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L-Dopa Improves Restless Legs Syndrome and Periodic Limb Movements in Sleep But Not Attention-Deficit-Hyperactivity Disorder in a Double-blind Trial in Children

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Abstract

Background—In a previous open-label study, dopaminergic agents improved Restless Legs Syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS), as well as Attention-Deficit-Hyperactivity Disorder (ADHD) in children with both disorders. We therefore conducted a double-blind placebo-controlled trial of L-DOPA in ADHD children with and without RLS/PLMS.

Methods—Two groups of patients (total n=29), those with ADHD only or those with ADHD and RLS/PLMS were randomized to L-DOPA or placebo therapy. At baseline and after therapy patients were assessed with Conners' Parent and Teacher Rating Scales; polysomnography; RLS rating scale; and neuropsychometric measures of memory, learning, attention, and vigilance.

Results—L-DOPA improved RLS/PLMS symptoms in all patients with those disorders compared with placebo (p = .007). When assessed by the Conners' Scales before therapy, ADHD was more severe in children without RLS/PLMS than in children with RLS/PLMS (p=0.006). L-DOPA had no effect on Conners' scales, sleep, or neuropsychometric tests when all patients treated with drug were compared to those on placebo or when patients with ADHD only were compared to those with ADHD and RLS/PLMS.

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Conclusions—In this first double-blind study of a dopaminergic therapy in children with RLS/PLMS, L-Dopa significantly improved RLS/PLMS but not ADHD. These results, however, should be interpreted carefully since they may have been influenced by the relatively small sample size and the baseline differences in severity of ADHD symptoms. Further work needs to be done to elucidate the relationship between dopamine, ADHD and RLS/PLMS.

Keywords

Attention-Deficit-Hyperactivity Disorder; Restless Legs Syndrome; Periodic Limb Movements in Sleep; L-DOPA; Children

INTRODUCTION

Recent literature has shown a higher prevalence of Restless Legs Syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS) in both children and adults with Attention-Deficit-Hyperactivity Disorder (ADHD) (1–6). Although the relationship of PLMS to ADHD has been less consistently reported than that of RLS to ADHD (7,8), a recent meta-analysis of polysomnographic studies verified that PLMS occur more commonly in children with ADHD than normal controls (9). The reverse relationship is also true, i.e., there is a higher prevalence of ADHD in children and adults with RLS/PLMS (4–6, 10–14).

Links between ADHD and RLS/PLMS have been described elsewhere (4, 6). There are reports (4,6) that children diagnosed with RLS appear hyperactive because they cannot sit at their school desks as a result of leg discomfort and this leads directly to inattention. In addition, the sleep disruption from RLS/PLMS may lead to symptoms consistent with ADHD. Yet another possibility is that ADHD and RLS/PLMS share a dopaminergic deficit. There are abnormalities in the brain dopaminergic system in both disorders as determined by Positron Emission Tomography (PET), although the distribution is somewhat different (15,16). In addition, genetic studies have shown alterations in dopamine transporters and receptors in ADHD patients in comparison with normal controls (17). An alternative possibility is that RLS/PLMS and ADHD may share a genetic link that is independent of dopaminergic function. Indeed this seems to be the case as the Protein Tyrosine Phosphatase Receptor type Delta (PTPRD) gene and the Nitric Oxide Synthase (NOS1) seem to be related to either condition (18–20). Lastly, both RLS/PLMS and ADHD have been independently shown to be characterized by iron deficiency (21–23) and an interaction of symptomotology of both disorders has been postulated with iron deficiency as intermediary (24,25).

Because of these observations and the effectiveness of dopaminergic therapy in adults with RLS/PLMS (26), we conducted an open-label study of L-DOPA in RLS children with ADHD (27). The results indicated not only improvement in RLS/PLMS symptoms, but improvement in ADHD symptoms as well. Based upon the open-label study, we conducted the current double-blind placebo-controlled study of L-DOPA to determine if ADHD symptoms improve differentially in children with and without RLS/PLMS. Our primary hypothesis was that ADHD would improve more in children with RLS/PLMS because of allied improvement in sleep disruption. A secondary hypothesis was that L-DOPA would improve symptoms of RLS/PLMS in children under double-blind conditions. To our knowledge, this is the first double-blind placebo controlled study of a dopaminergic agent for the treatment of RLS/PLMS in children.

