REVIEW

Treatment of restless legs syndrome

Tratamento da síndrome das pernas inquietas

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Abstract

Objective: *Restless legs syndrome is a neurological disorder characterized by a desire to move limbs, which is usually only present or worsens during rest or at night. The objective of this article was to review the available literature about pharmacological treatment for this disorder.* ***Method:*** *A search of recent literature was undertaken on online databases (Medline, Pubmed, Scielo and Lilacs).* ***Results:*** *502 articles were retrieved, of which 30 were selected. Dopaminergic agents, anticonvulsants, opioids, benzodiazepines, zolpidem, entacapone and ketamine were all effective on the restless legs syndrome treatment. One study showed that iron was not effective.* ***Conclusions:*** *Based on few double-blind, randomized, controlled trials, it seems that the best options to treat restless legs syndrome patients are gabapentin and L-dopa associated to its sustained release formulation.*

Descriptors: *Restless legs syndrome; Parasomnias; Sleep disorders; Treatment; Literature review*

Resumo

Objetivo: *A síndrome das pernas inquietas é um transtorno neurológico caracterizado por um desejo incontrolável de mover os membros, que comumente está somente presente ou piora ao descanso ou à noite. O objetivo do trabalho foi a revisão da literatura disponível sobre o tratamento farmacológico para a síndrome das pernas inquietas.* ***Método:*** *Pesquisa da literatura recente realizada em bases de dados eletrônicas (Medline, Pubmed, Scielo e Lilacs).* ***Resultados:*** *Quinhentos e dois artigos foram encontrados, dos quais 30 foram selecionados. Os agentes dopaminérgicos, os anticonvulsantes, os opióides, os benzodiazepínicos, o zolpidem, o entacapone e a ketamina foram eficazes no tratamento da síndrome das pernas inquietas. Um estudo mostrou que o ferro não foi eficaz.* ***Conclusões:*** *Baseado nos poucos estudos duplo-cegos, randomizados e controlados, parece que as melhores opções para tratar os pacientes com síndrome das pernas inquietas são a gabapentina e L-dopa associada à sua formulação de liberação lenta.*

Descritores: *Síndrome das pernas inquietas; Parassonias; Transtornos do sono; Tratamento; Literatura de revisão*

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Introduction

Restless legs syndrome (RLS) is a classical neurological ailment which has components of both sleep and movement disorders.[1] It can present a wide range of symptoms mostly sensorial. These include unpleasant sensations in the lower limbs which cause an urge to move one's legs. These symptoms are not necessarily painful but distressing. They are described as sensations such as 'creeping', 'crawling', 'tingling', 'burning', 'cramping', 'itching', 'electric chocks', 'stinging', 'tension' or 'discomfort' in the lower limbs between the ankle and the knee. Occasionally it involves the whole limb or only its upper part.[2-3] Commonly, the symptoms only occur during rest, usually when lying down or sitting. They worsen during the evening or at night, making it difficult to initiate or maintain sleep.[4]

RLS is frequently described as one of the most common undiagnosed diseases.[1] It is not an uncommon condition, but it is often misdiagnosed or even not diagnosed, primarily because the patients do not seek medical attention or their symptoms are erroneously thought to be caused by anxiety or stress.[3] Several studies show ranges of 4-15%, increasing with age,[5] with a slightly higher incidence in women.[1] Two studies based on an elderly population found values ranging from 0.6% to 9.8%.[6-7] Available data concerning the prevalence of RLS in pregnancy range from 11 up to 33%.[8] In patients with end-stage renal disease the prevalence of RLS is 20-40%.[9] More than two thirds of RLS-affected patients report a positive family history.[10]

The pathogenesis of RLS is unknown, but there is little doubt that it results from an abnormal functioning of dopamine metabolism in the nervous system.[11] There are two kinds of RLS: idiopathic/primary and symptomatic/secondary. The idiopathic form seems to be related to family history.[12] The secondary form is related to certain medical conditions, such as iron deficiency, uremia, pregnancy, hypothyroidism, diabetes, rheumatoid arthritis and leg varicosities.[13-14]

The severity of the disturbance varies over the course of several weeks, as well as during the night, provoking instantaneous awakening and making it difficult to return to sleep.[4] Periodic limb movements during sleep (PLMS) are often associated with RLS. It is defined as a repetitive, periodic flexing of lower limb joints, e.g. hip, knee or ankle, and a stereotypical Babinsky-like flexing of the legs with extension of the foot and toe for periods of 0.5-5.0 seconds, at intervals of 5-90 seconds.[2,13] PLMS can represent the continuation of the RLS during sleep, but they are different entities.[4] Studies demonstrated PLMS in 80-100% of the patients with RLS. However, the absence of PLMS does not exclude RLS. PLMS are also present in 20-40% of the elderly population, the majority of whom do not report RLS symptoms.[3]

The treatment of RLS is symptomatic, not curative. It can be non-pharmacological and pharmacological. The non-pharmacological treatment is first based on avoiding substances which can provoke or exacerbate RLS symptoms, such as caffeine, nicotine and alcohol.[11,13] On secondary RLS cases, the treatment should be aetiological (for example: kidney transplantation in end-stage renal disease).[11] For pharmacological treatment, there currently are several substances available such as dopaminergic agents, opioids, benzodiazepines, anticonvulsants, iron, adenosine, adrenergic drugs, magnesium and others. Nevertheless, these medications have weak evidence-based recommendations, due to a lack of a larger number of randomized, placebo-controlled and double-blind clinical trials.[11,13] An important and common complication observed after pharmacological treatment, especially with dopaminergic agents, is augmentation,[15-16] which consists of a temporarily RLS symptoms increase, earlier onset of RLS symptoms during daytime, shorter latency to the beginning of symptoms at night and involvement of other parts of the body (e.g., trunk or upper limbs).[11-12,15] Another consequence of drug therapy is the rebound effect, which is characterized by the worsening of symptoms at the end of a dosing period, resulting in RLS expressions during the late night or morning.[17-19] The aim of this study is to review the available literature about the pharmacological treatment for RLS.

