Sleep, 19(3):205–213

Augmentation of the Restless Legs Syndrome With Carbidopa/Levodopa

Richard P. Allen and Christopher J. Earley

Department of Neurology of the Johns Hopkins School of Medicine at Bayview Medical Center and the Johns Hopkins University Sleep Disorders Center, Baltimore, Maryland, U.S.A.

Summary: Dopaminergic agents and carbidopa/levodopa have become the preferred treatment for both the restless legs (RL) syndrome and for periodic limb movements in sleep (PLMS). For once-nightly treatments with carbidopa/levodopa, a problem with morning end-of-dose rebound increases in leg movements has been reported to occur in the about one-fourth of the patients. In our clinical studies a previously unreported but far more significant problem of markedly augmented RL symptoms occurred in the afternoon and the evening prior to taking the next nightly dose. A systematic prospective evaluation of this augmentation in 46 consecutive patients treated with carbidopa/levodopa for RL syndrome or PLMS disorder found this augmentation to be the major adverse effect of treatment. Augmentation occurred for 31% of PLMS patients and 82% of all RL patients. It was greater for subjects with more severe RL symptoms and for patients on higher doses (≥50/200 mg carbidopa/levodopa) but was unrelated to gender, age or baseline severity of PLMS. This augmentation was severe enough to require medication change for 50% of the RL patients and 13% of PLMS patients. Augmentation resolved with cessation of the medication and could be minimized by keeping the dose low. **Key Words:** Restless legs syndrome—Periodic limb movements in sleep—Dopaminergic agents—Carbidopa—Levodopa.

The restless legs (RL) syndrome, a fairly common sleep-related disorder, affects at least 5% of adults (1,2). This syndrome is characterized by four clinical features: 1) episodes of periodic (and at times continuous), distressing, excruciating, but often not painful, sensations with irresistible "urges to move" (akathisia) localized in the extremities, usually the legs; 2) relief of the sensations by movement of the affected extremity; 3) episodes of frequent periodic and repetitive movement of the affected extremity and 4) symptoms that are worse at rest and in the evening and night (3,4). Patients experience RL episodes while awake that are often so extreme that they cannot sit or even stand still. The increasing severity both at night and when at rest makes falling asleep difficult. Almost all patients with the RL syndrome also have a related disorder characterized by periodic movements of one or both legs, persisting throughout much of sleep. The periodic leg movements (PLM) in sleep can often be very disruptive to normal sleep. Although almost all patients with the RL syndrome also have PLM during sleep, there are many patients with PLM but without the akathisia or paresthesia that characterize the RL syndrome (3). Patients with the primary disorder of PLM in sleep without RL symptoms will be referred to in the following pages as having a periodic limb movements in sleep (PLMS) disorder.

Several recent studies have indicated that dopaminergic medications provide an effective treatment for the RL syndrome. These benefits were first documented in an open clinical trial by Akpinar (5) and subsequently by Montplaisir et al. (6). They were then confirmed in double-blind, placebo-controlled clinical trials using both levodopa (7) and bromocriptine (8). Prior to this, opiates had been considered the only effective treatment for the RL syndrome, as had been shown by Ekbom (1).

In two double-blind, placebo-controlled trials comparing carbidopa/levodopa to propoxyphene, the dopaminergic treatment was far more effective than the opiate for reducing leg movements before and during sleep (9,10). These studies also showed that dopaminergic treatment was effective even for patients with the PLMS disorder. Dopaminergic medications have, therefore, gained increasing acceptance as the treatment of choice for both the RL syndrome and the PLMS disorder.

Two open clinical trials have followed patients with the RL syndrome treated with levodopa for at least 6 months. No significant adverse effects were reported

Accepted for publication December 1995.
Address correspondence and reprint requests to Dr. Richard P. Allen, Hopkins Sleep Disorders Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, U.S.A.

in 26 patients treated with levodopa and beneserazide for 2 years (11). However, in another group of 44 patients followed for 6 months while on treatment with carbidopa/levodopa, 4 failed to respond, 2 reported loss of efficacy and 5 stopped medication because of side effects, mainly nausea. For the 33 patients who continued the medication for 6 months, 8 (24%) developed RL symptoms in the morning. In seven of these eight patients, these new symptoms were severe enough to warrant an added morning dose of carbidopa/levodopa taken after 7:00 a.m. (12).

This morning increase in RL symptoms was also reported in two other studies on treatment of the RL syndrome (6,13). The morning increase was the most common adverse effect in these studies. It occurred shortly after levodopa had ceased to be active and could be viewed as a medication withdrawal state from this short-acting medication. Thus, the open, long-term studies have shown that whereas levodopa therapy provides effective treatment with relatively few side effects, it also has significant adverse effects of increased RL symptoms in the morning.