METHODS

General Study Design, Subject Recruitment, and Initial Screening

In this double-blind study, children with ADHD who were on no ADHD medications were divided into two groups: ADHD only or ADHD with co-morbid RLS/PLMS. After baseline measurements, they were randomized to receive either Carbidopa/L-DOPA or placebo for 8 to 13 weeks. Polysomnography, Conners' rating scales and neuropsychometric testing were performed at baseline and endpoint. For most children with RLS, rating of severity of symptoms was also performed at baseline and endpoint.

This study was carried out between 2003 and 2006 at 4 academic medical centers (The New Jersey Neuroscience Institute, Edison, NJ; Robert Wood Johnson Medical School, New Brunswick, NJ; The University of Illinois/Carle Foundation Hospital, Urbana, IL; and the Children's National Medical Center, Washington, DC). Institutional Review Board approval was obtained at each site. Written parental consent and verbal assent from the child were obtained for each participant. Any patients who had received central nervous system-active pharmacologic therapies in the three months before entering the study were excluded. The initial patients who met first level screening criteria consisted of fifty-three children ages 7 to 12 years diagnosed with Attention-Deficit-Hyperactivity Disorder (ADHD) using DSM-IV criteria with the onset of ADHD symptoms before the age of 7 years and persistence of symptoms for at least 6 months prior to recruitment (28). No child was on treatment for RLS/PLMS at the time of the study and none were permitted to take iron supplements during the study. Children with attention problems, hyperactivity, or both were included. Ten parents refused to have their children participate because of either the desire to begin standard therapy for ADHD immediately, objection to the use of drug in this study, or logistics of traveling to the center for multiple visits.

The remaining 43 children were screened for intellectual dysfunction using the parts of the Weschler Intelligence Scale for Children-Third Edition (WISC-III) (29), severe learning problems with the Wide Range Achievement Test-Third Edition (WRAT III) (29), and psychiatric disorders with the NIMH Diagnostic Interview Schedule for Children Version 4.0 (DISC-4.0) (30). Four children failed these screening procedures.

Polysomnographic Measures

The remaining 39 children underwent 2 nights of baseline polysomnography in the hospital-based sleep laboratory at their respective site. Trained technicians conducted the polysomnographic studies. Studies were performed and scored prior to the introduction of the new criteria for polysomnography and the scoring of sleep related events (31,32). During the polysomnographic study, wakefulness and sleep stages were measured by electroencephalography (EEG), electrooculography (EOG) and chin electromyography (EMG). Time in bed, total sleep time, sleep latency, REM latency, and wakefulness after sleep onset were recorded in addition to the percentage of the various stages of sleep (Stage N1, N2, N3, and REM) in relation to total sleep time.

Respiratory parameters were assessed by monitoring abdominal and thoracic movements, airflow by both pressure transducer and thermal sensors, arterial oxygen saturation by oximetry, and snoring by microphone. EKG, infrared video monitoring, and a sensitive intercom were also used to monitor patients. An obstructive apnea was defined as a decrease of ≥75% in airflow from the baseline value for at least two breaths with continuing respiratory effort. A hypopnea was defined as a discernible decrease in airflow as measured by nasal pressure transducer accompanied by either a decrease in oxygen saturation of ≥3% or followed by an arousal. Central apnea was defined as cessation in airflow accompanied by absence of effort either lasting 20 seconds or more or of shorter duration but

accompanied by oxygen desaturation > 3% or >25% decrease in heart rate. Any child with more than one respiratory event per hour of sleep was excluded from further analysis. This resulted in the exclusion of 2 subjects who had obstructive events.

