Long-Term Treatment of Restless Legs Syndrome with Dopamine Agonists

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Abstract

Background: Restless legs syndrome (RLS) may effect more than 10% of the population. Although several controlled trials robustly demonstrate short-term efficacy of dopamine agonist (DA), little is known about their long-term efficacy, long-term adverse events, and the predictors and frequency of tolerance and symptom augmentation.

Methods: We queried all subjects seen in the Baylor College of Medicine Movement Disorder Clinic from 1996 – 2002 and specifically followed those initiated on any DA. Demographics, efficacy, adverse events, and augmentation were tracked over time.

Results: After eliminating all RLS patients with factors that could effect DA dosing or the accuracy of data, 84 subjects were followed with at least six months use of DA. In general, efficacy was maintained over time (mean 33 months) but at the expense of a moderate but significant increases in dose of about 25%, ($p < 0.05$). Some augmentation occurred in 31% of subjects and was only predicted by a postive family history of RLS ($p < 0.05$).

Conclusion: DA are effective first line therapy for RLS and are generally well tolerated. Augmentation is not uncommon, but is generally much less severe than that historically reported with levodopa.

Introduction

Restless legs syndrome (RLS) as defined by the International Restless Legs Syndrome Study Group criteria [1] may occur in more than 10% in predominately Caucasian populations. [2-4] Historically, numerous treatments have been employed with varying degrees of success, however evidence based medicine most consistently supports the use of levodopa and dopamine agonists (DA). [5] These studies, however, are mostly from single centers and of short duration.

Less data addresses the long term use of DA for RLS. [6-8] Some reports have raised concerns about both the development of tolerance and dopaminergic induced augmentation, a poorly defined scenario associated with a earlier phase shift of symptom onset and increased intensity. This is most notably with levodopa, which has the shortest T ½ of any dopaminergic treatment [9], but is also reported with pergolide [8,10,11] and pramipexole [12,13], but, to date, not with cabergoline. [14,15] No report has ever evaluated the longitudinal use of multiple dopaminergic medications concurrently in order make efficacy and tolerability comparisons. Furthermore, factors that might predict problems with continued DA treatment for RLS have not been systematically evaluated.

Methods

All patients seen with RLS at the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC) between the January 1996 and January 2003 were initially included in a chart review. The onset coincides with when we began using DA for RLS. Patients with concurrent Parkinson's disease (PD) or other diseases that required dopaminergic therapy, patients previously started on DA elsewhere, patients who never started a DA, patients with RLS associated with uremia, and patients who did not meet strict criteria for RLS were immediately excluded. Patients followed for less than 6 months since the initiation of treatment were not included, as we did not feel that they would facilitate our evaluation of long-term treatment.

Collected data included patient demographics and disease specific features (age of onset, family history of RLS, ferritin, previous treatments etc.). At every visit, and every phone call that resulted in a medication change, we recorded the medication(s), dose(s), treatment response, and the presence and severity of augmentation symptoms. Responses were rated by the investigator but were entirely based upon the subjective report of the patient. Efficacy was rated as (5) essentially complete relief of RLS symptoms and excellent nocturnal sleep, (4) essentially complete relief but continued subjective sleep problems of any cause, (3) 75% – 99% improvement, (2) 25% – 74% improvement, (1) 1% – 24% improvement, and (0) no improvement. There is no formal widely accepted definition of augmentation. We stratified augmentation based on a clinically relevant paradigm: (0) no change in onset of RLS symptoms, (1) mild, earlier onset RLS not requiring any intervention, (2) earlier onset of symptoms that require the earlier use, but not additional dose of a DA, and are not worse in severity than the original nocturnal RLS, (3) earlier onset of symptoms that require an additional dose of a DA, but were not worse in intensity than the original nocturnal symptoms, and (4) severe, earlier onset of symptoms that require additional medication changes and have increased intensity than the original nocturnal symptoms.

We calculated a DA equivalent dose (dose = pramipexole/1 + pergolide/1 + ropinirole/3.5 + bromocriptine/10 + carbergoline/0.5).

