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Successful Treatment of the Idiopathic Restless Legs Syndrome in a Randomized Double-Blind Trial of Oxycodone Versus Placebo

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Summary: In a double-blind randomized crossover trial, oxycodone or placebo was given in divided night-time doses to 11 patients with idiopathic restless legs syndrome (RLS) for 2 weeks prior to appropriate polysomnographic studies. Under double-blinded conditions, patients were asked to do daily ratings of their leg sensations, motor restlessness and daytime alertness on a 1–4 scale for the 2 weeks prior to the polysomnographic studies and for the nights of the polysomnographic studies as well. Leg sensations ($p < 0.009$), motor restlessness ($p < 0.006$) and daytime alertness ($p < 0.03$) were significantly improved on oxycodone as compared to baseline or placebo. Patients were studied polysomnographically under double-blinded conditions for 2 nights in each phase of the protocol. On an average dose of 15.9 mg oxycodone (equivalent to approximately three 5-mg tablets of commercial preparation), there was a statistically significant reduction in the number of periodic limb movements in sleep [(PLMS)/hour sleep ($p < 0.004$)] and in the number of arousals/hour sleep ($p < 0.009$) on drug as compared to baseline or placebo. A statistically significant improvement was also noted in sleep efficiency ($p < 0.006$) and 10 of the 11 patients preferred oxycodone over placebo. We conclude that oxycodone is an effective treatment for RLS and PLMS. **Key Words:** Restless legs—Periodic limb movements in sleep—Opioids—Oxycodone.

Previous non-blinded studies have indicated improvements in the signs and symptoms of idiopathic restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS) by opioids (1–6). Allen et al. showed improvement in sleep efficiency and decrements in arousals associated with PLMS in two small double-blind studies of 100 mg (7,8), 200 mg (7) and 300 mg (8) of the opioid propoxyphene in patients with PLMS (7,8). However, there was no significant effect of propoxyphene on the number of PLMS (7,8). Some of the patients had RLS (R. Allen, personal communication), but motor restlessness and paresthesias were not quantitated (7,8).

Because the only double-blind study of opioids in PLMS was largely negative, we decided to perform our own double-blind study to investigate the effect of higher dosages of a more potent opioid, oxycodone, on the signs and symptoms of a larger group of patients, all of whom had idiopathic RLS.

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METHODS

Subjects

Clinical characteristics

Eleven patients (five women and six men, ages 36–74) with idiopathic RLS were recruited from the Lyons VA Medical Center, UMDNJ-Robert Wood Johnson University Hospital and the Sleep Disorders Center of Columbia Presbyterian Medical Center. All 11 patients had the four classic symptoms of RLS: 1) paresthesias (abnormal sensations) primarily in the legs; 2) motor restlessness such as floor pacing, tossing and turning

in bed, etc.; 3) worsening of the paresthesias and motor restlessness at night and 4) at rest, i.e. lying and sitting (9,10). All patients also had subjective complaints of sleep disturbances, such as difficulty with sleep onset and maintenance or excessive daytime somnolence (11,12). All patients also had periodic limb movements in sleep (PLMS), which are repetitive, stereotypic flexions of the hips, knees and ankles that recur at regular intervals of 5–90 seconds (11–15). Some patients also had repetitive, stereotypic periodic or aperiodic flexions of the hips, knees and ankles that recurred during wakefulness while the patients were sitting or lying (11,12,16–18). These movements are similar in appearance to PLMS, and we have previously published some of these involuntary movements in videotape form (18). In addition, three patients were aware of a suggestive autosomal dominant family history, as has been previously reported (16,19–21) and four patients had incidental sleep apnea of the central, mixed or obstructive type (patients #2, 8, 9, 10).

Exclusion criteria

Patients whose restlessness was secondary to peripheral neuropathy, neuroleptic-induced akathisia or other causes were excluded from the study by physical examination. When the physical examination was in doubt, an electromyogram (EMG) and nerve condition studies were performed to exclude peripheral neuropathy or radiculopathy. Patients with a history of drug abuse or addiction were also excluded from the study.