In our double-blind studies, in which we compared the use of carbidopa/levodopa and propoxyphene given only in single doses before bed, we also reported increased RL symptoms. Although these occasionally occurred in the morning, they were even more prevalent in the afternoon and early evening (9,10) and caused significant clinical management problems. Because increased RL symptoms at this time had not been previously reported, we started a routine inquiry about the RL symptoms in the afternoon and day. We discovered that indeed patients reported an increase in their RL symptoms later in the day that persisted for >4 weeks and appeared to get worse with increases in medication. We refer to this afternoon and evening increase in RL occurring after carbidopa/levodopa treatment as RL augmentation to distinguish this from the morning RL "rebound" previously reported by others. This augmentation of the RL symptoms is defined as the usual daily onset of RL symptoms starting earlier than they did before treatment. As the augmentation becomes worse, the symptoms become progressively earlier in the day, but once started they follow the usual pattern for RL of generally persisting for the rest of the day unless treated either with medication or patient activity. Thus, unlike morning rebound, RL augmentation does not start occurring first in the morning nor is it followed by any significant daytime period free of symptoms.

From our clinical experience, RL augmentation represents the major complication of dopamine treatment of the RL syndrome and PLMS disorder. Further data are, however, needed to document not only prevalence and severity but also factors contributing to this augmentation. The data presented here come from a systematic prospective clinical inquiry designed to answer these questions. These represent the first systematic study of the dopamine-induced RL augmentation.

METHODS

Subjects

Each patient presenting at the Sleep Disorder Center and diagnosed as having either the RL syndrome or PLMS disorder was offered treatment starting with carbidopa/levodopa unless this was medically contraindicated or it was judged that the patient's symptoms were not severe enough to warrant treatment. The RL syndrome diagnosis required clinical symptoms of bothersome sensations in the legs that resolved quickly when the legs are moved, occurred predominantly in the evening just before bed and were worse while at rest. These diagnostic criteria correspond with those established by the International Study Group on the Restless Legs Syndrome (4). For this study the diagnosis of a clinically significant PLMS disorder required that the rate of PLM exceed 25/hour in nonrapid eye movement (NREM) sleep, with at least 10% of the PLMS associated with an electroencephalographic (EEG) arousal. For inclusion in the study the patient with the PLMS disorder must have also reported clinically significant complaints of both sleep disruption and daytime consequences associated with the sleep disturbance. Only patients that were followed in treatment for at least 4 weeks were included in the study. Pregnant or nursing women, patients on dialysis and patients with another significant sleep disorder diagnosis (e.g. sleep apnea, narcolepsy) were excluded from this study. Patients with iron deficiency were excluded if the RL symptoms no longer persisted after treatment resolved the anemia. Patients with significant psychiatric disorders (e.g. major depressive disorder, schizophrenia) were also excluded. Two subjects refused carbidopa/levodopa treatment: one because she intended to get pregnant and the other because she preferred not to start a new medication.

This provided a consecutive case series representative of the population of patients treated at sleep disorders centers for idiopathic RL syndrome or idiopathic PLMS disorder.

Polysomnograms

All patients had a standard diagnostic polysomnogram to confirm the presence of PLM. Any medications that were expected to affect the leg movements were discontinued prior to the polysomnogram, allowing enough time for the medication effects to have abated.

This study included sleep EEG [C3-A2, C3-O1, bilateral electro-oculogram (EOG), submental electromyogram (EMG)], a modified two-lead electrocardiogram (ECG), respiration measures (nasal and oral air flow, thoracic and abdominal respiratory movements, finger oximetry) and bilateral recording of anterior tibialis EMG. PLMS rates were determined based on counting for NREM sleep all anterior tibialis EMG increases lasting 0.5–5 seconds and occurring in a series of at least four events spaced 5–120 seconds apart, similar to the criteria used by Coleman et al. (14).

Medication protocol

The treatment for all of the patients except one started with 1/2 to 1 tablet of carbidopa/levodopa 25/100 mg that was given 20–30 minutes before bed. The dose was increased by 1/2 tablet every 3 days until satisfactory sleep occurred for the first 3 hours in bed or the dose reached a maximum of 4 tablets. If significant adverse side effects occurred, other than RL augmentation, then the medication dose was either decreased or not increased for an added 3-day period. If early morning awakening occurred, with difficulty returning to sleep because of RL symptoms, then an additional 1/2 to 2 tablets of carbidopa/levodopa 25/100 mg were added to the treatment at the time of the awakening but not after 3:30 a.m. The final effective treatment dose established within the first 2 months of treatment was used in this analysis. This treatment protocol gave a final maximum daily dose of six tablets of carbidopa/levodopa 25/100 mg.