Method

The studies used for the accomplishment of this article were identified by a large research on online databases, which were Medline, Pubmed, Lilacs and Scielo. Included in the research were articles written in English or Portuguese, between 1999 and 2003, or not referred to pharmacological treatment of RLS. Keywords were: *treatment* and *restless legs syndrome*. The articles that were only reviews or not referring to pharmacological treatment were excluded.

Results

In the research, 502 articles were found and, out of these, 30 were selected. Drugs used were mainly dopaminergic agents (including L-dopa, Pergolide, Pramipexole, Ropinirole, Cabergoline, Alpha-dihydroergocryptine, Amantadine, and Piribedil), an anticonvulsant agent (Gabapentin), opioid agents (such as Tramadol, Apomorphine, and Morphine) and other agents including Iron, Clonazepam, Zolpidem, Entacapone, and Ketamine.

1. L-dopa

Benes et al., in a double-blind, randomized, placebo-controlled multicenter cross-over trial, treated 35 patients with one capsule daily of either 100 mg L-dopa plus 25 mg benserazide or placebo, during two cross-over periods of 4 weeks each.[20] The dosage could be increased to two capsules if the symptoms did not improve. Thirty-two patients finished the study. The results showed that L-dopa/benserazide was superior to placebo in reducing the number of PLM/hour, in increasing the percentage of time in bed without limb movements, and in improving the quality of sleep. These effects were significantly superior in L-dopa/ benserazide only during the first half of the night (hours 1-4), but not during the second half (hour 5 to waking). An increase in RLS severity, diarrhea, reduced general drive, nausea and muscle weakness were reported by seven patients receiving L-dopa/benserazide. Two patients withdrew due to adverse events (clinically unconfirmed cardiac symptoms with concomitant anxiety in one, and worsening of pre-existing iron-deficiency anemia in the other), but both were in the placebo group. No augmentation or rebound effects were reported.

A double-blind, placebo-controlled, randomized, cross-over trial[21] evaluated the efficacy of the combination of regular-release (rr) L-dopa and sustained-release (sr) L-dopa/ benserazide in RLS treatment. Twenty-one patients received placebo one night, and 100 mg of each kind of L-dopa the other night. After this, a clinical follow-up of four weeks was conducted, with 18 patients. The results showed that rr-L-dopa and sr-L-dopa/benserazide decreased PLM/h of sleep, total number of PLM, PLM/h of time in bed, PLM/h of REM and non-REM, PLM/h of wake time and PLM-arousals/h of sleep

shortly after administration, but the subjective sleep quality only improved after chronic treatment. One patient reported augmentation. Other adverse events reported were nausea, stomachache, tachycardia, dry mouth, headache and nycturia.

Collado-Seidel et al. suggested that a therapy of rr-L-dopa combined with sr-L-dopa was more effective for RLS than a rr-L-dopa monotherapy, even in severely-affected patients.[22] A randomized, controlled, double-blind, cross-over trial was accomplished with patients showing improvement on RLS symptoms and sleep quality in the first half of the night under rr-L-dopa usage but with two or more awakenings in the second half. During two cross-over periods of four weeks each, 37 patients received 100 to 200 mg of rr-L-dopa plus either 100 mg of sr-L-dopa plus 25 mg benserazide or placebo. Four patients were excluded due to noncompliance or insufficient data. Three discontinued because of myositis, angina pectoris and vertigo. Thirty patients finished the study with improvement in subjective sleep quality, PLM index (number of PLMs per hour of time in bed), and time in bed without movements using combined therapy (rr-L-dopa + sr-L-dopa) compared to monotherapy (rr-L-dopa + placebo). These patients reported the following as side effects: dry mouth, nightmares, dizziness, nervousness, dyspepsia, epigastric pain, cardiac rhythm disorder and abnormal visus. No augmentation phenomena were observed.