Bilateral anterior tibialis electromyography (EMG) was recorded to assess Periodic Limb Movements in Sleep (PLMS). The criteria used were those extant at the time of this study (33). PLMS were defined as a sequence of four or more limb movements of 0.5 to 5.0 seconds in duration, separated by more than 5 and less than 90 seconds, and amplitude greater than or equal to 25% of toe dorsiflexion during calibration. The PLMS index was calculated by dividing the PLMS by the total number of hours of sleep. Leg movements associated with respiratory events were not scored (33). Two nights of polysomnography were repeated at the conclusion of therapy (see below). The data from the two baseline studies were averaged for analysis, as were the data from the final studies. All polysomnograms were scored by experienced sleep technicians and over read on an epoch-by-epoch basis by a sleep specialist (SJE or DLP).

RLS Diagnosis

Definite or probable RLS was diagnosed by the obligate criteria established by the International Restless Legs Syndrome Study Group (IRLSSG) (34) as modified for children at the NIH consensus conference on RLS (21). When possible, the biological parents also were interviewed to establish the RLS diagnosis. For most of those children with an RLS diagnosis, the severity of RLS was assessed at baseline and at the conclusion of therapy using the RLS Rating Scale, which has been validated in adults with RLS by the International Restless Legs Syndrome Study Group (35). On this rating scale, there are 10 questions each scored from 0 to 4 with 0 indicating the absence of symptoms and 4 the most severe symptoms. In some cases, when it was deemed necessary, the parents helped the child complete the rating scale.

Assignment and Administration of Therapy

After exclusions cited above, 37 children were entered into the study and randomly assigned to receive either carbidopa/L-DOPA 25/100 CR (marketed by Bristol-Myers Squibb, Princeton, NJ) or placebo. The drug and placebo were packaged identically (Drug Product Services Laboratory, University of California, San Francisco, CA). The physician in charge of treatment was blinded to the study group to which a child was assigned. Nausea is common with L-DOPA, and, for this reason, domperidone 10 mg was provided for use as needed for nausea. Domperidone was chosen because, unlike other anti-nausea medications, it does not cross the blood-brain barrier and therefore does not counteract the effects of L-DOPA centrally. Two patients dropped out of the study before completion—one because of relocation to another country and one because of drowsiness on medication—leaving 35 patients, all of whom were diagnosed with ADHD. Of these 35 patients, twenty-two children were diagnosed with RLS and/or with a PLMS index ≥ 5 per hour of sleep. Half of these patients received drug and half placebo. Of the thirteen remaining patients with only ADHD, 6 received placebo and 7 the drug.

The drug (25 mg carbidopa/100 mg levodopa CR per tablet) or placebo was increased gradually by half a tablet every 4 days to a maximum dosage of 1 and a half tablets four times a day (breakfast, lunch, afternoon, and evening) depending on patient response. Dosage was increased if reports of symptoms of ADHD, sleep disruption, or symptoms of RLS/PLMS had not resolved as assessed by the participating physician during clinic visits and phone consultations. Final dosages ranged from 2.5 to 6 tablets per day (250 to 600 mg of L-DOPA).

Conners' Rating Scales and Neuropsychometric Testing

Before initiation of therapy (baseline) and 8 to 13 weeks after achieving maximum drug dosage (endpoint), ADHD severity was assessed using the short form version of the Conners' parent and teacher rating scales. The same parent always completed the form. We recruited subjects from October to March for initial entry into the study to ensure that the same teacher completed the forms during a single school year. The data were recorded as T scores for age and gender. Four scores were measured for each patient at each time point for both the parent and teacher ratings: Oppositional, Cognitive Problems/Inattention, Hyperactivity, and ADHD Index. A high T score indicates more severe symptoms.

At baseline and endpoint, several neuropsychometric tests were administered. These included the Wide Range Assessment of Memory and Learning (WRAML) yielding 3 verbal, 3 visual, and 3 learning subtests (36); the Trail Making test that assesses mental control processes (37); and the Integrated Visual and Auditory (IVA) continuous performance test which assesses different attention parameters (38).

All scoring of polysomnograms, RLS rating scales, Conners' rating scales, and neuropsychometric tests were performed by investigators blinded to the therapy.

Ferritin Levels

We obtained single blood samples for analysis of ferritin on a subset of the patients diagnosed with RLS/PLMS taken near the end of the study.

