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This section is being introduced in this issue as a forum for discussion of controversial topics in sleep medicine, particularly controversial diagnoses and treatments of specific disorders. Papers will be requested by the Editorial Board.

—Eds.

Controversies in Sleep Medicine

The Treatment of the Restless Leg Syndrome With or Without Periodic Leg Movements in Sleep

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Summary: There are presently three main treatments for restless leg syndrome-periodic leg movements in sleep (RLS-PLMS). The benzodiazepines (especially clonazepam) are considered by most clinicians to be the treatment of choice in mild cases, especially in young subjects. In our experience, however, L-dopa and bromocriptine are more effective treatments, although no controlled studies have ever been conducted to compare their therapeutic benefits and the side effects of benzodiazepines and dopaminergic drugs. The use of opioids should be restricted to patients who have severe symptoms and who fail to respond to benzodiazepines or L-dopa. Propoxyphene was found less effective than L-dopa in decreasing PLMS, but some patients resistant to L-dopa may exhibit a masked therapeutic response to opioids. However, there is currently no method to predict the response to any treatment modality. **Key Words:** Restless leg syndrome—Benzodiazepines—Opioids—L-dopa.

The restless leg syndrome (RLS) is characterized by leg paresthesia occurring at rest that induces an irresistible urge to move (1). In severe cases, arm paresthesia may also be reported. In the majority of cases, symptoms worsen with increased sleepiness and are relieved by movements. Many patients also experience severe paresthesia upon awakening in the middle of the night. In a recent unpublished study, 60 patients presenting a typical history of RLS were recorded for one or two consecutive nights in our sleep laboratory and periodic leg movements in sleep (PLMS) were seen in 48 (80%).

A major difficulty in assessing treatment of RLS relates to the evolution of the condition. In fact, the severity of RLS can vary greatly throughout a patient's lifetime. Sometimes, motor symptoms may be present several times during the day; at other times they may be totally absent. Sudden remissions, which may last for months or even years, are as difficult to explain as relapses, which appear without any apparent reason (2).

EVALUATION METHODS

There are three methods available to quantify the various symptoms of RLS. Questionnaires are commonly used to assess the presence and the severity of paresthesia, irresistible leg movements and nocturnal sleep disruption. Nocturnal polysomnographic (PSG) recording is used to count leg movements during wakefulness prior to sleep onset or upon awakening in the middle of the night. PSG recording also allows quantification of PLMS (3) and the calculation of several indices of sleep disturbance. In RLS, it is useful to quantify leg movement during waking prior to sleep

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onset or upon awakening during the night. However, movements are rarely counted during waking because patients with severe RLS often ask to walk around when they experience severe paresthesia. Objective methods are currently being validated to evaluate the effectiveness of treatment for RLS.

The first test to be developed was the Suggested Immobilization Test (SIT) (4), during which the patient is asked to remain in bed for 1 hour with legs outstretched while electromyographic (EMG) potentials from right and left anterior tibialis muscles are recorded. This test was found to be sensitive to the effects of L-dopa on RLS (4).

A modified version of the test, called the Forced Immobilization Test (FIT) has recently been developed (5). During this test, legs are immobilized in a splint and patients are asked to signal awareness of sensory events with a push-button while EMG from right and left anterior tibialis muscles is recorded. This method allows assessment of both sensory and motor aspects of the condition (6).

TREATMENTS

Over the years, several medications have been proposed to treat RLS, but very few of these have been systematically evaluated. Three families of pharmacological compounds are commonly being used, namely benzodiazepines, dopaminergic agents and opioids. These treatments will be reviewed in more detail, although the therapeutic benefits of other medications will be discussed more briefly.