2. Pergolide

Wetter et al. reported that pergolide improved sensorimotor symptoms and sleep disturbance in a randomized, double-blind, placebo-controlled, cross-over clinical trial.[23] Thirty patients were treated with either pergolide plus domperidone, and then placebo plus domperidone, or vice versa, for four weeks each. The initial dosage of pergolide was 0.05 mg. The patient could increase the dosage by 0.05 mg per night, in the first two weeks of both treatment periods, until the best improvement was obtained. Twenty-eight patients completed the study. The mean dosage was 0.51 ± 0.18 mg (range 0.25 to 0.75) for pergolide and 0.69 ± 0.15 mg (range 0.25 to 1.10) for placebo. Eight patients on pergolide took 0.75 mg, the maximum dosage allowed in the protocol, as well as 17 patients on placebo. The results showed that pergolide was superior to placebo in the reduction of the PLM index, in the prolongation of total sleep time, and in the improvement of subjective sleep quality, quality of life and severity of RLS. The side effects related were nausea (n = 12), headaches (n = 6), rhinitis (n = 6), vomiting (n = 5), abdominal pain (n = 4), dizziness (n = 4), abnormal vision (n = 3), diarrhea (n = 3), rash (n = 3), dry mouth (n = 2) and dreams (n = 1) with pergolide, but only 19 of these events were associated to therapy. Five events (vomiting in three patients and nausea and dizziness in one each) were considered severe. Headaches (n = 9), abdominal pain (n = 7), constipation (n = 4), nausea (n = 3) and rash (n = 3) were reported during placebo treatment. One patient of the 30 initial patients withdrew from the study due to much abdominal pain, after the start of cross-over period 1 (treatment with placebo). No augmentation phenomena were reported.

In the follow-up[24] of this study, all 28 patients who had participated in the previous study received up to 0.75 mg pergolide and 20 mg domperidone. The dosage could be decreased until the lowest effective dose was achieved. Twenty-two patients completed the follow-up, whose mean period was 426.4 ± 92.3 days (range 316 to 665). There was a persistent improvement of PLM index, PLMS arousal index (number of PLMs during sleep associated with arousals per hour of total sleep time), total sleep time, and sleep efficiency. Five patients (of 28) dropped out due to side effects (such as nausea, headaches, vomiting, constipation, rash and skin changes), and one as he did not want to take drugs anymore. One of the subjects who withdrew also reported loss of efficacy. Six patients (27.3%) developed augmentation phenomena of RLS symptoms.

Walters et al. treated seven children with either L-dopa/carbidopa or pergolide during six months.[25] The children had attention-deficit-hyperactivity disorder (ADHD) plus either RLS (n = 1) or PLMS (n = 1) or both (n = 5). The dosage ranged from 75 mg to 300 mg for L-dopa and from 0.4 mg to 1 mg for pergolide daily. Five of the seven children received L-dopa/carbidopa, and two received pergolide. The RLS symptoms improved in all six children with RLS. The total number of PLMS per night of sleep, the PLMS index and the arousals per night of sleep associated with PLMS significantly decreased. ADHD improved in all seven patients. Five of the seven children continued to receive dopaminergic therapy three years after initiation and continued to report improvement in RLS/PLMS, ADHD and sleep.

3. Pramipexole

Montplaisir et al. studied the use of pramipexole in a randomized, double-blind, cross-over trial.[26] Ten patients received either pramipexole or placebo during two treatment periods of four weeks, with a two-week washout period between these phases. The initial dosage was 0.375 mg/d, with an increase to 0.75 mg/d after one week and to 1.5 mg/d after the second week. If persistent side effects were experienced, the patients went back to their previous dosage. In the pramipexole-treatment period, six subjects took a dosage of 1.5 mg/d, whereas four subjects took 0.75 mg/d. Pramipexole reduced 98% of the number and the index of PLMS, returning the PLMS index to a normal value. Pramipexole also decreased the number and the index of periods of wakefulness during the night. However, there was no significant improvement in the variables which evaluate the continuity of sleep, such as sleep latency, total sleep time, sleep efficiency, and number of awakenings. The side effects reported included nausea, constipation, loss of appetite, dizziness and daytime fatigue.

In the follow-up[27] of this study, seven patients were treated with pramipexole during a mean period of 7.8 months. The initial dosage was 0.25 mg, which was increased until the optimal improvement was obtained. The optimal dosage was 0.25 mg for one patient, 0.5 mg for five patients and 0.75 mg for one patient. There was a significant decrease in RLS symptoms, with no evidence of reduction in the therapeutic effect of pramipexole. The side effects reported were mild nausea and daytime sleepiness. No morning rebound or afternoon augmentation phenomena of leg restlessness were reported.

A single-blind, placebo-controlled, cross-over trial[28] investigated pramipexole in the treatment of RLS. Eleven patients received placebo one night and 0.27 mg pramipexole the other night. Acute effects were a significant decrease of RLS/PLMS variables and a slight improvement of objective sleep efficiency and subjective sleep quality. The four-week follow-up showed that pramipexole improved the total scores of the International RLS Study Group (IRLSSG) questionnaire, sleep quality, daytime sleepiness, depression and quality of life.

4. Ropinirole

Saletu et al. compared twelve formerly-untreated RLS patients, then using ropinirole, with twelve controls during three nights (adaptation, placebo and ropinirole night).[29] After an administration of 0.5 mg ropinirole, polysomnography, self-rating, visual analog scales and psychometric tests were applied. The conclusion was that ropinirole induced an increase in total sleep time, sleep efficacy, stage 2 sleep (S2) and stage shifts, and an improvement in fine motor activity and reaction time performance, although somatic complaints increased slightly. In a second publication[30] on the same study, Saletu et al. reported that ropinirole improved the index PLM/h of total sleep time by 75%. Other PLM variables, such as the number of PLM, PLM/h of time in bed, PLM/h of REM sleep, PLM/h of non-REM sleep and PLM/h awake, also improved. Arousals due to PLM decreased, while spontaneous arousals increased.