Design

Eleven patients were studied in a double-blind randomized crossover design employing various dosages of oxycodone. Patients were tapered off L-Dopa, benzodiazepines, carbamazepine, clonidine, baclofen, previous opioids, tricyclic antidepressants and all medications known to positively or negatively affect RLS prior to two baseline polysomnographic studies. Nonessential medications were discontinued and only essential medications, such as those to treat hypertension or coronary artery disease, were retained. Patients rated their symptoms daily for the two nights of the baseline polysomnographic studies. They then were given either oxycodone or placebo and the dose was gradually increased to therapeutic effect over approximately 2 weeks. During these 2 weeks, the patients also rated their symptoms on a daily basis. The patients were then studied polysomnographically for another two nights under double-blinded conditions on the appropriate capsule and a daily subjective rating of symptoms was obtained for these two nights as well. The capsules were tapered to zero over 3 days, after which upward titration of capsules for the second phase of the study was done over another 2 weeks. Dosage increases, subjective ratings and polysomnographic studies were as in the first phase.

Dosing

Each study capsule contained either lactose (placebo) or lactose plus one-half of a 5-mg oxycodone tablet. Oxycodone (Roxycodone) was obtained from Roxane. The amount of oxycodone in each capsule is equivalent to one-half the amount contained in commercial preparations such as Percodan [5 mg oxycodone and 325 mg acetylsalicylic acid (ASA)] or Percocet (5 mg oxycodone and 325 mg acetaminophen). In the 2 weeks prior to each set of placebo or drug polysomnographic studies, the patients titrated their own dosage to maximum therapeutic benefit with the aid of daily calls from a member of the research team. During this time, reports of any side effects were monitored and dosages were adjusted accordingly. Titration was stopped at a maximum of 25 mg of oxycodone (equivalent to five 5-mg tablets of commercial preparation) or 10 tablets of placebo. Dosages were divided so that patients were taking capsules 2 hours prior to bedtime, at bedtime and in the middle of the night as needed. Percodan and Percocet were not used in this study to avoid potential confounding effects of ASA or acetaminophen.

Subjective ratings

For each phase of the protocol, paresthesias, motor restlessness and daytime alertness were rated on a daily basis under double-blinded conditions using a 0–4 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe symptoms). For the baseline, ratings were obtained from the patients for the two nights of baseline polysomnographic study and averaged. For the drug and placebo phase of the study, a combined rating for each symptom was obtained by adding daily ratings for the 2 weeks prior to the drug or placebo polysomnographic studies and ratings for the two nights of the appropriate polysomnographic studies. These values were then averaged. For the subjective rating portion of the study, mean daily oxycodone dosages were similarly obtained (average of dosages from the 2 weeks of the drug trial and the two nights of polysomnographic study on oxycodone combined). The average ratings for each of the 11 patients were compared for the baseline, placebo and drug phases of the study with a Friedman nonparametric rank sums test and a post-hoc Wilcoxon signed rank to test the differences between the three periods. At the end of the study, pa-

TABLE 1. *Patients' mean subjective data*

	Age	Sex	Oxycodone mean dose/day (mg)	Leg sensations[a]			Restlessness[b]			Drowsy next day[c]		
				B	P	D	B	P	D	B	P	D
Patient												
1	73	M	20.00	3.50	3.89	3.33	2.00	3.89	1.78	2.50	3.89	2.33
2	63	F	2.92	3.00	2.94	0.08	3.00	3.06	0.33	3.00	2.11	0.17
3	36	M	9.45	1.67	0.56	0.11	1.67	0.56	0.11	1.33	1.00	1.00
4	60	F	8.13									
5	62	M	15.20	3.00	3.57	3.65	3.00	3.71	3.29	0	0	0.41
6	50	M	15.28	3.00	3.85	2.67	3.00	3.54	2.44	4.00	3.85	2.78
7	44	F	8.55	3.00	1.89	0.08	2.67	1.89	0.46	2.67	1.23	1.17
8	46	M	13.00	2.67	1.27	0.20	2.67	1.09	0.20	0	0.05	0
9	59	M	10.73	2.33	2.09	0.29	2.67	2.09	0.36	1.67	1.55	0.57
10	74	F	10.35	2.33	4.00	0.71	3.33	4.00	1.43	3.33	3.33	1.21
11	41	F	11.68	2.00	2.08	1.75	0.50	1.92	1.67	3.00	0.92	1.42
Mean			11.39	2.65	2.61	1.29	2.45	2.58	1.21	2.15	1.79	1.11

