we don't know what the specific side-effect profile of magnesium in RLS patients is. The sole RCT indicates a clinically significant problem with diarrhea.
- The role of magnesium in the pathogenesis of RLS/PLMS in any subset of patients has yet to be demonstrated.
- We do not recommend routine testing of magnesium levels in RLS patients to guide any clinical decisions.

Research Agenda

- It is not clear whether magnesium is either an effective or ineffective therapy for RLS/PLMD because of the paucity of published clinical studies. The apparent widespread use of this remedy leads to recommend that adequately powered double blind studies be conducted. We would also recommend that safety data be collected in these trials in compliance with ICH/GCP.
- This is particularly important when patient reports of their RLS severity appear to be subject to significant placebo effects [36].
- We also think it worth noting that the best quality observational study to date has not clearly indicated that RLS is associated with lower circulating magnesium levels [20]. Future trial investigators may want to select or stratify patients based on their baseline magnesium levels.

Conflicts of interest

The authors declare that they have no conflicts of interest with respect to this article.

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Appendix A. Supplementary data

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