Daytime doses of carbidopa/levodopa were always strongly discouraged except for occasional p.r.n. use prior to sedentary activities that were unusual and would cause major problems with RL symptoms (e.g. longer airplane or car trips). Patients reported doing this on average less than once every 2 weeks and none did this on a regular weekly basis.

One patient came to the Center on large doses of carbidopa/levodopa and Sinemet CR for Parkinson's disease. His Parkinson's disease was rather mild, but he had severe RL that appeared to be poorly managed with his medications. He was first withdrawn from all daytime dopaminergic medication and started on one tablet of carbidopa/levodopa 25/100 mg and one tablet of Sinemet CR taken before bed. His dose was then adjusted with increasing doses of carbidopa/levodopa, following the schedule above, but always including the one tablet of Sinemet CR before bed that was included in the calculation of his total daily dose. To make this a consecutive case series he was included in the data despite being the only subject also using CR. A separate analysis of the data without this subject showed the same satistically significant findings as reported below.

Clinical inquiry

The RL symptoms before treatment were classified for severity based upon the earliest time of day the patient regularly reported onset of symptoms disturbing enough that it was hard to remain in a sitting position. This was arbitrarily classified into two categories: mild to moderate RL for the symptoms beginning after 6:00 p.m. and severe for symptoms beginning at or before 6:00 p.m. Because patients with the PLMS disorder had no RL symptoms, this gave three levels of severity of RL: none, mild–moderate and severe. This was treated as a nominal variable for all analyses except for regression analyses, where it was coded as 0, 1 or 2 for increasing severity. One clinician rated all of the subjects based on the clinical records from the initial visit in the sleep center without reference to the response to medication. Thirteen subjects were randomly selected to be independently rated by another clinician who did not know the ratings of the first clinician or the response to medication. The ratings were identical for 12 of the 13 subjects (92% agreement) and only disagreed by one category for 1 subject.

Within the first 2 months of treatment and after at least 3 weeks on the established effective dose of carbidopa/levodopa, each patient was asked about RL symptoms during a regular clinic appointment or telephone consultation. The patient was specifically asked if any change in RL symptoms had occurred during the morning, afternoon, evening or night since starting treatment. Any change in severity of symptoms at these times was noted. The degree of this change and any change in the time of onset of RL symptoms were both noted. In particular, any change in the earliest time of onset of RL symptoms was noted. The severity of any *change* in RL symptoms was coded as tolerable if the symptoms could be tolerated by the patient or intolerable if increasing the dose or changing medications was needed to relieve the symptoms. The occurrence of morning rebound, as previously described by others, was also coded for all subjects.

The patients also reported three major symptoms associated with augmentation, i.e. increased severity of the RL symptoms, shorter time for sitting still before RL symptoms started at the time the symptoms normally occurred and increasing involvement of other parts of the body besides the legs (generally the arms). These symptoms were retrospectively coded as present or absent for those patients who reported augmentation.

Two clinicians independently rating augmentation symptoms and severity for 13 randomly selected subjects agreed for all but 1 patient (92% agreement).

TABLE 1. *Subject characteristics*

Characteristic	Patient diagnoses				
	All	RL syndrome	PLMS disorder[a]	Unpaired[b]	p
Number	46	30	16		
Age (years)	57.6 (± 10.0)	57.5 (± 11.3)	57.5 (± 7.2)	0.049	NS
Gender (% male)	56.5	50	68.8	[c]	NS
PLM/hour of NREM	70.1 (± 49.0)	72.5 (± 48.6)	65.8 (± 51.1)	0.44	NS
% PLM with arousal	47.1 (± 28.1)	58.1 (± 25.7)	27.9 (± 21.6)	3.98	0.0003
Carbidopa/levodopa dose (mg)	60/238 (± 30/118)	67/267 (± 5.8/24)	45/180 (± 4.5/18)	2.36	0.023
Number with early a.m. dose	7	7	0	[d]	0.04

Values are average ± standard deviation (SD). NS, not significant ($p > 0.05$).
[a] The PLMS disorder included only patients without the waking sensory disturbances of the RL syndrome.
[b] Statistical test comparing patients with RL syndrome to those with the PLM disorder without RL symptoms.
[c] $\chi^2 = 1.75$, $p > 0.05$.
[d] $\chi^2 = 4.4$, $p = 0.04$.