Sixteen patients with RLS used ropinirole (dose ranging from 0.5 to 12.0 mg) in an open-label trial.[31] Three related rash and nervousness as side effects and discontinued medication. The other thirteen reported a 58.7% improvement as judged by the IRLSSG questionnaire.

5. Cabergoline

Stiasny et al., in an open trial, suggested that cabergoline was effective and well-tolerated by patients with moderate-to-severe RLS.[32] Nine patients with a history of insufficient L-dopa treatment and/or daytime augmentation were involved in a twelve-week trial. Five were still using L-dopa (400-800 mg). At first, domperidone 20 mg was used as a co-medication. At the end, all subjects have stopped domperidone due to good tolerability and were on cabergoline monotherapy ranging from 1 to 4 mg (mean dosage 2.1 mg). All patients reported significant relief or the end of RLS symptoms. Polysomnography showed improvements in the number of PLM, PLM arousals and PLM awakenings. Total sleep time and sleep efficiency improved. Patients who had experienced augmentation phenomena under L-dopa also reported improvement in daytime symptoms.

These results stimulated a subsequent double-blind, randomized, placebo-controlled, multicenter study[33] with a large population. At the time of publication, the study was still ongoing. At the time, 78 patients were evaluated during 47 weeks. Nausea, dizziness, allergic reaction and cardiac pain were observed as side effects. Further data were not available due to the double-blind code.

6. Alpha-dihydroergocryptine

Tergau et al., in an open study, suggested that alpha-dihydroergocryptine (DHEC) could be used in RLS treatment.[34] Sixteen patients were evaluated during five weeks. Doses from 10 to 40 mg of DHEC were administered, showing significant reduction of sensory discomfort, involuntary movements, motor restlessness and improvement in sleep quality. One patient reported having nausea as a side effect, and withdrew.

7. Amantadine

An open-label trial[19] with 21 RLS patients concluded that amantadine could be an effective alternative for RLS treatment, as monotherapy or as add-on therapy, even in severe cases. During approximately one year, these patients were treated with amantadine from 100 to 300 mg. Eleven subjects were considered as responders. Six had 95% or more improvement. Three had complete resolution of RLS symptoms. Response varied from 0 to 13 months with nine responders still having benefits at the last follow-up. None developed augmentation or rebound. As side effects, drowsiness, fatigue, insomnia, dry mouth, leg edema and weight loss were reported. Amantadine was considered a well-tolerated drug.

8. Piribedil

Evidente suggested that piribedil was effective in RLS treatment, in an open-label trial. Thirteen patients were followed during one year.[35] Three had idiopathic RLS, four had Parkinson's disease and six had clinical signs of neuropathy. Of these six, one was on regular dialysis due to uremia. Three were using L-dopa, two were using clonazepam and one, zolpidem, with insufficient benefits. Piribedil was administered in doses of 25 to 350 mg. Domperidone 10-20 mg was also used to prevent nausea and vomiting. Eleven patients showed improvement on the subjective response and the RLS score (which consisted of frequency, severity and duration of symptoms). Two had no response. The duration of response for the eleven responders ranged from one to 15 months until the last follow-up. No patient reported augmentation phenomena. Three reported side effects: sleepiness, mental clouding, chest pain and palpitations. The authors suggested that piribedil could be used as a first-line drug for RLS treatment.

9. Gabapentin

In a thirteen-week, double-blind, randomized, cross-over study of 24 patients with RLS who took from 600 mg to 2,400 mg of gabapentin per day, Garcia-Borreguero et al. found an improvement on the total score of the RLS Rating Scale, PLM index, total sleep time, sleep efficiency, slow wave sleep and stage 1 sleep (S1) in the treatment group, compared to placebo.[36] The more severe the symptoms, the better the results. No cases of augmentation of RLS symptoms were seen, and there were no significant differences in the side effects between gabapentin and placebo. The authors suggested that gabapentin was a potent agent for treatment of severe RLS.

Another randomized, double-blind, placebo-crossover study[37] showed that gabapentin was effective for the treatment of RLS patients undergoing hemodialysis. During two cross-over periods of six weeks each, 16 patients were treated with either placebo or 200 to 300 mg of gabapentin. Two patients discontinued study due to lethargy and one died of myocardial infarction. Eleven subjects responded to gabapentin. One responded to both, and one, to placebo.

Happe et al. conducted an open-label trial with nine RLS patients treated with gabapentin.[38] After four weeks of treatment, the doses of gabapentin ranged from 300 to 1,200 mg/d (mean 733 $\pm$ 400 mg/d). The number of PLMS, the PLMS index, the PLMS arousal index and the arousal index were reduced ($p \leqslant 0.004$), but other parameters (such as sleep efficiency, total sleep time, sleep latency, and duration of slow wave sleep) did not show any significant changes. After six to ten months, eight patients were still taking an average of 533 $\pm$ 328 mg of gabapentin (range 300 to 900 mg), but one patient increased the dosage up to 3,600 mg without any symptom relief. However, the other eight patients showed improvement in RLS symptoms after treatment when compared to baseline. The side effects reported were numbness, dizziness, sleepiness and headaches.

