The treatment of restless legs syndrome and periodic limb movement disorder

Hening W, Allen R, Earley C, Kushida C, Picchietti D, Silber M

Authors' objectives
To review the therapy of the restless legs syndromes or periodic movements in sleep.

Searching
MEDLINE was searched through April 1998 using the following keywords: restless legs both as a subject or textword; a combination of myoclonus and periodic; combination of sleep with dyskinesia, myoclonus, or restless; and a combination of sleep, periodic and movements. A review was conducted of Current Contents and Sleep Research indices to September 1997 and articles discovered during other research. Articles in English, French, German, Italian and Spanish were included.

Study selection
Study designs of evaluations included in the review
Published peer-reviewed studies that involved at least five patients and used a defined outcome to assess therapy were included. Included studies were of the following designs: double-blind randomised placebo-controlled cross-over trials; clinical series; unblended parallel study; single blind non-randomised cross-over; case-control; randomised open parallel study; and open label. Articles with an inadequate definition of RLS or PLMS or in which the number of patients could not be determined were excluded.

Specific interventions included in the review
The following treatment types were studied: dopaminergic medications including levodopa compounded with a dopa-decarboxylase inhibitor and dopamine agonists including bromocriptine and pergolide; opioids including oxycodone and proxyphene; benzodiazepines including clonazepam, triazolam, nitrazepam and temazepam; anticonvulsant medications including carbamazepine and gabapentin; medications drawn from other classes including propranolol, clonidine, baclofen, and vitamins and minerals; avoidance of specific medications; and non-pharmacological therapy including accommodative strategies and sleep hygiene, behavioural and stimulation therapies, invasive therapies, and nutritional considerations.

Participants included in the review
Patients with restless leg syndrome (RLS) or periodic limb movement disorder (PLMD) were included. Some studies appeared to have included patients with other diagnosis, such as narcolepsy, and some studies had unclear criteria for the diagnosis of RLS. Definitions were as reported in the International Classification of Sleep Disorders Criteria (1990, Revised 1997). Special patient groups were considered (children, pregnant women and the elderly).

Outcomes assessed in the review
Subjective and objectives measures included the following: count of periodic limb movement) PLM; K and K alpha complexes; structured questionnaires; polysomnography (PSG) measures; periodic limb movement in sleep (PLMS) with arousals; global symptoms; sleep diary; multiple sleep latency test (MSLT); actigraphy; PLMS with arousal index (PLMAI) from PSG; questionnaires on specific symptoms; PLMS with awakening; suggested immobilization test (SIT); requested refills of medications; sleep quality; periodic limb movement index (PLMI) on PSG; nocturnal myoclonus syndrome (NMS) cluster disturbed time; PLM asleep and awake; home ambulatory monitoring; dysesthesias; nocturnal leg jerking; analogue scale for symptom severity and symptom improvement; number of attacks per week; RLS sensations per day; patient preference for drug or placebo or neither; O'Keefe scale; and reported benefits.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.
Assessment of study quality
Validity was not formally assessed though the level of evidence according to criteria for the treatment related data was listed in the tables of study characteristics (see Other Publications of Related Interest no.1).

Data extraction
Two authors extracted the following data: study design; definition of RLS and PLMD; exclusion and inclusion factors; subject characteristics and drop-outs; outcome measures; side effects evaluated; biases; and conclusions. Discrepancies were resolved by discussion.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative review.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Forty-five articles were included.

Methodological flaws in the primary studies included small sample size, RLS history unclear, concomitant therapy, errors in ascertainment of exposure to intervention, inclusion of patients with narcolepsy, non-systematic group assignment in studies described as randomised, short wash-out periods in cross-over trials, no statistical analyses, and vague end points and clinical criteria.