Patients were contacted to complete any missing demographic or disease specific data. We did not try to complete any missing response or augmentation data that was greater than six month old, as we did not trust its reliability. We also attempted to contact all patients who were not seen within the last year. Therefore, if a patient was started on a medication by us and then followed elsewhere, we may only have the initial data and data from our phone call (2 points in time), whereas patients seen regularly by us may have more than 20 data points.

Univariate analysis determined which factors were associated with augmentation, while multivariate regression analysis assessed the probability of developing augmentation via the relationship between survival time and a set of predictors. The predictors/factors of interests included age at onset, age of initial treatment with a DA, sex, serum ferritin level, previous treatment with levodopa, specific initial DA used (i.e., pramipexole), and family history of RLS. We then calculated efficacy and dose, and constructed survival curves for the first indication of augmentation of at

Table 1:

Group Demographics

	Core Group			Control Group		
	n	Mean ± SD		n	Mean ± SD	
Sex	84	30 M	54 F	74	28 M	46 F
Age	84	56.9 ± 14.1		74	57.8 ± 14.8	
Age onset of RLS	81	33.3 ± 18.3		70	35.2 ± 18.3	
Family history of RLS	81	60 Y	21 N	73	36 Y	37 N *
Evidence of neuropathy	62	22 Y	40 N	44	14 Y	19 N
Arm involvement	83	24 Y	59 N	74	21 Y	53 N
Serum ferritin level	54	77.0 ± 70.2		39	84.1 ± 98.2	

* $p < 0.05$

Table 2:

Cox Regression Analysis on Survival Time From Augmentation in RLS Patients

Covariate	β	*df*	*p*	Odds ratio
Sex	0.032	1	0.94	1.03
Age onset of RLS	0.023	1	0.12	1.02
Age of initial DA treatment	-0.015	1	0.38	0.99
Serum ferritin level	0.373	1	0.40	1.45
Previous treatment with levodopa	-0.789	1	0.23	0.45
Start of DA with pramipexole	0.282	1	0.52	1.33
Family history of RLS	-1.579	1	0.03	0.21

Figure 1:

Efficacy and Dose Over Time

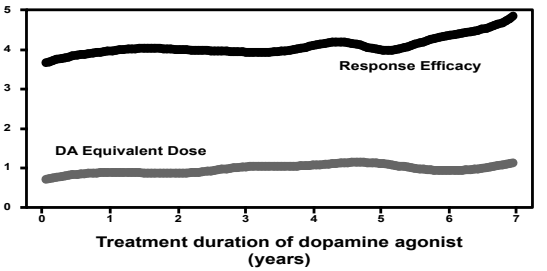
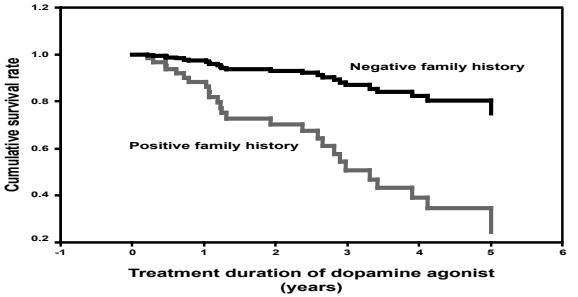


Figure 2:

Lack of Onset of Augmentation



Results

We initially identified 262 patients with RLS. Seventeen patients did not meet strict criteria for RLS and were eliminated from further analysis. We excluded 59 for the concurrent diagnosis of a parkinsonian condition, and 14 for having RLS associated with uremia. Fifty-six were never started on a DA, mostly early in the cohort. Thirty-four were previously started elsewhere on a DA and were thus eliminated from analysis. This left 100 subjects who were initially started on a DA by us. Sixteen of these lacked six months data because: they were started on a DA within the past six months (3), were lost to follow-up (2), stopped the DA due to logistical, financial, or compliance issues (3), stopped due to lack of efficacy (3), stopped due to adverse events (2), or stopped because their RLS symptoms improved such that they no longer required therapy (3). Therefore, 84 patients initially started on a DA by us, were followed for at least six months of treatment and met all a priori inclusion criteria.