10. Iron

Davis et al. assessed the effect of iron in a randomized, double-blind, controlled trial.[39] Fourteen patients received ferrous sulfate 325 mg b.i.d., and fourteen received placebo, for twelve weeks. The results showed that there were no significant differences between iron and placebo group for quality of sleep, percent of nights wakened by RLS and level of RLS effect on life at the end of the study. Side effects reported were nausea, constipation, dark-colored stools, tooth discoloration, vertebral fracture, worsening of RLS symptoms and spasms. The authors suggested that iron did not appear to be an effective treatment for RLS.

A case report by Barton et al. showed a middle-aged man diagnosed with hemochromatosis after a high intake of iron.[40] Previously he had RLS symptoms, which were controlled by a self-made iron therapy. This article suggested that patients with iron deficiency might be benefited by an iron therapy. It was proposed though that patients should have a regular evaluation on serum iron parameters to monitor the risks of developing hemochromatosis.

11. Opioids

Walters et al. suggested that opioids could be effective on a long-term basis in the treatment of RLS.[41] This follow-up study was based on the analysis of 36 patients with RLS who used opioids (25 mg tilidine, 60 mg dihydrocodeine, 5 mg oxycodene, 30 mg codeine, 65 mg propoxyphene, 10 mg methadone) as monotherapy. Twenty patients still maintained treatment for an average of 5 years and 11 months. During this time, only one of the 16 subjects who dropped out the study had problems with tolerance and addiction. Some side effects were also observed, such as an increase in daytime fatigue, migraine headaches, hangover, grogginess, paradoxical hyperalerting response and constipation. Of the patients who continued the treatment, seven were submitted to a polisomnography, which showed improvement in sleep quality, sleep latency, stages 3 and 4 sleep (S3 and S4), stage REM sleep, total sleep time, sleep efficiency, PLM index, PLMS arousals index and periodic movements while awake index. However, two of the seven subjects had sleep apnea.

12. Tramadol

An open study about tramadol was conducted by Lauerma et al. with twelve patients who were treated with 50 to 150 mg of this opioid during an average of 22.8 months (range 15-26 months).[42] After treatment, ten subjects reported great improvement in their symptoms, and one reported slight amelioration of his symptoms. Only one patient had no effect at all. As adverse events, there were reported dizziness, feelings of tremor, itching sensation on the skin and severe abdominal pain. Five patients showed signs of tolerance. The authors recommended intermittent treatment.

13. Apomorphine

Reuter et al., in an open trial, demonstrated that the use of an overnight apomorphine infusion was effective in severe refractory RLS treatment.[43] Six parkinsonian and two RLS L-dopa refractory patients were analyzed in the study. RLS patients were treated with subcutaneous doses of 12 mg and 18 mg, respectively. There was improvement of nocturnal freezing and early morning akinesia, mean nocturnal awake off periods, mean frequency of nocturnal awakenings, sleep quality, nocturnal pain, dystonia, nocturia, excessive daytime sleepiness and assessment of clinical global state. After a one-year follow-up, the sleep benefits persisted in all patients. As side effects, all subjects presented subcutaneous nodules, biopsed as paniculitis. A double-blind placebo infusion was administered to one RLS patient. Placebo infusion did not improve the symptoms.

14. Morphine

In a case report, Jakobsson et al. presented two patients with severe RLS who were treated with an implanted pump for intrathecal morphine and bupivacaine delivery.[44] One patient was a 67-year-old man who had been unsuccessfully treated with L-dopa. His dura was punctured between the second and third lumbar vertebra and a silicone catheter was inserted with the tip located at the level of the eleventh thoracic vertebra. The catheter was connected to a pressure-driven pump delivering 0.5 mg morphine and 5 mg bupivacaine a day. After six months of treatment the bupivacaine was removed, and after 16 months the morphine dose decreased to 0.25 mg a day. At the end of the treatment, the RLS symptoms improved completely. Side effects such as slight nausea and disturbance of micturition were observed. The other patient was a 52-year-old woman who had tried every kind of drugs. She received an epidural catheter for the administration of morphine, bupivacaine and clonidine. After two months, the symptoms disappeared completely. It was decided, thus, to implant a pump for intrathecal delivery with the same technique as described above. Three and a half years later, the symptoms have not returned and no adverse effects were reported, on a dosage of 0.08 mg morphine per day.

15. Clonazepam

Saletu et al. assessed the effect of clonazepam in ten patients with RLS and 16 patients with PLMD in a placebo-controlled, cross-over study.[45] The subjects received placebo at one night and 1 mg clonazepam the other night. The study was single-blind due to the long elimination half-life of clonazepam ($t_{1/2}$ = 20-60 h); therefore the placebo had to be administered first. As compared to placebo, clonazepam significantly improved objective sleep efficiency, subjective sleep quality, total sleep time, stages 2 and 4 sleep (S2 and S4), slow-wave sleep, wake-time within the total sleep period and number of awakenings, in both patient groups, but failed to decrease the index of PLM/h of total sleep time. There were no significant inter-group differences on PLM/h of time in bed, PLM/h of REM, PLM during wake-time, apnea-hypopnea index and desaturation index. The authors suggested that clonazepam had an acute therapeutic efficacy regarding insomnia, which was quite different from the mode of action of dopamine agents.