Statistical analyses

The data permitted analysis of occurrence and severity rates for RL augmentation in relation to total daily dose of medication, use of an early morning dose, occurrence of morning rebound and subject factors including diagnosis, gender and age. Multiple regression was used to determine the variables most related to the occurrence of the RL augmentation. The hypotheses tested were that RL augmentation increased with increasing dose, was more common for patients with the RL syndrome than those with the PLMS disorder and was not related to gender, age, morning rebound or use of morning dose. For exploratory purposes similar analyses were conducted for morning rebound.

RESULTS

Subject characteristics and medication doses

Forty-six subjects, including 20 females, met the criteria for this study: 30 with the RL syndrome and 16 with the PLMS disorder. For all 46 patients the average age was 57.5 years, average PLM rate in NREM sleep was 70.1 per hour, average percentage of all PLM in sleep associated with arousal was 47.1% and the average treatment dose was 60/238 mg of carbidopa/levodopa. There were no significant differences for age, gender and PLM rate between those patients with the RL syndrome and those with the PLMS disorder. The percentage of PLM with arousal was, however, significantly greater for the patients with the RL syndrome than for those with the PLMS disorder (58.1% vs. 27.9%, $t = -3.98$, $p < 0.001$), and the carbidopa/levodopa dose was also greater for those with RL (67/267 vs. 45/180, $t = 2.36$, $p = 0.023$). Only seven (15%) of the patients required an early morning (1:00–3:30 a.m.) dose, and all seven of these had the RL syndrome (Table 1).

Occurrence of RL augmentation and related symptoms

Of the 46 patients, 27 (59%) reported RL augmentation. For the 30 patients with the RL syndrome, 22 (82%) reported augmentation, compared to only 5 (31%) of the 16 patients with the PLMS disorder (Table 2). For all patients, 17 (37%) had an intolerable augmentation and required a dose decrease or medication change to reduce the augmentation. Fifteen (50%) of the RL syndrome patients had it to an intolerable degree, compared to two (13%) of the PLMS disorder patients.

The percentages of patients with augmentation who reported the three major symptoms associated with augmentation were 100% for increased severity, 56% for shorter onset time at rest and 11% for involvement extending to other limbs or body parts. All of these symptoms occurred more commonly for patients with RL than for those with PLMS (82% vs. 31%, $\chi^2 = 5.40$, $p \leq 0.02$ for intensity; 33% vs. 31%, $\chi^2 = 0.10$, $p > 0.10$ for shorter onset time at rest and 10% vs. 0% for other limbs; (Table 2).

Occurrence of morning rebound

The morning rebound was reported by only 6, or 13%, of the 46 patients. All of these six were patients with the RL syndrome; thus 20% of the RL compared to 0% of PLMS patients reported morning rebound (Table 2).

Variables related to the occurrence of augmentation

A step-wise multiple regression analyzed the occurrence of the RL augmentation as a function of age, sex, diagnosis, total carbidopa/levodopa dose, use of early morning dose and baseline PLM rate and baseline percentage of PLM with arousal. The two signif-

TABLE 2. *Occurrence of augmentation, augmentation symptoms and morning rebound by patient diagnoses*

Characteristic	Patient diagnoses			χ^2	p ≤
	All	RL syndrome	PLMS disorder[a]		
Number	46	30	16		
Agumentation—all	27	22 (82%)	5 (31%)	5.41	0.02
Augmentation symptoms:					
Increased intensity of RL	27	22 (82%)	5 (31%)[b]	5.41	0.02
Shorter onset time at rest	15	10 (33%)	5 (31%)[b]	0.10	NS
Involved other limbs	3	3 (10%)	0 (0%)	1.71	NS
Augmentation severity:					
Tolerable (no medicine change)	10	7 (23%)	3 (19%)		
Intolerable (medicine change)	17	15 (50%)	2 (13%)	8.55 (df = 2)[c]	0.02
Morning rebound	6	6 (20%)	0 (0%)	3.68	0.06

In the columns below the headings RL syndrome and PLMS disorder, the numerals outside parentheses indicate the number of patients with characteristics for that diagnostic condition. The numerals inside the parentheses followed by a % sign indicate the percentage of patients by diagnosis (all, RL or PLMS) who have the characteristic. NS, not significant (p > 0.05).

[a] The PLMS disorder includes only patients without the waking sensory disturbances of the RL syndrome.

[b] Because before treatment there were no RL, any RL occurrence was considered to have both increased intensity and shorter rest time.

[c] Statistical test for three levels of augmentation severity: none, tolerable, intolerable vs. patient diagnosis.

icant variables were pretreatment severity of the RL symptoms (none, mild–moderate, severe) and dose, with the *F* values smaller than 3.0 for the other variables (Table 3). The patients with "severe" pretreatment RL symptoms were more likely to develop augmentation (16/17, 94%) than those with mild–moderate RL symptoms (7/13, 50%). Similarly, the patients with higher doses of carbidopa/levodopa (≥2 tablets of 25/100 mg) were far more likely to report RL augmentation than those at the low dose (0.5–1.5 tablets of 25/100 mg) (67% vs. 14%) (Table 4).