Demographics of the group are summarized in Table 1, and were generally similar to the group who were excluded either because they did not start a DA or were previously started on a DA (N = 74).

The initial DA was pramipexole (54), ropinirole (17), and pergolide (13). The duration of DA therapy that we followed averaged 32.3 ± 22.4 months (range: 6.0 – 90.7). Twenty-six (31%) subjects changed DA at some point, and seven of these changed more than once. Twenty (24%) subjects required additional treatment: with a narcotic (6), gabapentin (9), and a benzodiazepine (6). Twelve subjects stopped DA after six months: for lack of efficacy (4), adverse events (2), natural improvement in symptoms (3), logistical/financial reasons (2), and other medical conditions (1). Excessive daytime sleepiness was reported by two subjects. AE, however, were generally very mild.

Efficacy was maintained over time, but at the cost of a modest but significant dose augmentation ($p < 0.05$). [Figure 1] Mild augmentation (earlier onset of symptoms) was fairly common, but severe augmentation (requiring additional doses and/or augmented daytime symptoms) was uncommon. Only two people had intensity augmentation.

Univariate analyses revealed no statistical differences in sex, age at onset, age of initial treatment with a DA, serum ferritin level, and previous treatment with levodopa between those patients with or without augmentation. Univariate chi square analyses did reveal trends towards augmentation with a positive family history of RLS and those who did not start with pramipexole ($ps < 0.09$). These variables were entered as covariates in the survival regression model at step 1, while family history of RLS and start of a DA with pramipexole were entered into the model at step 2. Survival time was not well predicted by the set of covariates, $R^2 = 0.02$, however, there was a reliable effect of family history of RLS, but not the initial DA, after adjusting for sex, age at onset, age of initial treatment with a DA, serum ferritin level, and previous treatment with levodopa, $G^2_{(2)} = 6.1$, $p < 0.046$. [Table 2] Based on the survival analysis, Risk = 0.03(males) + 0.02(age at onset) – 0.02(age of initial DA treatment) + 0.37(serum ferritin level) – 0.79(previous treatment with levodopa) + 0.28(start of a DA with pramipexole) – 1.58(family history of RLS). Having a negative family history of RLS protected against the development of augmentation, odds ratio = 0.21, $CI_{(95\%)} = 0.05$ to 0.88. [Figure 2]

Discussion

Our results demonstrate that DA effectively treat RLS for greater than six months. Efficacy is generally maintained over time but at the cost of a moderate but significant dose increase. The medications are very well tolerated and AEs are uncommon after the dose initiation. Modest augmentation, as defined by an earlier onset of symptoms occurs frequently but severe augmentation is relatively uncommon, and usually managed by dose adjustments. Patients with a family history of RLS had significantly more augmentation. Overall, our results support the first-line use of DA in RLS.

The pathophysiology of augmentation is not known. Empirical evidence suggests that dopaminergics with shorter half-lives, especially levodopa, increase the risk of augmentation, whereas longer acting DA protect against augmentation. This could result from the simple fact that more continuous dopaminergic stimulation will "cover up" the symptoms, or more intriguingly, may result from some biological advantage of continuous dopaminergic stimulation as is suggested in PD. Our data, which suggests that a family history of RLS protects against augmentation also suggests some intrinsic biological difference between genetic and non-genetic RLS.

We prospectively set up very formalized criteria for data collection in an attempt to minimize features such as recall bias. Nevertheless, this is predominately retrospective data and suffers from all the intrinsic weaknesses of such. We, as a tertiary referral center are also subject to potential referral biases toward more severe or refractory RLS cases. In order to assure accurate and detailed results, we eliminated 62% of all subjects seen by us. Although this is a potential weakness, we do not feel that this group differed from those non-parkinsonian RLS sufferers as a whole. The large number of RLS subjects with PD that were eliminated from evaluation is likely explained by our status as a movement disorder center. Furthermore, we suspect that RLS can be a non-motor symptom in PD and that this group is intrinsically different than RLS as a whole. [16]

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