Patients rated leg sensations, motor restlessness and daytime alertness on a daily basis under double-blinded conditions on a 1–4 scale (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe and 4 = very severe). Symptoms were rated during the baseline (B), placebo (P) and drug (D) periods. Ratings for baseline are an average of those obtained from the patients for the 2 nights of baseline polysomnographic study. For the drug and placebo phases of the study, the ratings were averaged over approximately 2 weeks and included assessments made at home and during the polysomnographic studies. A mean oxycodone dose/day was similarly obtained for the drug phase of the study. Only partial subjective data were obtained for patient #4. Therefore, her data were not included in the statistics. Group data showed a statistically significant decrease in leg sensations, motor restlessness and daytime drowsiness on oxycodone as compared to baseline or placebo.

[a] $p < 0.009$.
[b] $p < 0.006$.
[c] $p < 0.03$.

tients were asked under double-blinded conditions whether they preferred the phase I or phase II capsule for treatment of their symptoms.

Polysomnographic studies

Patients received two polysomnographic studies at baseline, two on placebo and two on drug according to previous methods (22). Approximately 2 weeks separated each phase of the protocol. Sleep parameters and PLMS were quantitated under blinded conditions by previous methods (13,22,23). Sleep stages were calculated as a percentage of sleep period time. Body movements that occurred after an apnea or hypopnea were eliminated from consideration as possible PLMS (24). Awakenings and arousals were scored by previously published methods (23,25,26) and arousals or awakenings that occurred after an apnea or hypopnea were excluded from the total. Periodic and aperiodic limb movements while the patients were awake and lying down were not quantitated for this study. Drug dosages and polysomnographic data were averaged for the appropriate two nights of polysomnographic study. Sleep parameters and PLMS were then compared for the 11 patients across the baseline, placebo and drug phases of the study by a Friedman nonparametric rank sums test with a post-hoc Wilcoxon signed rank.

Studies included monitoring of electroencephalogram (EEG) (C_3–A_2, C_4–A_1), electrooculogram (EOG) (LOC, ROC), electrocardiogram (EKG), chin electromyogram (EMG) and EMG of both anterior tibialis muscles. Monitoring of respiration was by standard measures of air flow (oral/nasal thermocouple; Rochester Electro-Medical, Tampa, FL), effort (RESP-EZ chest and abdominal belts containing piezo electric crystals; EPM Systems, Midlothian, VA) and oxygen saturation (finger pulse oximetry; Ohmeda Biox 3700, Boulder, CO). Studies were performed at either the Clinical Research Center (CRC) of the Robert Wood Johnson University Hospital or the Sleep Disorders Center of Columbia Presbyterian Medical Center on either a Grass 8-20D or Nihon-Kohden 4221 EEG Machine.

RESULTS

At the end of the study, the patients were asked under double-blinded conditions which capsule they preferred overall and 10 of 11 patients chose oxycodone over placebo. The eleventh patient (#11) felt that oxycodone gave her a mild relief of RLS symptoms compared to placebo, but it also gave her mild daytime lethargy at the dosages employed. On the subjective rating scale, leg sensations and motor restlessness were statistically improved on an average of 11.39 mg of oxycodone (equivalent to approximately two 5-mg tablets of commercial preparation) as opposed to baseline or placebo ($p < 0.009$ and $p < 0.006$ respectively) (Table 1). On the subjective rating scale, drowsiness the day after the capsules were given was also signifi-