1. Dopaminergic medications:
Levodopa (8 double-blind trials ranging from 1 to 4 weeks duration, 107 patients): inconsistent results with some studies reporting no significant difference between treatments and others favouring levodopa over placebo for some outcome measures. 7 clinical series reported that the emergence of rebound or augmentation was the greatest problem.

2. Opioids:
Two double blind RCTs with 18 patients compared oxycodone (reported benefit from oxycodone compared to placebo) and proxyphene (no difference from placebo).
Benzodiazepines: two double blind cross-over studies, 1 to 4 weeks duration, 12 patients studied RLS and reported inconsistent results.

3. Anticonvulsant medications: Carbamazepine: one double blind RCT of five weeks duration and 181 patients reported carbamazepine was significantly better than placebo. A large placebo effect was noted. One RCT cross-over with six patients had no statistical analyses.
Gabapentine: two open label series with 22 patients neither of which reported statistical analyses.

4. Medications drawn from other classes: Clonidine: two double blind RCT, duration from 3 days to 3 weeks, 20 patients both reported significant benefit from clonidine compared to placebo.
Iron: one case-control with 18 patients reported benefit only for patients with ferritin <= 45 mg/l. Two case series with 45 patients treated with iron in the form of intravenous iron, oral iron and blood transfusion reported benefit from iron.
Non pharmacological therapy: Cognitive therapy vs clonazepam: one study, 4 weeks duration, 16 patients. Statistics were not clearly presented.
Authors’ conclusions
The authors’ conclusions appear to be as follows.

No single agent has been studied in large, multicentre trials or in large-scale long-term studies. Many agents which have shown preliminary positive results, such as dopamine agonists, many opioids and the anticonvulsants, have not yet been thoroughly studied. Except for rare case reports, studies have not addressed routes of administration and have only minimally examined therapy in children and pregnant women. There are few comparative studies that compare different agents on the same population of patients and there have been no studies that look specifically at combination therapy. Few studies have attempted any assessment of quality of life effects and there are few published reports of nutritional, behavioural or herbal therapies. At this point the most promising focus for further study might include agents that have been shown in published studies to be successful. In dopaminergic therapy, the possible use of the dopamine agonists (pergolide, pramipexole, ropinerole, cabergoline, and others) needs more investigation. Preliminary investigations suggest that these medications offer good acceptability and carry relatively robust benefit to risk ratios. Supplementation of iron may also provide another approach to dopaminergic therapy. Other promising avenues to explore included the opioids, anticonvulsants, and sclerotherapy.

CRD commentary
The aims and inclusion criteria were stated though some studies appear to have included patients in whom the diagnostic criteria were not clear. Relevant study characteristics were clearly presented in tabular format. Though comments were made on the methodological flaws in the individual studies, validity was not formally assessed and criteria used to determine the level of evidence offered were not specified.

No attempt was made to locate unpublished studies thus raising the possibility of publication bias. Methods used to select primary studies, extract data and award level of evidence were not stated. Given the apparently poor quality of many of the studies, it may have been more appropriate to restrict the review only to studies of a specified minimal quality rather than included all studies in the review.

The authors conclusions were supported by the evidence though it must be borne in mind that the validity of studies purporting to show benefit for therapies was not adequately assessed.

Implications of the review for practice and research
Practice: The authors do not report any clinical implications of the review.

Research: The authors state that further research should be undertaken of agents which have been shown in published studies to be successful. In dopaminergic therapy, the possible use of the dopamine agonists (pergolide, pramipexole, ropinerole, cabergoline, and others) needs more investigation. Other promising avenues to explore included the supplementation with iron, opioids, anticonvulsants and sclerotherapy. Other areas requiring research included the development of subjective and objective recording and quality-of-life instruments.

Bibliographic details

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10566916

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Diagnosis, Differential; Electromyography /methods; Humans; Nocturnal Myoclonus Syndrome /diagnosis /etiology /therapy; Quality of Life; Restless Legs Syndrome /diagnosis /etiology /therapy; Severity of Illness Index

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.