Statistical Analysis

A two by two factorial analysis of covariance (ANCOVA) was used to analyze the data from all 4 groups (ADHD only treated with placebo, ADHD only treated with drug, ADHD with RLS/PLMS treated with placebo, ADHD with RLS/PLMS treated with drug). One factor was ADHD with RLS/PLMS versus ADHD without RLS/PLMS, and the other factor was drug versus placebo. A one way ANCOVA was used to determine differences between groups in either the RLS/PLMS groups or in those without RLS/PLMS. The covariate for each measure was the baseline score as a mechanism to adjust for baseline differences between groups. The focus of these analyses was on the drug group by diagnosis interaction to determine whether the drug-placebo difference was greater for the patients with RLS/PLMS, or for those who did not have RLS/PLMS. ANCOVA adjusts for baseline differences between groups and is a robust method to statistically analyze before-after change (39), because it uses linear regression to create a change score that is more appropriate and more likely to obtain significance than a simple difference score.

ANOVA was used to assess age differences between the groups. The Fisher exact test MANOVA, and T-tests with Bonferroni correction were also used for some analyses as indicated in the Results section.

Six patients with RLS only in the RLS/PLMS groups did not have complete data for the RLS Rating Scale. Statistical analyses were performed on data for ADHD severity, neuropsychometric and sleep parameters with or without inclusion of these children. No differences in statistical significance in endpoints were found and, therefore, only the analyses excluding these children are reported. This yielded a final sample size of 29 patients with ADHD, 16 of whom had RLS, PLMS or both. All data were assessed for site differences, and since none were found, data were pooled.

All tests were two-sided and a p value < 0.05 was considered significant. The Conners' rating scales were the primary endpoint.

RESULTS

The demographic data of the analyzed patient groups are presented in Table 1. There were no significant age differences between groups as assessed by ANOVA ($p = 0.15$). As predicted based on the incidence of ADHD in children, a larger number of males were enrolled into the study. No patients experienced severe adverse side effects from the drug therapy and only one patient dropped out of the study due to side effects (drowsiness). The only other side effects reported were headache and nausea. Transient headaches were reported in 5 children, 3 of whom were on placebo. Only 4 children in the study required use of domperidone for nausea, 2 receiving drug and 2 on placebo.

Improvement in RLS/PLMS

Objective measures of improvement in RLS/PLMS were available at baseline and endpoint for 8 children treated with L-DOPA and 8 treated with placebo (Table 2). In the L-DOPA treated group there were 5 children with baseline PLMS Index ≥ 5 per hour of sleep with or without RLS and 3 with RLS only. In the placebo group there were 6 children with baseline PLMS Index ≥ 5 per hour of sleep with or without RLS and 2 with RLS only. Because of small sample size, we jointly analyzed improvement in RLS and PLMS. If individuals had both RLS and PLMS Index≥ 5, they had to show improvement in both to be considered as responding to treatment. Eight of the 8 children in the drug group showed improvement in RLS, PLMS or both while only 2 of the 8 children in the placebo group showed improvement in RLS, PLMS or both ($p=0.007$ by Fisher's exact test). Furthermore, 4 of 5 children with PLMS indices ≥5 at baseline_who received drug had a reduction in PLMS indices below the clinical cutoff of ≥ 5 per hour of sleep on their post therapy polysomnograms, while none of the 6 children with PLMS indices ≥5 at baseline receiving placebo improved to below this cutoff point.

For the 11 children with RLS/PLMS in which ferritin values were obtained near the end of the study, 7 of the 11 fell below the age appropriate 95% confidence intervals recently reported for ferritin in the US population (40). The mean ferritin level for these 11 patients was 26.9 ng/ml with a standard deviation of 11.3.

ADHD Symptoms

Baseline and endpoint parent rating scales were available for all but one patient who was in the non-RLS/PLMS group, and one teacher rating scale was not completed for a patient in the RLS/PLMS drug group. At baseline, the patients without RLS/PLMS were noted to have higher scores on 7 of the 8 Conners' subscales as measured by T-score (MANOVA $F(8,18) = 4.18$, $p = .006$), indicating significantly more severe impairment in the non-RLS/PLMS group on the subscales as a whole (Table 3). When individual subscales were compared by T-test with Bonferroni correction, the differences between the RLS/PLMS group and the ADHD only group were statistically significant for both the Parent and Teacher Hyperactive subscales.