Clonazepam and other benzodiazepines

Several benzodiazepines, including alprozolam, clonazepam, nitrazepam, temazepam and triazolam (7–17), have been used to treat RLS and PLMS. Among these, clonazepam is by far the most-studied benzodiazepine. Several reports have mentioned its beneficial effects in RLS and PLMS (7–9), even in cases of RLS that are secondary to uremia (10). Two controlled studies of RLS treatment with clonazepam without PSG have been conducted. In the first study (11) of six patients, clonazepam was found to be superior to placebo in improving sleep quality and in suppressing leg dysesthesia, but not in reducing leg jerking. In the second study of six patients (12), clonazepam was not found to be superior to placebo in the treatment of leg jerking or paresthesia. In two studies of PLMS patients investigated with PSG, results were contradictory. In the first (13), clonazepam was effective in reducing the number of leg movements per hour of sleep, whereas in the second (14), it was not. Mitler et al. (14) showed, in fact, that benzodiazepines such as clonazepam and temazepam reduced the number of arousals and awakenings associated with leg jerks rather than the number of leg movements. Bonnet and Arand (15) found that another benzodiazepine, triazolam, also increased total sleep time and sleep efficiency without significantly reducing leg movements during sleep.

In summary, there is controversy regarding the therapeutic effects of benzodiazepines on the motor manifestations of RLS and PLMS. One explanation of this is the small number of patients examined in these studies and the high variability of the therapeutic response among patients. In a recent review of 40 RLS patients treated with clonazepam in our clinic, 22 (55%) reported an initial satisfactory therapeutic response. Side effects more frequently reported by patients treated with clonazepam were excessive somnolence in the morning and decreased libido. It should be remembered, however, that benzodiazepines are potent central nervous system (CNS) depressants and that they may induce or aggravate sleep apnea syndrome, especially in elderly patients.

Propoxyphene and other opioids

The therapeutic action of opioids was mentioned in the original description of RLS by Ekbom (1). Recently, this effect has been further documented in several open clinical trials (18–21). Morphine, methadone, codeine and propoxyphene were all found effective in treating RLS, but these studies have all been conducted in small patient populations. Not all patients responded to opioids. Dramatic improvements were reported in a small group of patients, whereas others were completely unresponsive. More recently (22), a double-blind placebo controlled study of propoxyphene and L-dopa was conducted in six patients with PLMS. Propoxyphene produced only a mild reduction of PLMS but a significant reduction in the percentage of PLMS associated with arousals.

Although opioids are potent suppressors of RLS and PLMS in a subgroup of patients, the risk for abuse and the danger of addiction associated with their use considerably limit their clinical utility. In severe cases, however, and especially in those patients undergoing hemodialysis, opiates may be an alternative treatment. The smallest doses of short-acting opioids should be used, and the most addictive compounds should be avoided. Every patient should be followed closely for the development of tolerance and dependency.

L-dopa and other dopaminergic drugs

Several studies have shown that L-dopa given with a peripheral carboxylase inhibitor is effective in treat-

ing RLS and PLMS (4,23–25). A controlled study using PSG and a double-blind design also showed that 100 mg of L-dopa administered twice at night produced a significant reduction of RLS at bedtime and of PLMS throughout the night (4). A two-year follow-up study showed long-term beneficial effects of L-dopa in RLS (26). This study showed that relief of symptoms of RLS did not wear off with the passage of time, that side effects were minimal even with long term use and that the dose needed to obtain relief may increase as well as decrease.

To avoid nausea, L-dopa is often administered with food. However, it should be stressed that meals reduce peak plasma L-dopa concentration and delay absorption (27). In addition, high-protein meals, containing phenylalanine, leucine or isoleucine, were found to reverse the therapeutic effect of infused L-dopa, probably by competition for transport from plasma to the brain between these amino acids and L-dopa (27). Such interference with absorption or transport may be responsible for fluctuations in clinical response.

In our experience, two major side effects are frequently seen in patients treated with L-dopa. The first one is the increase of daytime symptomatology when patients are treated only at night. We previously noted (23) that a single dose of L-dopa administered at bedtime was followed by a suppression of PLMS in the first third of the night and by a rebound in the last third when L-dopa was no longer effective. Similarly, when L-dopa administration is repeated in the middle of the night, approximately ⅓ of severe cases will experience de novo paresthesia and restlessness during the daytime. Increased daytime restlessness was also noted by others (22) in two out of four patients after 2 months of treatments with L-dopa. Repeated dosages during the daytime or the use of the sustained-release form of L-dopa (Sinemet CR) may partly alleviate this problem. The sustained-release form may also prevent the need for repeated dosages during the night, but this medication should be specifically studied before it is recommended in the treatment of RLS.