There was no significant effect of the early morning dose. Augmentation occurred for 85% of the patients with an early morning dose compared to 55% of those without this added dose ($\chi^2 = 1.91$, $p = 0.27$).

Variables related to the occurrence of morning rebound

A step-wise multiple regression analyzed the occurrence of the morning rebound as a function of age, sex, diagnosis, total carbidopa/levodopa dose, use of early morning dose and baseline PLM rate and baseline percentage of PLM with arousal. The only significant variable was the use of the early morning dose, with the other variables having values of *F* to enter smaller than 2.0 (Table 5). Morning rebound occurred for 71% of the patients with the a.m. dose compared to only 2.6% of the patients without the a.m. dose ($\chi^2 = 19.1$, $p = 0.001$).

TABLE 3. *Step-wise multiple regression analysis for variables affecting RL augmentation*

Multiple *r*	*F*-test	df	p
0.65	14.4	(2, 40)	*0.01*
Factors entered	Coefficient	*F* to remove	p
1. Sinemet dose	0.15	7.23	0.01
2. RL severity	0.25	10.34	0.01
Factors not entered		*F* to enter	p
Gender		2.25	NS
Age		0.53	NS
PLM/hour		0.56	NS
PLM% arousal		0.25	NS
Early a.m. dose		1.11	NS
Morning rebound		0.02	NS

NS, not significant.

DISCUSSION

This concurrent prospective study provides both the first clinical description of RL augmentation and demonstrates that this adverse effect of carbidopa/levodopa treatment for RL and PLMS is a common reason for changing medications. RL augmentation is a relative worsening of RL symptoms occurring with the use of carbidopa/levodopa. Daily increments in carbidopa/levodopa result in greater incidence of the RL symptoms and an overall progressive worsening of the RL condition. RL augmentation was characterized by the following four clinical features.

The first and defining clinical feature was a temporal expansion of RL symptoms that was always retrograde (occurring earlier relative to the time the medication was taken). Thus, symptoms that prior to treatment occurred primarily at bedtime now occurred earlier in the evening and at bedtime. Symptoms that before treatment occurred only in the evening and at bedtime expanded to include occurrence in the late afternoon as well as the evening and nighttime. As the dose of medication increased, the symptoms advanced to times even earlier in the day. Eventually, in severe cases, the symptoms extended throughout a 24-hour day with little diurnal variation.

TABLE 4. *Percentage of patients with augmentation by diagnosis, medication and dose*

Diagnosis	All	Carbidopa/levodopa dose (mg)		χ^2	p
		Low (<50/200)	High (≥50/200)		
All	58.7% (46)	14.3% (7)	66.7% (39)	6.72	0.01
PLM disorder, no RL	31.3% (16)	00.0% (3)	38.5% (13)	1.68	NS
Mild RL syndrome	56.2% (13)	00.0% (2)	54.5% (11)	2.03	NS
Severe RL syndrome	94.1% (17)	50.0% (2)	100% (15)	7.97	0.01
All RL syndrome	73.3% (30)	19.2% (4)	80.7% (26)	5.51	0.02

The number in parentheses is the number (n) of patients in each condition (sample size). The number preceding the % sign is the percentage of n patients with augmentation. The χ^2 statistic indicates the percentage of augmentation by low and high dose of carbidopa/levodopa. NS, not significant.

The second most common feature, occurring for all but one of the patients with augmentation, was a relative increase in symptom intensity. Moderately disturbing sensations at bedtime became much more distressing and disruptive. Mild evening and afternoon symptoms increased in the reported levels of distress. Some patients who reported increasing severity of the symptoms at night also reported decreased benefit from the carbidopa/levodopa at night and a longer time before relief of the symptoms occurred after taking the medication.

The third feature, reported by about a quarter of the patients with augmentation, was a decrease in the time they could stay at rest before the symptoms started, e.g. the amount of time the patient could remain sitting before the symptoms began was much less. In more extreme cases, RL symptoms started at any time of rest.

A few (7%) of the patients with augmentation showed a striking fourth feature, of increasing body involvement. Although the initial RL symptoms presented in the legs, with increasing carbidopa/levodopa use symptoms appeared in the upper limbs, pelvis or trunk as well as the legs. Although most of these patients showed this condition as the carbidopa/levodopa dose reached higher levels, one patient had this as the first major indication of RL augmentation, occurring concurrently with the retrograde temporal expansion.