16. Zolpidem

Bezerra et al. suggested that zolpidem might be effective in the treatment of RLS.[46] A prospective, non-controlled, open-label study with eight patients with RLS refractory to other treatments was carried out. The dose was 10 mg/day. The subjects had RLS classified from severe to moderate and had complete relief of the symptoms after an average of four days. Effects were reported to last from 1 year to 30 months. No side effects were observed. Two patients stopped medication and the symptoms returned but were relieved when they resumed treatment.

17. Entacapone

A case report showed the use of entacapone in a 62-year-old woman with RLS during one month.[47] She also had hypertension, hypercholesterolemia and iron-deficiency anemia, and was on hemodialysis. Formerly she had been using quinine, clonazepam, pramipexole and gabapentin with either intolerable side effects or no relief for her RLS symptoms. Carbidopa/L-dopa was prescribed with 25-10 mg three times

daily. Initially, this dosage satisfactorily improved the symptoms, but after three months the patient reported only 2-3 hours relief from symptoms after each dose of carbidopa/L-dopa. The dosage was then changed to 50-200 mg three times daily. On the next follow-up visit, the patient reported that the latency till the onset of action had increased from one hour to 90 minutes following each dose, and the duration of relief of RLS symptoms had also increased from 2-3 hours to up to 4 hours, with no satisfaction. Thus, 200 mg entacapone was added along with each tablet of carbidopa/L-dopa three times daily. The duration of symptoms relief increased to up to 5 hours, but the patient started experiencing nausea. The benefit of entacapone lasted during the one month of use.

18. Ketamine

Kapur et al. suggested that oral ketamine might be helpful in RLS treatment.[48] Two case reports about RLS patients were carried out. A 70-year-old woman have accomplished an ineffective use of dopaminergic agonists, pergolide and oxycodone. After 20 minutes of administration of 30 mg ketamine, she reported improvement of the RLS symptoms. She felt relaxed and noted no dizziness or other distressing symptoms. After 6 months using 60 mg daily, the improvement on RLS and sleep persisted. A 61-year-old man used tramadol, rofecoxib, gabapentin, quinine and steroid injections without success. After 15 minutes of administration of 50 mg ketamine, he reported improvement of the RLS symptoms. He also reported subjective improvement in walking. After one month of 80 mg daily, the patient still reported improvement on RLS and sleep. Both patients had improvement on abnormal limb sensations and insomnia and noted pain relief.

Discussion

The large variety of therapeutic options for RLS treatment makes it complicated due to a lack of consensus about the best choice. In this study, we reviewed the available articles, ranging from 1999 to 2003, related to the various pharmacological treatments for RLS. The majority of articles focus on the evaluation of dopaminergic agents. Other drugs included anticonvulsants, iron, opioids and benzodiazepines.

Among the dopaminergic agents, the most studied drug was L-dopa. The studies show that L-dopa is effective to improve RLS symptoms and PLMS without rebound effects, with only one case of augmentation phenomena, though this is common with the use of L-dopa.[16] As monotherapy, RLS symptoms last only during the first half of the night. However, when sr-L-dopa is associated, the benefits extend to the second half of the night. Moreover, the case report about entacapone also suggests that its association can be helpful in increasing the duration of L-dopa action. Side effects are mainly gastrointestinal.

Other dopaminergic agents, such as pergolide and pramipexole, seem to be another treatment option. Five articles about these medications show a significant improvement of RLS symptoms, sleep quality and PLMS variables. An absence of rebound effect and low occurrence of tolerance are observed, but augmentation phenomena and important side effects were found.

There are few articles about amantadine, cabergoline, piribedil, alpha-dihydroergocryptine and ropinirole. All these medications have a satisfactory level of improvement of RLS symptoms and sleep quality. No augmentation phenomena or rebound effect was found, but a large variety of side effects were reported. As these articles are open-label trials, randomized, double-blind, placebo-controlled studies are needed.

Three articles were found about gabapentin, which is an anticonvulsant. All of them show efficacy in reducing especially PLMS variables. Side effects are reported only in the unique open-label trial. Augmentation is not found with this drug.

Opioids are also options for RLS treatment. Four articles about tramadol, apomorphine, morphine and other opioids were found. They seem to provide good amelioration of RLS symptoms, although tolerance, addiction and severe side effects are reported. As they are neither double-blind nor randomized, studies with this design are required.

In the case report about iron, the total control of the RLS symptoms suggests that this substance can be an alternative option of treatment, especially in iron-deficient patients. However, the randomized, double-blind, placebo-controlled study showed that there are no significant differences between iron and placebo.

The studies about clonazepam, zolpidem and ketamine, even though suggesting good results, are insufficient for analysis, due to their design methods.

Most of the articles have small samples, short treatment periods, no follow-up and inadequate study designs. Based on the few double-blind, randomized, placebo-controlled studies, it seems that the best options to treat RLS patients are gabapentin and L-dopa associated with sr-L-dopa. Pergolide and pramipexole presented augmentation and severe side effects while opioids presented tolerance, addiction and important adverse events, thus they could be used as second choice medications.