TABLE 2. *Polysomnographic data*

	Oxycodone mean dose/day (mg)	PLMS			PLMS/hour sleep[a]			Sleep efficiency[b]			Arousals/hour sleep[c]		
		B	P	D	B	P	D	B	P	D	B	P	D
Patient													
1	25.0							2.1	2.8	48.9			
2	2.5	9	25	3	1.7	5.6	0.7	67.4	80.1	83.7	11.4	13.6	9.0
3	15.0	114	43	20	20.6	9.7	3.5	91.0	90.0	90.1	28.7	17.0	16.2
4	12.5	110	75	64	81.8	117.3	26.6	16.7	9.4	43.6	67.9	107.6	40.1
5	25.0	224	173	213	68.4	84.8	82.9	56.2	34.6	45.1	78.4	48.2	82.1
6	25.0							32.4	1.2	26.1			
7	10.0	222	205	142	45.0	63.6	23.1	75.9	58.1	92.8	47.3	61.4	45.3
8	17.5	194	227	2	50.1	73.9	0.4	71.5	60.4	89.1	60.9	76.5	26.8
9	15.0	109	132	104	58.4	54.2	22.3	36.2	45.8	82.4	37.7	49.3	7.9
10	12.5	10	50	0	4.6	49.7	0	40.4	30.1	78.6	8.5	56.0	3.6
11	15.0	92	101	37	18.4	17.1	6.3	84.1	90.0	94.1	10.9	12.0	8.7
Mean	15.9	120.4	114.6	65.0	38.8	52.9	18.4	52.2	45.7	70.4	39.1	49.1	26.6

Patients were studied polysomnographically under double-blinded conditions. All values including dosages represent the average for two nights of polysomnographic study during either baseline (B), placebo (P) or drug (D) conditions. Drug dosages were titrated as described in the methods. Patients #1 and #6 slept so little (<15 minutes) at either the baseline or placebo that a meaningful figure for PLMS, PLMS/hour sleep, arousals/hour sleep and awakenings/hour sleep could not be obtained. Group data showed a statistically significant decrease in the PLMS/hour sleep and in the arousals/hour sleep and an increase in sleep efficiency.

[a] $p < 0.004$.
[b] $p < 0.006$.
[c] $p < 0.009$.

cantly improved on oxycodone as opposed to baseline or placebo ($p < 0.03$) (Table 1).

On the polysomnographic portion of the study, the number of PLMS/hour of sleep was significantly reduced ($p < 0.004$) and sleep efficiency was significantly improved ($p < 0.006$) on an average of 15.9 mg of oxycodone (equivalent to approximately three 5-mg tablets of commercial preparation) (Table 2). There was also a statistically significant reduction in the number of arousals/hour sleep on drug as compared to baseline or placebo ($p < 0.009$). The PLMS fragmented sleep, but the percentage of PLMS associated with arousals remained unchanged at 80% for baseline, 74% for placebo and 73% for drug. There was a tendency toward a decrease in sleep latency and toward an increase in the percentage of rapid eye movement (REM) sleep, but these changes did not quite reach statistical significance (Table 2). There was no significant change in the number of awakenings/hour sleep or in the percentage of slow wave sleep (Table 2).

For the four patients with sleep apnea, there was no significant difference in the average combined apnea/hypopnea index (number of combined apneas and hypopneas/hour sleep) at baseline (5.34), placebo (9.52) or on oxycodone (6.27), nor was there any significant change in the lowest average O_2 saturation experienced by the patients at baseline (84), placebo (87) or on oxycodone (83).

The only side effects encountered were minimal constipation in two patients (patients #7 and #10) and minimal daytime lethargy at higher dosages in one patient (patient #11). The lethargy in this patient decreased when the dosage was reduced. No patients dropped out from the study.