In the extreme condition of RL augmentation, the symptoms for a least two of the patients became diffuse throughout the body, with loss of focal or segmental components and an associated loss of temporal pattern. Leg paresthesias became diffuse inner restlessness or aching. There was little diurnal variation, and the symptoms persisted, though to a milder degree, even during walking. Carbidopa/levodopa became essentially ineffective, and increasing the dose provided only very temporary symptom relief. The symptoms slowly but clearly evolved to look more like dopamine-antagonist-induced akathisia than the RL syndrome.

The morning rebound reported by others was also reported by our patients. The number of patients with RL symptoms reporting rebound was about the same in our study as that reported by Becker et al. (12) (20% vs. 24%). Morning rebound is not at all the same as RL augmentation. Not only does the morning rebound occur at a different point in time, but it was also reported by our patients to extend with increasing severity to later into the morning, in contrast to the retrograde expansion with augmentation. Rebound was also not reported to have any of the other three clinical features of RL augmentation and in particular has not been associated with expansion of symptoms to include other parts of the body. Thus the morning rebound does not present as a general worsening of the RL condition. Moreover, unlike augmentation, morning rebound appears to be related to the use of a second morning dose and shows no relationship to pretreatment RL symptom severity.

It was striking that not only did 73% of the RL patients report augmentation, but these adverse symptoms were also severe enough to lead to medication change for 50% of these patients. This is by far the most common reason for changing treatment. Given the high rate of occurrence of the augmentation and the significant symptoms engendered, it is somewhat surprising that augmentation had not been previously

TABLE 5. *Step-wise multiple regression analysis for variables affecting morning rebound*

Multiple *r*	*F*-test	df	p
0.69	37.6	(1,41)	0.01
Factor entered	Coefficient	*F* to remove	p
Early a.m. dose	0.64	37.551	0.01
Factors not entered		*F* to enter	p
RL severity		0.45	NS
Gender		0.09	NS
Age		0.79	NS
PLM/hour		1.48	NS
PLM% arousal		1.26	NS
Carbidopa/levodopa dose		1.93	NS
RL augmentation		2.43	NS

NS, not significant.

observed. A similar situation occurred for the end-of-dose morning rebound of RL symptoms. The first clinical reports did not include any description of such a rebound, but when later studies asked about this expected end-of-dose rebound it was in fact reported in each of the studies (6,12–14). Similarly, we found that morning rebound occurred, but almost four times as many patients reported augmentation. Apparently not expecting to see an effect, the earliest studies did not ask about morning rebound or may have confounded the issues by permitting late morning and daytime doses. Even the more recent studies did not specifically ask about changes in the RL symptoms at their more usual occurrence times in the afternoon and evening and thus would have missed the RL augmentation. Presumably patients with augmentation either continued to suffer with the more extreme symptoms or were among those who added daytime medications or discontinued the medication.

One would expect that if end-of-dose rebound and RL augmentation were similar processes, just temporally displaced, then the occurrence or increase of one would be correlated with the other. But, to the contrary, there was no significant relationship between the two effects (Table 5). A major significant correlate of early morning rebound was the addition of an early morning dosage. Because our protocol called for an early morning dose if symptoms occurring in the very early morning caused awakenings, it may be that those subjects with very early morning symptoms (around 3 a.m.) would also be the ones to have morning rebound a bit later in the morning (around 7 a.m.). It is not clear whether the very early morning symptoms represented some true rebound phenomenon with symptoms worse than would have occurred without treatment, or instead were the normal level of symptoms now presenting after the treatment had worn off. Because the half-life of carbidopa/levodopa is 1.5–2 hours, this is probably part of the problem. Guilleminault et al. (13), giving the long-acting Sinemet CR (half-life 4–6 hours) to patients with symptoms at early morning awakenings, reported reduced very early morning symptoms; however, they did not specifically address whether or not symptoms occurred upon later awakening. The absence of such symptoms would support the view that the early morning phenomenon is an efficacy issue and not a "rebound" state. The report by Becker et al. (12), that seven patients took added doses after 7 a.m., suggests, however, that they had symptoms at a time previously free of symptoms, consistent with an end-of-dose rebound. Further work needs to be done to clarify this.

Any theoretical discussion about the nature of RL augmentation rests first in understanding the pathophysiology behind the RL syndrome itself. There are at least seven published studies (5,7–10,12,15) that demonstrate the efficacy of dopaminergic agonist in the treatment of the RL syndrome. Levodopa, in particular, demonstrated >90% effectiveness in the present study, as well as in others (9,10,12). Consistent with the positive effects of dopamine agonists is the finding that dopamine antagonists worsen the RL syndrome (1,5) Indirect support for a dopaminergic role comes from Montplaisir et al. (16), who reported that improvements in RL symptoms with codeine did not occur after pretreatment with a dopamine antagonist (pimozide). It is worth noting that improvements in symptoms with dopamine agonists were *not* reversed by an opiate antagonist (5).

