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Original Article

Restless legs syndrome (RLS) augmentation associated with dopamine agonist and levodopa usage in a community sample

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ABSTRACT

Objective: Assess the rate of augmentation as it occurs during standard long-term dopaminergic treatment of RLS, potential risk factors or predictors of augmentation, the relationship between treatment duration and augmentation, and the clinical impact of augmentation on subjects' health outcomes.
Methods: Two hundred sixty-six patients with dopamine-treated RLS completed a one-time online survey. All subjects were recruited by their PCP/neurologist and were 18 or older. Augmentation was assessed using NIH guidelines and an augmentation classification system was developed through this research.
Results: Overall, 20% of the patients were classified as having definitive or highly suggestive clinical indications of augmentation. Five factors were considered likely to reflect increased risk of developing augmentation, including more frequent RLS symptoms pre-treatment, greater discomfort with RLS symptoms before treatment, and longer treatment duration. RLS augmentation occurred at a rate of about 8% each year for at least the first 8 years of dopamine treatment. Subjects reporting definite or highly suggestive clinical indicators of augmentation had an average IRLS score of 23.6, indicating generally inadequate treatment with generally poor clinical outcomes. Only 25% of the patients reported no indications of augmentation and they were the only group to show on average a low (<15) IRLS score and good clinical outcomes.
Conclusions: As currently used, long term dopaminergic treatment for an average ± SD of 2.7 ± 2.4 years produced significant augmentation problems in at least 20% of the patients and only 25% of the patients were totally free of this problem. It is important for physicians to carefully screen patients for changes in RLS symptoms for as long as they are on dopamine agents, with particular attention paid to those patients who present with the most severe RLS symptoms prior to treatment initiation. Given the marked increase in suffering with augmentation, a method for early detection and intervention would be an important contribution to the effective management and treatment of RLS.

1. Introduction

The serendipitous discovery of dopaminergic treatment for restless legs syndrome (RLS) offered relief from this disturbing and sometimes disabling life-long disorder. The excitement of finding a treatment offering relief from the discomfort, pain and leg akathisia of RLS was soon tempered by the unexpected adverse consequence, for some, of a profound worsening or augmentation of RLS symptoms associated with longer-term use of levodopa and dopamine agonists [1]. The initial definition of augmentation was developed based on clinical experience [2]; several years later, the definition was expanded to incorporate severity and clinical significance, based on empirical data from clinical studies [3,4]. Augmentation is an increase in symptom severity defined in prior studies as an earlier than usual onset of symptoms by 2 h or by at least two of the following: shorter time to symptom onset following rest, spreading of symptoms to other body parts, shorter duration of relief from treatment, new or worsening periodic limb movements in sleep, or either medication increase (making symptoms worse) or decrease (making them better) [2]. Mild augmentation may present first as treatment tolerance, but as it becomes more severe the RLS symptoms become worse relative to the onset experienced before treatment and usually occur earlier in the day

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than prior to treatment initiation [1,4,6]. Severe augmentation produces intense symptoms occurring 24 h a day with reduced benefits from dopaminergic treatment. Augmentation has been reported to occur in 60–85% of patients on levodopa treatment for 6 months or more [1] and in 30% of patients on the dopamine agonist pramipexole for at least 3 years [5]. Augmentation is considered the primary factor limiting successful long-term use of dopamine agonists for RLS [3,6].

Despite the clinical significance of augmentation, relatively little is known about it. The natural developmental course and pathophysiology of augmentation is poorly understood. Studies to date suggest that it continues to occur for up to 9 years after treatment onset [7]. But it is not known if the incidence abates after longer duration of treatment. It is also not clear how rapidly augmentation develops or if it usually progresses over time to a more severe state. While treatment duration is a factor affecting augmentation, the exact relationship remains clear; more and better evaluation is needed. Perhaps most importantly, little is known about augmentation's impact on RLS patients currently receiving long-term treatment with dopaminergics.

This study attempts to address four questions: (1) What is the rate of augmentation as it occurs during standard long-term dopaminergic treatment of RLS as practiced in the USA in 2009? (2) What are the potential risk factors or predictors of augmentation? (3) What is the relationship between treatment duration and symptom augmentation? (4) What is the clinical impact of augmentation on subjects' health outcomes?

Addressing the study questions requires both a large sample of RLS patients treated with dopaminergic agents in real-world clinical settings from multiple physicians and also development of a scale for identification of augmentation from answers to a patient survey questionnaire. This scale would assess the likelihood of augmentation (spanning the range from highly specific and sensitive identification of augmentation to no indication of augmentation) based on an algorithm related to clinical indicators providing a metric for evaluating augmentation status and clinical impact.