DISCUSSION

This study shows that oxycodone decreases paresthesias, motor restlessness, nighttime arousals and PLMS and improves daytime alertness and sleep efficiency in idiopathic RLS (Tables 1 and 2). All aspects of the syndrome were thus improved. Dosages averaged 10–15 mg of oxycodone (equivalent to 2 or 3 tablets of Percodan or Percocet) and side effects were minimal. This study adds to our previous blinded evaluation of intravenous infusions of the opiate receptor blocker naloxone (or saline placebo) in two RLS patients successfully treated with opioids (1,2). In that study, treatment with naloxone but not saline resulted in a quantitative return of the signs and symptoms of RLS, indicating that the therapeutic effect of the opioids is specific to the opiate receptor. Because all of the opioids that are therapeutically successful are primarily mu opiate receptor agonists (1–8), the mu opiate receptor is the subtype that is most likely to be primarily or secondarily implicated in the pathogenesis of idiopathic RLS (1,2). The current study also confirms our own nonblinded polysomnographic and nonpoly-

Table 2. *Continued.*

	Awakenings/ hour sleep			Sleep latency			%REM			%3 & 4		
	B	P	D	B	P	D	B	P	D	B	P	D
Patient												
1				154.0	98.5	33.0	0	0	10.3	0	0	1.1
2	1.9	2.0	2.1	4.3	24.5	9.5	12.7	22.9	29.7	6.7	12.4	13.6
3	1.8	2.6	2.7	14.5	17.0	17.5	8.9	14.2	11.4	11.6	10.5	11.0
4	9.9	21.3	16.8	94.3	115.0	32.0	0	0	0.1	0	0	0
5	2.8	2.2	15.1	50.5	208.0	95.5	22.1	8.9	6.2	7.4	24.7	3.3
6				138.8	92.0	128.8	0	0	7.1	1.0	0	0.8
7	2.8	4.6	2.0	9.8	5.0	5.3	13.7	6.1	17.0	16.0	6.6	5.3
8	5.3	5.8	3.3	8.3	26.2	11.0	8.9	5.1	4.7	6.9	7.1	0.3
9	3.1	4.1	1.9	106.5	23.0	6.8	10.6	9.6	19.9	0	0	0.1
10	4.6	10.7	4.2	11.3	15.8	7.3	8.4	1.8	9.4	0	0.4	3.5
11	2.9	3.1	2.1	15.0	7.0	6.3	15.0	17.0	19.6	16.2	14.8	10.0
Mean	3.9	6.3	5.6	55.2	57.5	32.0	9.1	7.8	12.3	6.0	7.0	4.5

somnographic studies of opioids in RLS, which documented a long-term therapeutic effect in RLS patients who had been treated with opioids for several years (2,3). The current study also confirms the positive results obtained in nonblinded studies of opioids in RLS by two other groups (4,5).

Present data are also consistent with the only other similarly designed double-blind studies of opioids in patients with PLMS and sleep disturbances (7,8), where similar improvements were noted in sleep efficiency and some decrements were noted in arousals. However, the current study stands in contrast to these other double-blind studies (7,8) in that we document a decrease in the number of PLMS/hour of sleep. In our study, opioids had a more potent effect on the PLMS than on sleep, whereas in the studies of Allen et al. the opposite was shown (7,8). We suggest that these differences are most likely due to the fact that we did not employ a fixed dosing regime, but instead allowed each patient to increase the dose of oxycodone to therapeutic effect and, indeed, some patients required a larger dose (Table 2). Our large sample size may also have allowed us to achieve greater statistical significance. In addition, only some of the patients in each of the other double-blind studies had RLS (7,8). It is therefore possible that the authors of these studies were dealing with a therapeutically heterogeneous population (7,8). Because we studied only patients with idiopathic RLS, we were able to document improvements in features like motor restlessness and paresthesias that were not measured in the other double-blind studies (7,8). These features are important because paresthesias and motor restlessness are primary to RLS and often lead to sleep onset insomnia.

Opioids now join L-Dopa, DA agonists, benzodiazepines, baclofen and carbamazepine as agents whose therapeutic efficacy has been shown in blinded studies of either idiopathic RLS, PLMS or both (7,8,27–35). We have also successfully employed opioids in a double-blind study of a parallel form of motor restlessness, acute neuroleptic-induced akathisia, and the therapeutic effect can also be reversed by naloxone (36,37).