Examining individual groups on the subscales of the Conners', improvements were noted in the majority based on obtaining lower average scores at endpoint compared with baseline (Table 3). None of these differences reached statistical significance by T-test after Bonferroni correction. Furthermore, when analyzed with ANCOVA, L-DOPA had no effect on ADHD symptoms by Conners' rating scales when all patients treated with drug were compared statistically to those on placebo. Also, L-DOPA had no differential effect on ADHD symptoms when those with ADHD only were compared statistically by ANCOVA to those with comorbid RLS/PLMS (Table 3).

Changes in Sleep Indicators

The sleep data are presented in Table 4 for each of the 4 groups at baseline and endpoint. No significant differences were found for any of the sleep parameters measured.

Neuropsychometric Tests

No significant differences between groups were found for improvement on the WRAML, Trail Making, or IVA tests between groups by ANCOVA.

DISCUSSION

The major finding of this double blind, placebo controlled trial is that L-DOPA improves RLS/PLMS in children under blinded conditions. This is consistent with the well-established response to dopaminergic therapy in adults with RLS/PLMS (26). There have been several previous small open-label studies of L-DOPA in ADHD that showed only a modest benefit (41–45). To our knowledge, however, this is the first double-blind trial of a dopaminergic agent for RLS/PLMS in children.

A second major finding of this study is that, as opposed to previous studies, ADHD was worse in children without RLS/PLMS than in children with RLS/PLMS (3,11,24,25). One hypothesis to explain this result is that RLS/PLMS produces secondary ADHD symptoms that are milder in nature and degree than primary ADHD symptoms. This is comparable to the results in one study of ADHD where overnight polysomnography indicated that obstructive sleep apnea was present in 5% of those with significant ADHD symptoms, 26% of those with mild ADHD symptoms, and 5% of those with no ADHD symptoms. A similar explanation was put forth by the authors suggesting that sleep apnea leads to milder ADHD symptoms that mimic primary ADHD (46). But if mild ADHD symptoms in RLS/PLMS are truly secondary to the symptomatology of RLS/PLMS, improvement in ADHD would have been expected to occur in parallel with the improvement in RLS/PLMS and this was not the case in our study.

It is also possible that more severe pure ADHD cases and more mild RLS/PLMS associated ADHD cases were recruited for the study because of referral bias. We do not believe that this is the case but cannot exclude this possibility. It should be noted, in any case, that baseline differences in ADHD severity were corrected by ANCOVA as part of the process of analyzing therapeutic response.

In this study, we did not find any significant improvement of ADHD symptoms, sleep parameters, or neuropsychometric measures in ADHD patients treated with L-DOPA as compared to those given placebo. We were also unable to show a greater improvement in those parameters in those patients with ADHD and RLS/PLMS compared to those with ADHD only as we originally hypothesized. These negative results may be attributable to small sample size. But given that there were no discernible trends for the Conners' rating scales, a larger sample size may not have yielded significant results. It also is possible that a longer follow-up period might have been necessary to identify a decrease in ADHD symptoms. Another possibility is that given the relatively low severity of ADHD symptoms in the RLS/PLMS group at baseline, large changes in T scores may not have occurred, limiting our ability to detect statistically significant differences.

Yet another possibility is that bona fide idiopathic ADHD and bona fide RLS occur together because of a non-dopaminergic genetic link. RLS and ADHD, for example, both show abnormalities in the PTPRD and NOS1 genes (18–20). In this case improvement in RLS symptoms would not necessarily lead to improvement in ADHD symptoms.

L-DOPA was chosen over one of the dopamine agonists for this study because of our pilot data showing benefit in an open-label study (27), greater experience with L-DOPA in children for other disorders (47), and limited data at the time of study proposal for dopamine agonists in RLS. In addition, L-DOPA is the prototypical dopaminergic agent with impact on all dopamine receptor subtypes, and we therefore considered it the ideal agent to probe the putative ADHD-RLS-dopaminergic link. Whether a dopamine agonist with longer half-life might produce better results for pediatric RLS and ADHD is a currently unresolved issue.