2. Methods

2.1. Study design

In this observational, cross sectional study, a one-time, 20-min online survey was developed and administered to 266 subjects who were identified by their doctor as being treated with dopaminergic agents for RLS. The survey assessed RLS treatment characteristics, treatment satisfaction and adherence, comorbid conditions, disease severity and impact, quality of life, and occurrence of clinical factors related to augmentation and early morning rebound (EMR). The following validated scales were also used to assess RLS impact: International RLS Rating Scale (IRLS) [8], Johns Hopkins RLS Quality of Life Questionnaire (RLS-QOL) [9], and Medical Outcomes Study Sleep Scale (MOS Sleep Scale) [10]. The IRLS scale was used in its standard form except that it was completed by the subject without the presence of a clinician.

2.2. Recruitment and study population

Subjects were referred via their primary care physician or neurologist. All neurologists/sleep specialists and a random sample of the primary care physicians (PCPs) in the Harris interactive physician panel were contacted via email or postal mail and invited to complete a brief online screening survey. This panel provides a population adjusted geographic distribution of PCPs and neurologists matching that of the USA. Physicians reporting treating a minimum of 20 RLS patients were asked to participate in the study. In total, 336 physician (215 PCPs and 121 neurologists/sleep specialists) participants met criteria and agreed to participate in the study. Each was mailed a welcome packet that included additional information about the study and 20 sealed invitations to mail or hand out to their patients diagnosed with RLS and currently treated by them with dopamine agents, thus protecting patient anonymity and ensuring data confidentiality. In total, 433 RLS patient subjects entered the survey, 271 qualified for participation, and, of these, 266 (98.2%) completed the on-line survey (178 from PCPs and 88 from neurologists/sleep specialists). Both physicians and subjects received a modest cash honorarium in exchange for participation. This study was reviewed and approved by the Essex Institutional Review Board.

Inclusion criteria for subject participation were US residency; minimum age of 18; RLS diagnosis for at least 1 year; current primary RLS treated with levodopa or a dopamine agonist for at least 6 months; and symptom frequency of at least 2–3 days per week before treatment. Subjects with a diagnosis of peripheral neuropathy, kidney failure, or pregnancy were excluded, but those with a diagnosis of iron-deficiency anemia were not excluded.

2.3. Augmentation classification system

Augmentation was determined by the patient's report of RLS symptoms meeting one of the two NIH criteria for augmentation [2]. These require that either RLS symptoms occur at least 2 h earlier than was typical prior to the initial course of treatment or that two or more specified symptom changes from augmentation criterion 2 are present (Fig. 1). In addition, to definitively conclude that augmentation is present, the symptoms meeting augmentation criteria must also occur for a minimum of 1 week and for at least 5 days in that week. The questionnaire directly asked about each feature of augmentation and if reported asked about how frequently it occurred. There should also be no other medical, psychiatric, behavioral, or pharmacological factors that could explain the exacerbation of RLS and augmented symptoms. The questionnaire items covered each of these major factors (Supplementary material on line).

Due to the self-reported nature of the study it was not possible to engage in direct clinical assessments of the subjects. Therefore, clinical indicators of augmentation, as identified by clinical experts of RLS (authors RA, WO and EB), were used to develop a likelihood of augmentation scale for those not meeting one of the NIH criteria. Each indicator was a question in the survey, and based on indicators present, subjects were classified as having a definite clinical indication of augmentation (i.e., met one of the NIH criteria), highly suggestive, possible or no clinical indication. The categories of augmentation and the indicators used for determining each were set prior to data collection as provided in Fig. 2.

The clinical indicators assessed in this study are not mutually exclusive; therefore subjects can report having multiple indicators within or across the augmentation categories. Subjects were classified based on the criteria giving the strongest indication of augmentation since the indicators for the higher risk categories are considered more suggestive of true augmentation. The definite and highly suggestive augmentation groups were combined for quantitative analyses regarding treatment duration, factors associated with development of augmentation and of the health effects of augmentation.

2.4. Statistical analysis

Descriptive statistics were used to characterize our sample using group mean and standard deviations. Group differences were assessed using *t*-tests for means. Significance testing used alpha <0.05 level unless otherwise noted.