Our previous studies have indicated that the opioids can be successfully used long term with little risk of addiction (2,3). In our original non-blinded study of opioids in RLS, five patients continued receiving long-term benefit from 1.5–6 years of therapy (2). In a further long-term follow up, eight of 10 of our patients continued to find satisfactory benefit without significant side effects from 6 months to 15 years of therapy (3). When alternative satisfactory drug regimens are unavailable and the severity of the symptoms warrants it, we recommend opioids as a long-term treatment for the signs and symptoms of idiopathic RLS. We agree with Monplaisir et al. that it is probably best to start with the least-potent opioid (38) at a dose of one capsule at bedtime. The dosage may then be gradually increased over a matter of weeks and, when higher

dosages are required, we have found divided dosages at 2 hours prior to bedtime, at bedtime and in the middle of the night as needed to be most helpful and best tolerated.

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REFERENCES

1. Walters A, Hening W, Côte'L, Fahn S. Dominantly inherited restless legs with myoclonus and periodic movements of sleep: a syndrome related to the endogenous opiates? In: Fahn S, Marsden CD, Van Woert MA, eds. *Myoclonus. Advances in neurology,* Vol. 43. New York: Raven Press, 1986:309–19.
2. Hening WA, Walters A, Kavey N, Gidro-Frank S, Côte'L, Fahn S. Dyskinesias while awake and periodic movements in sleep in restless legs syndrome: treatment with opioids. *Neurology* 1986;36:1363–6.
3. Hening WA, Walters AS. Successful long-term therapy of the restless legs syndrome with opioid medication. *Sleep Res* 1989; 18:241.
4. Trzepacz PT, Violette EJ, Sateia MJ. Response to opioids in three patients with restless legs syndrome. *Am J Psychiatry* 1984; 141:993–5.
5. Sandyk R, Bamford CR, Gillman MA. Opiates in the restless legs syndrome. *Int J Neurosci* 1987;36:99–104.
6. Kavey N, Walters A, Hening W, Gidro-Frank S. Opioid treatment of periodic movements in sleep in patients without restless legs. *Neuropeptides* 1988;11:181–4.
7. Allen RP, Kaplan PW, Buchholz DW, Walters JK. Double-blinded, placebo controlled comparison of propoxyphene and carbidopa/levodopa for treatment of periodic limb movements in sleep. *Sleep Res* 1991;20:199.
8. 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.
9. Ekbom KA. Restless legs. *Acta Med Scand [Suppl]* 1945;158: 1–123.
10. Ekbom KA. Restless legs syndrome. *Neurology* 1960;10:868–73.
11. Montplaisir J, Godbout R. Restless legs syndrome and periodic movements in sleep. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine.* Philadelphia: W.B. Saunders Company, 1989:402–9.
12. Lugaresi E, Cirignotta F, Coccagna G, Montagna P. Nocturnal myoclonus and restless legs syndrome. In: Fahn S, Marsden CD, Van Woert MH, eds. *Myoclonus. Advances in neurology,* Vol. 43. New York: Raven Press, 1986:295–307.
13. Coleman RM. Periodic movements in sleep (nocturnal myoclonus) and restless legs syndrome. In: Guilleminault C, ed. *Sleeping and waking disorders: indications and techniques.* Menlo Park, CA: Addison-Wesley, 1982:265–95.
14. Coleman RM, Pollak CP, Weitzman ED. Periodic movements in sleep (nocturnal myoclonus): relation to sleep disorders. *Ann Neurol* 1980;8:416–21.
15. Lugaresi E, Coccagna G, Berti-Ceroni G, Ambrosetto C. Restless legs syndrome and nocturnal myoclonus. In: Gastaut H, Lugaresi E, Berti-Ceroni G, eds. *The abnormalities of sleep in man.* Bologna: Aulo Gaggi, 1968:285–94.
16. Boghen D, Peyronnard JM. Myoclonus in familial restless legs syndrome. *Arch Neurol* 1976;33:368–70.