One weakness of the current study was that we did not directly test the impact of improvement of RLS symptoms on quality of life. Such improvements would be likely, however, based upon the close link between RLS severity and quality of life and the close link between improvement in RLS severity and quality of life with treatment (48, 49). In addition, the RLS severity scale used in the current study did show improvement. In this scale 4 out of the 10 items directly probe quality of life issues including sleep, mood and ability to carry on a satisfactory school and family life. The small sample size, however, precluded any meaningful analysis of these items. This factor should be included in future studies.

In summary, further research is warranted to elucidate the relationship between dopamine, RLS/PLMS and ADHD. In the meantime, we suggest that patients with ADHD should be evaluated for RLS/PLMS as they may benefit from dopaminergic, iron, or nonpharmacologic therapies on an individual basis. In addition, children with RLS should be evaluated for symptoms of ADHD which may require stimulant or behavioral therapies.

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Table 1

DEMOGRAPHICS

PLMS/RLS Diagnosis	Drug or Placebo	n	Mean Age (SD)	Gender (M:F)	Ethnicity* (C:A:H:M)
Yes	Placebo	8	9.6 (2.0)	5:3	7:0:0:1
Yes	Drug	8	9.3 (1.3)	6:2	5:1:0:2
No	Placebo	6	9.3 (1.0)	5:1	3:0:1:2
No	Drug	7	8.0 (0.8)	4:3	4:0:3:0

*Ethnicity: (C)aucasion:(A)frican American:(H)ispanic:(M)ixed

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Table 2

Baseline and Endpoint Measures of PLMS Index and IRLS Rating Scale for Patients with ADHD and RLS, PLMS or both.

Treatment	Patient	PLMS INDEX (# PLMs/hour of sleep)			RLS Diagnosis and Rating Scale Values		
		≥5 /hour Baseline	Baseline	Endpoint	RLS Diagnosis	Baseline IRLS	Endpoint IRLS
Placebo	1	Yes	22	28	Yes	N/A	N/A
	2	No	1	0	Yes	7	0
	3	Yes	8	9	Yes	13	4
	4	Yes	16	9	No	--	--
	5	Yes	5	7	Yes	N/A	N/A
	6	Yes	11	7	Yes	14	21
	7	No	0	1	Yes	13	15
	8	Yes	13	18	Yes	N/A	N/A
Drug	1	Yes	6	1	No	--	--
	2	Yes	17	0	No	--	--
	3	No	0	0	Yes	13	9
	4	No	1	0	Yes	7	0
	5	Yes	5	0	Yes	26	0
	9	No	0	0	Yes	14	7
	7	Yes	5	4	Yes	N/A	N/A
	8	Yes	12	11	No	--	--

See text for analysis. PLMS Indices were only compared if the baseline was ≥ 5 per hour of sleep. Note that the IRLS Rating Scale was only administered to patients meeting the criteria for a diagnosis of RLS (See Methods). Rating scale values are shown as – for those patients who did not meet criteria for a RLS diagnosis. Additionally, IRLS scales were not available (N/A) for 4 of the 12 patients diagnosed with RLS.

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Table 3A

PARENT CONNERS' T SCORE SUBSCALES IN PATIENTS WITH ADHD with or without RLS/PLMS

			BASELINE				ENDPOINT			
Diagnosis	**Treatment**	**n**	**Oppositional**	**Cognitive**	**Hyperactive**	**ADHD**	**Oppositional**	**Cognitive**	**Hyperactive**	**ADHD**
RLS/PLMS	PLACEBO	8	65 ± 9	77 ± 12	68 ± 15	75 ± 10	61 ± 14	74 ± 14	64 ± 18	73 ± 12
	DRUG	8	59 ± 9	67 ± 9	60 ± 12	68 ± 8	54 ± 7	62 ± 8	60 ± 13	63 ± 10
	TOTAL	16	62 ± 9	72 ± 12	64 ± 14	71 ± 9	57 ± 12	68 ± 13	62 ± 16	68 ± 12
NON RLS/PLMS	PLACEBO	6	75 ± 13	72 ± 8	78 ± 8	74 ± 7	62 ± 12	62 ± 8	68 ± 8	66 ± 6
	DRUG	6	70 ± 18	77 ± 11	85 ± 4	79 ± 8	67 ± 15	70 ± 15	69 ± 8	69 ± 13
	TOTAL	12	72 ± 15	75 ± 10	81 ± 7	76 ± 8	64 ± 13	66 ± 12	69 ± 8	68 ± 9

Mean ± SD

Note one patient of the 29 with ADHD in the non RLS/PLMS group did not have a completed Parent's Conner Scale.