These studies highlight the pivotal role of dopamine in the RL syndrome. The implications from these studies are that a relative or absolute decrease in dopamine availability is a central factor in this disorder. How levodopa can initially provide dramatic clinical benefits and then later lead to apparent clinical deterioration (RL augmentation) may have its answer in the regulator mechanisms underlying the dopaminergic systems. Dopamine agonists may have differential effects, depending upon whether "low" or "high" doses are used (17). In human studies on cerebral blood flow, levodopa and apomorphine either increased flow ("low" dose) or had no effect ("high" dose) on blood flow (18,19). This differential dose effect may be on the basis of a differential affinity to dopamine receptors. Dopamine itself is a D2 receptor agonist at low doses and a D2 and D1 receptor agonist at high doses (20). Other dopamine agents, particularly ergot derivatives, are D1 receptor antagonists at low concentrations and D2 receptor agonists at high concentrations (21). To further complicate the picture, D1 receptors with an inhibitory response and D2 receptors with an excitatory response were identified electrophysiologically in the caudate nucleus (22). Thus dopamine and its agonists demonstrate dose-dependent outcomes that are a consequence of a differential effect on receptors. It is tempting to postulate that the increasing incidence of RL augmentation with increasing total daily dose is a consequence of a differential effect on D1 vs. D2 receptors.

Another consequence of dopamine and its agonists is an inhibition of dopaminergic neuronal activity. If we postulate that RL syndrome occurs with a relative decrease in dopaminergic activity, then RL augmentation may be a continuation of that process on the basis of dopamine agonist-induced inhibition of dopamine activity. This inhibition also appears to operate through a receptor-mediated mechanism. Animal studies have suggested that dopamine agonists inhibit the nigrostriatal dopaminergic neurons (23,24) through a preferential effect on D2 autoreceptors (25–28). Thus,

increasing doses leads to an increasing differential receptor effect, which, in turn, leads to down-regulation of the endogenous dopamine production, with the outcome speculated to be worsening or augmentation of the RL syndrome.

Our clinical management of the augmentation relied upon two basic approaches. First, behavioral techniques were used to reduce the RL symptoms. Patients were encouraged to be physically active and in particular not to plan to be sitting or lying down for significant periods of time. They were encouraged to walk about as much as possible during the times the augmentation was most pronounced. Second, medication changes were made after the period of time included in this study. Medication earlier in the evening and even in some cases late afternoon was helpful for about half of the patients with augmentation. But when medication doses were given regularly in the daytime, the effectiveness of the medication decreased, because augmentation of the RL symptoms progressively increased and the period of carbidopa/levodopa efficacy decreased. Increasing daytime doses can quickly lead to large daily doses of carbidopa/levodopa being given, with catastrophic outcomes. The data for this study were, however, obtained from the initial treatment period before any evening or daytime medication changes were introduced to reduce augmentation. Use of alternate medications, such as dopamine agonists and opiates to reduce the RL augmentation, needs to be considered in future studies. The results in this study indicate that one good approach is to keep the total daily dose of carbidopa/levodopa low; the decreased dose appears to reduce the severity of the augmentation. Therefore, to reduce problems with RL augmentation, the recommended starting dose for treatment of the RL syndrome and the PLMS disorder is 1/2 tablet carbidopa/levodopa 25/100 mg. Increases in dosage should be made with caution, and daytime doses should be minimized.

Despite this problem with augmentation, carbidopa/levodopa offers the best initial treatment for most patients with either the RL syndrome or the PLMS disorder. It therefore remains the treatment of first choice. It also has the advantage of permitting a flexible occasional p.r.n. dose scheduled for unusual daytime events. If the augmentation becomes a problem, then alternate medications might be added or substituted, but increasing doses of carbidopa/levodopa should be avoided.