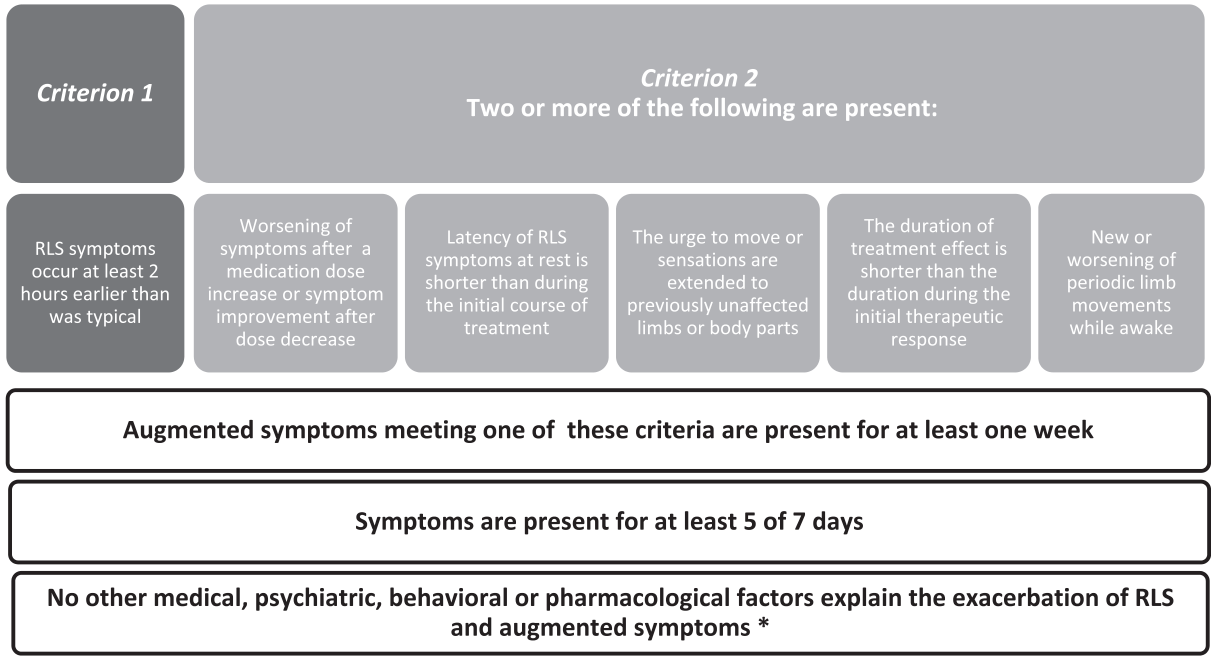


Fig. 1. NIH criteria for augmentation diagnosis.

A discriminant function analysis was carried out to identify variables significantly associated with definitive/highly suggestive vs. no clinical indications of augmentation. Variables included potential risk factors of augmentation: patient demographics, current treatment type (levodopa vs. dopamine agonist), treatment characteristics (whether dose levels have ever been increased and frequency of medication administration), duration of treatment usage, years since RLS diagnosis, comorbid conditions, reported severity and impact of RLS pre-treatment, and alcohol and tobacco use. Variables used to classify subjects as having highly suggestive or definite augmentation were excluded from the analysis. Patient-reported outcomes while on treatment were also excluded from the analysis, as these are likely a direct result of augmentation.

A logistic regression analysis evaluated the relationship between the duration of dopaminergic treatment and the probability of augmentation for those patients reporting definite/highly suggestive augmentation.