Table 3B

TEACHER CONNERS' T SCORE SUBSCALES IN PATIENTS WITH ADHD with or without RLS/PLMS

			BASELINE				ENDPOINT			
Diagnosis	**Treatment**	**n**	**Oppositional**	**Cognitive**	**Hyperactive**	**ADHD**	**Oppositional**	**Cognitive**	**Hyperactive**	**ADHD**
RLS/PLMS	PLACEBO	8	51 ± 9	58 ± 7	56 ± 10	63 ± 12	52 ± 9	60 ± 10	55 ± 8	60 ± 12
	DRUG	7	58 ± 17	67 ± 12	57 ± 10	63 ± 11	54 ± 13	62± 11	52 ± 12	60 ± 12
	TOTAL	15	54 ± 13	62 ± 11	56 ± 10	63 ± 11	53 ± 11	61 ±10	53 ± 10	60 ± 12
NON RLS/PLMS	PLACEBO	6	55 ± 18	57 ± 9	66 ± 11	70 ± 8	54 ± 14	59 ± 6	66 ± 11	68 ± 7
	DRUG	7	61 ± 17	64 ± 12	73 ± 11	75 ± 12	55 ±14	63 ± 9	64 ± 7	68 ± 11
	TOTAL	13	58 ± 17	61 ± 11	70 ± 11	73 ± 10	55 ± 13	61 ± 8	65 ± 9	68 ± 9

Mean ± SD

Note one patient of the 29 with ADHD in the RLS/PLMS group did not have a completed Teacher's Conner Scale.

TABLE 4

POLYSOMNOGRAPHIC DATA AT BASELINE AND ENDPOINT FOR ALL PATIENTS INCLUDED IN FINAL ANALYSIS

DIAGNOSIS	TREATMENT	N		Time In Bed (min)	Total Sleep Time (min)	SLEEP LATENCY (min)	REM LATENCY (min)	Wake After Sleep Onset (min)	N1 Sleep (%TST)	N2 Sleep (%TST)	N3 Sleep (%TST)	REM Sleep (%TST)
ADHD with RLS/PLMS	Placebo	8	Baseline	530(30)	458(41)	46(45)	142(62)	26(17)	5(3)	37(9)	41(14)	17(5)
			Endpoint	513(32)	466(50)	30(38)	164(48)	17(16)	3(2)	40(8)	40(10)	17(4)
	Drug	8	Baseline	542(28)	485(38)	27(16)	142(73)	29(23)	5(2)	39(12)	36(12)	20(4)
			Endpoint	529(23)	481(42)	19(24)	130(34)	28(16)	6(2)	41(10)	33(11)	21(3)
ADHD without RLS/PLMS	Placebo	6	Baseline	501(42)	446(42)	15(12)	194(58)	40(23)	4(2)	46(8)	31(8)	19(3)
			Endpoint	499(33)	448(35)	16(12)	178(57)	35(17)	5(3)	42(7)	36(9)	17(4)
	Drug	7	Baseline	522(43)	454(40)	38(32)	150(73)	30(21)	4(3)	41(8)	36(11)	19(4)
			Endpoint	523(46)	471(49)	20(14)	152(67)	32(23)	5(4)	45(12)	33(10)	17(7)

All polysomnographic data are reported as means with the numbers in parentheses as standard deviation. All patients in each of the four groups had complete polysomnographic data at both baseline and endpoint. N1 sleep, N2 sleep, N3 sleep, and REM sleep are reported as % of Total Sleep Time (TST). There were no statistical differences between groups as described in the text.