REFERENCES

1. Ekbom KA. Restless legs syndrome. *Neurology* 1960;10:868–73.
2. Bornstein B. *Restless legs. Psychiatr Neurol* 1961;141:165–201.
3. Diagnostic Classification Steering Committee, Thorpy MJ, chairman. *International classification of sleep disorders: diagnostic and coding manual.* Rochester, MN: American Sleep Disorders Association, 1990:396.
4. Walters A, Aldrich M, Allen R, et al. Towards a better definition of the restless legs syndrome. *Mov Disord,* 1995 (in press).
5. Akpinar S. Restless legs syndrome treatment with dopaminergic drugs. *Clin Neuropharmacol* 1987;10:69–79.
6. 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;9:456–63.
7. Brodeur C, Montplaisir J, Godbout R, Marinier R. Treatment of restless legs syndrome and periodic movements during sleep with L-dopa: a double-blind, controlled study. *Neurology* 1988;38:1845–8.
8. Walters AS, Hening WA, Kavey N, Chokroverty S, Gidro FS. A double-blind randomized crossover trial of bromocriptine and placebo in restless legs syndrome. *Ann Neurol* 1988;24:455–8.
9. Allen RP, Kaplan PW, Buchholz DW, Earley CJ, Walters JK. Double-blinded, placebo controlled comparison of high dose propoxyphene and moderate dose carbidopa/levodopa for treatment of periodic limb movements in sleep. *Sleep Res* 1992;21:166.
10. Kaplan P, Allen R, Buchholz D, Walters J. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. *Sleep* 1993;16:717–23.
11. vonScheele C, Kempi V. Long-term effect of dopaminergic drugs in restless legs: a 2-year follow-up. *Arch Neurol* 1990;47:1223–4.
12. Becker P, Jamieson A, Brown W. Dopaminergic agents in restless legs syndrome and periodic limb movements of sleep: response and complications of extended treatment in 49 cases. *Sleep* 1993;16:713–6.
13. Guilleminault C, Cetel C, Philip P. Dopaminergic treatment of restless legs and rebound phenomenon. *Neurology* 1993;43:445.
14. Coleman RM, Pollak CP, Weitzman ED. Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. *Ann Neurol* 1980;8:416–21.
15. vonScheele C. Levodopa in restless legs. *Lancet* 1986;2:426–7.
16. Montplaisir J, Lorrain D, Godbout R. Restless legs syndrome and periodic leg movements in sleep: the primary role of dopaminergic mechanisms. *Eur Neurol* 1991;31:41–3.
17. Aghajanian GK, Bunney BS. Pre- and postsynaptic feedback mechanisms in central dopaminergic neurons. In: Seeman P, Brown GM, eds. *Frontiers of neurology and neuroscience research.* Toronto: University of Toronto Press, 1974:4–11.
18. Montastruc JL, Celsis P, Agniel A, et al. Levodopa-induced regional cerebral blood flow changes in normal volunteers and patients with parkinson's disease: lack of correlation with clinical or neuropsychological improvements. *Mov Disord* 1987;2:279–89.
19. Sabatini U, Rascol O, Celsis P, et al. Subcutaneous apomorphine increases regional cerebral blood flow in parkinsonian patients via peripheral mechanisms. *Br J Clin Pharmacol* 1991;32:229–34.
20. Kebabian JW. Multiple classes of receptors in mamalian central nervous system: the involvement of dopamine-sensitive adenylyl cyclase. *Life Sci* 1978;23:479–83.
21. Pieri L, Keller HH, Burkard W, DaPrada M. Effects of lisuride and LSD on cerebral monoamine systems and hallucinosis. *Nature* 1978;272:278–80.
22. Ohno Y, Sasa M, Takaori S. Co-existence of inhibitory dopamine D-1 and excitatory D-2 receptors on the same caudate nucleus neurons. *Life Sci* 1987;40:1937–45.
23. Iwatsubo K, Clouet DH. Effects of morphine and haloperidol on the electrical activity of rat nigrostriatal neruons. *J Pharmacol Exp Ther* 1977;202:429–36.
24. Scarivati E, Forchetti C, Ciancarelli G, Pacitti C, Agnoli A. Responsiveness of nigral neurons to the stimulation of striatal dopaminergic receptors in the rat. *Life Sci* 1980;26:1203–9.
25. Carlson JH, Bergstrom DA, Walters JR. Neurophysiological ev-

idence that D-1 dopamine receptor blockade attenuates postsynaptic but not autoreceptor-mediated effects of dopamine agonists. *Eur J Pharmacol* 1986;23:237–51.
26. Mereu G, Casu M, Gessa GL. (−)-Sulpiride activates the firing rate and tyrosine hydroxylase activity of dopaminergic neurons in unanesthetized rats. *Brain Res* 1983;264:105–10.
27. Mereu G, Collu M, Ongini E, Biggio G, Gessa GL. SCH 23390, a selective dopamine D-1 antagonist, activates dopamine neurons but fails to prevent their inhibition by apomorphine. *Eur J Pharmacol* 1985;111:393–6.
28. Napier TC, Givens BS, Schulz DW, Bunney BS, Breese GR, Mailman RB. SCH 23390 effects on apomorphine-induced responses of nigral dopaminergic neurons. *J Pharmacol Exp Ther* 1986;236:838–45.