17. Walters AS, Hening WA, Chokroverty S. Frequent occurrence of myoclonus while awake and at rest, body rocking and marching in place in a subpopulation of patients with restless legs syndrome. *Acta Neurol Scand* 1988;77:418–21.
18. Walters A, Hening W, Chokroverty S. Review and videotape recognition of idiopathic restless legs syndrome. *Movement Disord* 1991;6:105–110.
19. Godbout R, Montplaisir J, Poirier G. Epidemiological data in restless legs syndrome. *Sleep Res* 1987;16:338.
20. Walters A, Picchietti D, Hening W, Lazzarini A. Variable expressivity in familial restless legs syndrome. *Arch Neurol* 1990; 47:1219–20.
21. Montagna P, Coccagna G, Cirignotta F, Lugaresi E. Familial restless legs syndrome: long-term follow up. In: Guilleminault C, Lugaresi E, eds. *Sleep/wake disorders: natural history, epidemiology, and long-term evaluation.* New York: Raven Press, 1983:231–5.
22. Carskadon MA. Basics for polysomnographic monitoring of sleep. In: Guilleminault C, ed. *Sleeping and waking disorders: indications and techniques.* Menlo Park, CA: Addison-Wesley, 1982: 1–16.
23. Rechtschaffen A, Kales A. *A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects.* Los Angeles: UCLA Brain Information Service/Brain Research Institute, 1968.
24. Fredrickson PA, Krueger BR. Insomnia associated with specific polysomnographic findings. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine.* Philadelphia: W.B. Saunders Company, 1989:476–89.
25. Downey R, Bonner M, Von Pohle W, Wilms DJ. Comparison of sleep stage and arousal indices in normal young adult sleepers, normal elderly adult sleepers and elderly adult insomniacs. *Sleep Res* 1989;18:137.
26. Hoelscher TJ, Ware JC, McBrayer RH. Insomnia with periodic EEG arousals occurring in the absence of apnea and myoclonus. *Sleep Res* 1989;18:245.
27. Guilleminault C, Flagg W. Effect of baclofen on sleep-related periodic leg movements. *Ann Neurol* 1984;15:234–9.
28. 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.
29. Walters A, Hening W, Kavey N, Chokroverty S, Gidro-Frank S. A double-blind randomized cross-over trial of bromocriptine and placebo in the restless legs syndrome. *Ann Neurol* 1988;24: 455–8.
30. Doghramji K, Browman CP, Gaddy JR, Walsh JK. Triazolam diminishes daytime sleepiness and sleep fragmentation in patients with periodic leg movements in sleep. *J Clin Psychopharmacol* 1991;11:284–90.
31. Peled R, Lavie P. Double-blind evaluation of clonazepam on periodic leg movements in sleep. *J Neurol Neurosurg Psychiatry* 1987;50:1679–81.
32. Montagna P, Sassoli de Bianchi L, Zucconi M, Cirignotta F, Lugaresi E. Clonazepam and vibration in restless legs syndrome. *Acta Neurol Scand* 1984;69:428–30.
33. Boghen D, Lamothe L, Elie R, Godbout R, Montplaisir J. The treatment of the restless legs syndrome with clonazepam: a prospective controlled study. *Can J Neurol Sci* 1986;13:245–7.
34. Telstad W, Sørensen Ø, Larsen S, Lillevold PE, Stensrud P, Nyberg-Hansen R. Treatment of the restless legs syndrome with carbamazepine: a double blind study. *Br Med J* 1984;288:444–6.
35. Lundvall O, Abom PE, Holm R. Carbamazepine in restless legs: a controlled pilot study. *Eur J Clin Pharmacol* 1983;25:323–4.
36. Walters A, Hening W, Chokroverty S, Fahn S. Opioid responsiveness in patients with neuroleptic-induced akathisia. *Movement Disord* 1986;1:119–27.
37. Walters A, Hening W. Opioids a better treatment for acute than tardive akathisia: possible role for the endogenous opiate system in neuroleptic-induced akathisia. *Med Hypotheses* 1989;28:1–2.
38. Montplaisir J, Lapierre O, Warnes H, Pelletier G. The treatment of the restless legs syndrome with or without periodic leg movements in sleep. *Sleep* 1992;15:391–5.