Table 1 – Evidence for treatment of RLS with pharmacological therapy

Author/year	Sample size	Medication/dosage	Duration	Study design	Results	Side effects	Augmentation phenomena or rebound effect	Comments
Benes et al.[21] (1999)	35 (32 completed)	100-200 mg levodopa + 25-50 mg benserazide	2 cross-over periods of 4 weeks each	Double-blind randomized controlled multicenter cross-over trial	Improvement in number of PLMs/hour, time in bed without limb movements and subjective sleep quality	Diarrhea, reduced general drive, nausea and muscle weakness	No augmentation phenomena or rebound effect	—
Saletu et al.[22] (2003)	3 nights: 21 4 weeks: 18	100-200 mg rr-L-dopa/ benserazide + 100-200 mg sr-L-dopa/ benserazide	3 nights and a follow-up of 4 weeks	3 nights: double-blind, controlled, randomized crossover trial. 4 weeks: open non-controlled trial	Acute L-dopa/ benserazide improved PLM/h of sleep, total number of PLM, PLM/h of time in bed, PLM/h of REM and non-REM, PLM/h of wake time and PLM-arousals/h of sleep, but the subjective sleep quality only improved after chronic treatment	Nausea, stomachache, tachycardia, dry mouth, headache and nycturia.	One patient reported augmentation phenomena	—

References

1. Weimerskirch PR, Ernst ME. Newer dopamine agonists in the treatment of restless legs syndrome. *Ann Pharmacother*. 2001;35(5):627-30.
2. Chaudhuri KR, Appiah-Kubi LS, Trenkwalder C. Restless legs syndrome. *J Neurol Neurosurg Psychiatry*. 2001;71(2):143-6.
3. Tan EK, Ondo W. Restless legs syndrome: clinical features and treatment. *Am J Med Sci*. 2000;319(6):397-403.
4. Reimão R. Sono: estudo abrangente. 2a ed. São Paulo: Atheneu; 1996. p. 273-7.
5. Philips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. *Arch Intern Med*. 2000;160(14):2137-41.
6. Tan EK, Seah A, See SJ, Lim E, Wong MC, Koh KK. Restless legs syndrome in an Asian population: a study in Singapore. *Mov Disord*. 2001;16(3):577-9.
7. Rothdach A, Trenkwalder C, Haberstock J, Keil U, Berger K. Prevalence and risk factors of RLS in an elderly population: the MEMO study. Memory and Morbidity in Augsburg Elderly. *Neurology*. 2000;54:1064-8.
8. Lee KA, Zaffke ME, Baratee-Beebe K. Restless legs syndrome and sleep disturbance during pregnancy: the role of folate and iron. *J Womens Health Gen Based Med*. 2001;10(4):335-41.
9. Janzen L, Rich JA, Vercaigne LM. An overview of levodopa in the management of restless legs syndrome in a dialysis population: pharmacokinetics, clinical trials, and complications of therapy. *Ann Pharmacother*. 1999;33(1):86-92.
10. Trenkwalder C, Seidel VC, Gasser T, Oertel WH. Clinical symptoms and possible anticipation in a large kindred of familial restless legs syndrome. *Mov Disord*. 1996;11(4):389-94.
11. Walther BW. Treating restless legs syndrome: current pathophysiological concepts and clinical trials. *Expert Opin Investig Drugs*. 2002;11(4):501-14.
12. Allen RP, Earley CJ. Restless legs syndrome: a review of clinical and pathophysiologic features. *J Clin Neurophysiol*. 2001;18(2):128-47.
13. Clark MM. Restless legs syndrome. *J Am Board Fam Pract*. 2001;14(5):368-74.
14. Reimão R. Síndrome das pernas inquietas: atualização terapêutica. *Rev Bras Neurol Psiquiatr*. 1998;2(3):95-8.
15. Hening W, Allen R, Earley C, Picchietti D, Silber M. The treatment of restless legs syndrome and periodic limb movement disorder. An American Academy of Sleep Medicine review. *Sleep*. 1999;22(7):970-99.
16. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. *Sleep*. 1996;19(3):205-13.
17. Montplaisir J, Godbout R, Poirier G, Bedard MA. Restless legs syndrome and periodic movements in sleep: physiopathology and treatment with L-dopa. *Clin Neuropharmacol*. 1986;9(5):456-63.
18. Guilleminault C, Cetel M, Philip P. Dopaminergic treatment of restless legs and rebound phenomenon. *Neurology*. 1993;43(2):445.
19. Evidente VG, Adler CH, Caviness JN, Hentz JG, Gwinn-Hardy K. Amantadine is beneficial in restless legs syndrome. *Mov Disord*. 2000;15(2):324-7.
20. Benes H, Kurella B, Kummer J, Kazenwadel J, Selzer R, Kohnen R. Rapid onset of action of levodopa in restless legs syndrome: a double-blind, randomized, multicenter, crossover trial. *Sleep*. 1999;22(8):1073-81.
21. Saletu M, Anderer P, Hogl B, Saletu-Zyhlarz G, Kunz A, Poewe W, Saletu B. Acute double-blind, placebo-controlled sleep laboratory and clinical follow-up studies with a combination treatment of rr-L-dopa and sr-L-dopa in restless legs syndrome. *J Neural Transm*. 2003;110(6):611-26.
22. Collado-Seidel V, Kazenwadel J, Wetter TC, Kohnen R, Winkelmann J, Selzer R, Oertel WH, Trenkwalder C. A controlled study of additional sr-L-dopa in L-dopa-responsive restless legs syndrome with late-night symptoms. *Neurology*. 1999;52(2):285-90.
23. Wetter TC, Stiasny K, Winkelmann J, Buhlinger A, Brandenburg U, Penzel T, Medori R, Rubin M, Oertel WH, Trenkwalder C. A randomized controlled study of pergolide in patients with restless legs syndrome. *Neurology*. 1999;52(5):944-50.
24. Stiasny K, Wetter TC, Winkelmann J, Brandenburg U, Penzel T, Rubin M, Hundemer HP, Oertel WH, Trenkwalder C. Long-term effects of pergolide in the treatment of restless legs syndrome. *Neurology*. 2001;56(10):1399-402.
25. Walters AS, Mandelbaum DE, Lewin DS, Kugler S, England SJ, Miller M. Dopaminergic therapy in children with restless legs/periodic limb movements in sleep and ADHD. Dopaminergic Therapy Study Group. *Pediatr Neurol*. 2000;22(3):182-6.
26. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology*. 1999;52(5):938-43.
27. Montplaisir J, Denesle R, Petit D. Pramipexole in the treatment of restless legs syndrome: a follow-up study. *Eur J Neurol*. 2000;7(Suppl 1):27-31.
28. Saletu M, Anderer P, Saletu-Zyhlarz G, Hauer C, Saletu B. Acute placebo-controlled sleep laboratory studies and clinical follow-up with pramipexole in restless legs syndrome. *Eur Arch Psychiatry Clin Neurosci*. 2002;252(4):185-94.
29. Saletu B, Gruber G, Saletu M, Brandstatter N, Hauer C, Prause W, Ritter K, Saletu-Zyhlarz G. Sleep laboratory studies in restless legs syndrome patients as compared with normal and acute effects of ropinirole. 1. Findings on objective and subjective sleep and awakening quality. *Neuropsychobiology*. 2000;41(4):181-9.
30. Saletu M, Anderer P, Saletu B, Hauer C, Mandl M, Oberndorfer S, Zoghlami A, Saletu-Zyhlarz G. Sleep laboratory studies in restless legs syndrome patients as compared with normal and acute effects of ropinirole. 2. Findings on periodic leg movements, arousals and respiratory variables. *Neuropsychobiology*. 2000;41(4):190-9.
31. Ondo W. Ropinirole for restless legs syndrome. *Mov Disord*. 1999;14(1):890-2.
32. Stiasny K, Röbbecke J, Schuler P, Oertel WH. Treatment of idiopathic restless legs syndrome (RLS) with the D2-agonist cabergoline – an open clinical trial. *Sleep*. 2000;23(3):349-54.
33. Stiasny K. Clinical data on restless legs syndrome: a dose-finding study with cabergoline. *Eur Neurol*. 2001;46(Suppl 1):24-6.
34. Tergau F, Wischer S, Wolf C, Paulus W. Treatment of restless legs syndrome with the dopamine agonist alpha-dihydroergocryptine. *Mov Disord*. 2001;16(4):731-5.
35. Evidente VG. Piribedil for restless legs syndrome: a pilot study. *Mov Disord*. 2001;16(3):579-81.
36. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. *Neurology*. 2002;59(10):1573-9.
37. Thorp ML, Morris CD, Bagby SP. A crossover study of gabapentin in treatment of restless legs syndrome among hemodialysis patients. *Am J Kidney Dis*. 2001;38(1):104-8.
38. Happe S, Klösch G, Saletu B, Zeitlhofer J. Treatment of idiopathic restless legs syndrome (RLS) with gabapentin. *Neurology*. 2001;57(9):1717-9.
39. Davis BJ, Rajput A, Rajput ML, Aul EA, Eichhorn GR. A randomized, double-blind placebo-controlled trial of iron in restless legs syndrome. *Eur Neurol*. 2000;43(2):70-5.
40. Barton JC, Wooten VD, Acton RT. Hemochromatosis and iron therapy of restless legs syndrome. *Sleep Med*. 2001;2(3):249-51.
41. Walters AS, Winkelmann J, Trenkwalder C, Fry JM, Kataria V, Wagner M, Sharma R, Hening W, Li L. Long-term follow-up on restless legs syndrome patients treated with opioids. *Mov Disord*. 2001;16(6):1105-9.

42. Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. *J Clin Psychiatr*. 1999;60(4):241-4.
43. Reuter I, Ellis CM, Ray Chaudhuri K. Nocturnal subcutaneous apomorphine infusion in Parkinson's disease and restless legs syndrome. *Acta Neurol Scand*. 1999;100(3):163-7.
44. Jakobsson B, Ruuth K. Successful treatment of restless legs syndrome with an implanted pump for intrathecal drug delivery. *Acta Anaesthesiol Scand*. 2002;46(1):114-7.
45. Saletu M, Anderer P, Saletu-Zyhlarz G, Prause W, Semler B, Zoghlami A, Gruber G, Hauer C, Saletu B. Restless legs syndrome (RLS) and periodic limb movement disorder (PLMD): acute placebo-controlled sleep laboratory studies with clonazepam. *Eur Neuropsychopharmacol*. 2001;11(2):153-61.
46. Bezerra ML, Martínez JV. Zolpidem in restless legs syndrome. *Eurol Neurol*. 2002;48(3):180-1.
47. Sharif AA. Entacapone in restless legs syndrome. *Mov Disord*. 2002;17(2):421.
48. Kapur N, Friedman R. Oral ketamine: a promising treatment for restless legs syndrome. *Anesth Analg*. 2002;94(6):1558-9, table of contents.