Some patients also complain of insomnia after treatment with L-dopa, in spite of a suppression of sensory and motor symptoms. L-dopa and other dopaminergic agonists are known to exert an alerting effect.

One question that often arises with regard to L-dopa therapy is the possibility of tardive dyskinesia. Recently, we examined patients taking L-dopa at a dosage of 100–500 mg daily for more than 5 years and found no signs of tardive dyskinesia, as seen in patients with Parkinson's disease treated with this medication. Dyskinesia associated with L-dopa treatment probably results from denervation supersensitivity due to the marked reduction of nigrostriatal DA neurons found in Parkinson's disease. This late side effect is very unlikely to occur in RLS-PLMS patients.

Other dopaminergic drugs have been shown to be effective in treating RLS and PLMS. In a double-blind crossover study (28), 7.5 mg of bromocriptine administered at bedtime was effective in treating restlessness and paresthesia in six patients with RLS. It also significantly decreased PLMS at night. As with L-dopa, bromocriptine is also effective in treating PLMS associated with narcolepsy (29,30).

Recently, five patients with RLS and PLMS were treated with selegiline (31), a medication known to inhibit monoamine oxydase type B (MAO type B). The latter enzyme is responsible for the degradation of dopamine in the central nervous system. Selegiline had a positive therapeutic effect, decreasing the frequency of PLMS at night. In addition, selegiline is rapidly converted into amphetamine and exerts an alerting effect, therefore afternoon or evening administration should be avoided. Further studies will be needed to assess the therapeutic value of seligiline in RLS. Because of its alerting effect, it may prove useful in the treatment of narcolepsy associated with PLMS.

Other pharmacological treatments

In several open clinical trials (32,33), carbamazepine was found effective in treating RLS. In a double-blind study, carbamazepine was reported to have a significant therapeutic effect in 174 patients affected with RLS (34). No inclusion criteria were given, and more than half of the subjects had concomitant treatments for other diseases. The therapeutic effect of carbamazepine was also shown in a more recent study, but no significant modifications of PLMS and their relationship to arousal during sleep were seen (35).

Several other treatments, such as quinine or vitamins B and E, are occasionally used to treat RLS, but these treatments have never been evaluated systematically. Clonidine, an adrenergic agonist, was also found effective in treating RLS (36,37), but this effect has not been found by others (38). Other treatments, such as iron sulphate, B-12 or folic acid have been reported to improve RLS. However, there have been no controlled studies of these drugs in primary RLS-PLMS without anemia.

RLS may be associated with several other medical conditions, such as anemia or kidney failure. In these cases, the primary conditions should be treated. However, in case of kidney failure, RLS often persists after treatment of renal disease. Moreover, as seen in several patients undergoing hemodialysis, a worsening of RLS may interfere with hemodialysis, which requires prolonged immobilization. In these cases, clonazepam, L-dopa or opiates are currently administered.

Nonpharmacological treatment

Two studies have investigated the effects of electrical stimulation in RLS. In the first study, vibratory stimulation applied at bedtime to one sural region for 15 minutes during 1 week produced no significant effects on sleep quality, dysesthesia or leg-jerking in six RLS patients (11). More recently, a single 30-minute period of stimulation of the dorsiflexors of the feet and toes was administered at bedtime in eight patients with PLMS, of whom four also had RLS. Patients were reevaluated 2 months later and found to have a reduced PLMS index. However, this was an uncontrolled study and therefore, as suggested by the author, the changes might be due to a placebo effect (39).

In conclusion, there are presently three main treatments for RLS-PLMS. The benzodiazepines (especially clonazepam) are considered by most clinicians to be the treatment of choice in mild cases and especially in young subjects. However, in our experience L-dopa and bromocriptine are more effective treatments, although no controlled studies have ever been conducted to compare their therapeutic benefits and the side effects of benzodiazepines and dopaminergic drugs. The use of opioids should be restricted to patients who have severe symptoms and who fail to respond to benzodiazepines or L-dopa. Propoxyphene was found to be less effective than L-dopa in decreasing PLMS, but some patients resistant to L-dopa may exhibit a masked therapeutic response to opioids. At the moment, however, no method will predict the response to any treatment modality.

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