3. Results

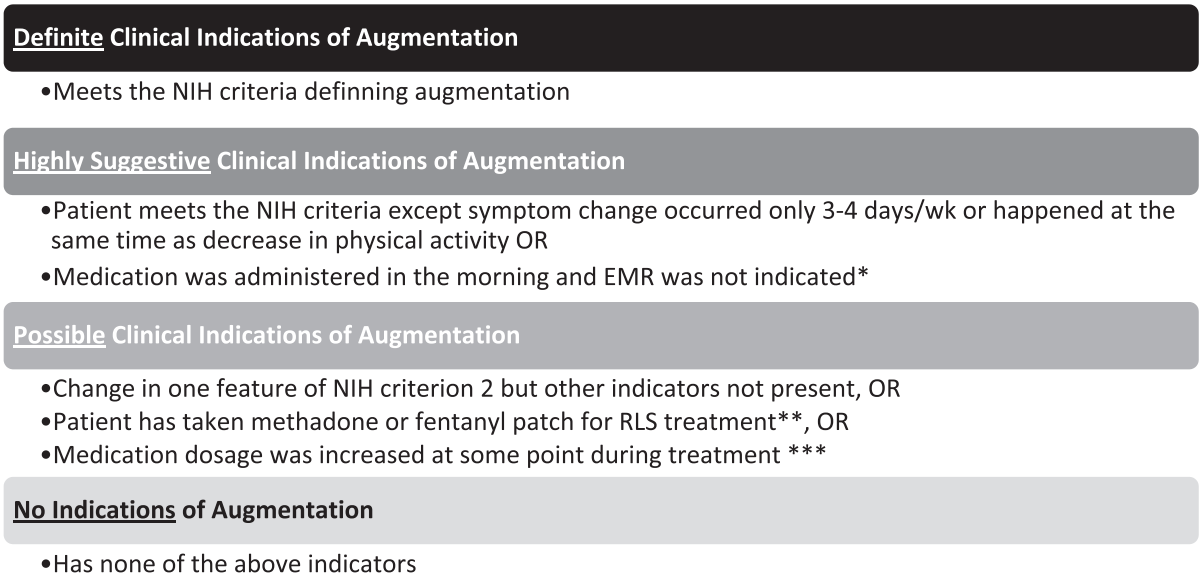
3.1. RLS patient and treatment profile

The 266 subjects who participated were predominantly female (66%) and Caucasian (85%) with a mean age of 58 years (SD: 13.1) (Table 1), somewhat older than the average for RLS sufferers in general [11]. Most (71%) completed at least some college and half (56%) reported a gross income between $35,000 and $99,999. Forty percent of subjects were employed full time, 25% were retired and 7% were unemployed due to disability or illness. Respondents were distributed throughout the United States. Primary RLS treatments used include ropinirole (57%), pramipexole (34%), carbidopa/levodopa (8%), and pergolide (1%). A majority (61%) was quite satisfied with their current treatment.

3.2. Rates of augmentation

Among the total sample on dopaminergic treatment for an average ± SD of 2.7 ± 2.4 years, 11 subjects (4.1%) met the NIH criteria for augmentation without any indication of other factors contributing to the change in RLS symptoms (Fig. 3). Another 5% met NIH augmentation criteria with minor exceptions (i.e., change in symptoms only occurred 3–4 days per week or was accompanied with a significant decrease in physical activity). A sizeable proportion of subjects (23%) met NIH augmentation criteria but major exceptions were present: the symptom change occurred for less than 1 week, fewer than 3–4 days per week, or there were other medical, behavioral or pharmacological factors present (e.g., current diagnosis of anemia or commencement of SSRI usage). Finally, 21% of subjects met only part of NIH Criterion 2 – only one change in the nature of symptoms was present. Treatment adjustments indicative of a physician response to possible augmentation of RLS symptoms were present at the following rates: morning dosing of dopaminergic treatment without signs of early morning rebound (14%), concomitant RLS treatment with methadone or a fentanyl transdermal patch (6%), and increase in the dose of dopaminergic treatment at any time during treatment (53%).

The likelihood of augmentation classification placed subjects into each of the following groups: Definitive Clinical Indications of Augmentation (4%), Highly Suggestive Clinical Indications of Augmentation (16%) or Possible Clinical Indications of Augmentation (56%). Twenty-four percent had no clinical indications of augmentation (Fig. 3). Classification rates varied by current medication type: current levodopa users were most likely to exhibit highly suggestive or definite clinical indications of augmentation, while pramipexole users were least likely to exhibit highly or definite indications of augmentation (Fig. 4).



Footnotes to Figure2

*Subjects who did not meet criteria for Early Morning Rebound (EMR) but who reported morning administration of their dopaminergic treatment were classified into the highly suggestive group, the rationale being that morning dosing would indicate a treatment response to symptom onset occurring earlier than usual. EMR is a differential diagnosis based on symptoms starting in the first part of the morning after final awakening followed by a symptom-free period later in the morning or afternoon.

**Subjects reporting use of methadone or a fentanyl transdermal patch to treat their RLS were classified as having possible indications of augmentation because these treatments are prescribed as an add-on to dopaminergic treatment when the RLS symptoms have progressed during treatment to become intense, even painful, a characteristic of severe augmentation. Note that subjects with neuropathy were excluded to avoid possible use of the same medication to treat both RLS and neuropathic pain.

***Subjects reporting a dosage increase at any point on treatment were also classified as having possible indications, as an increase in medication dose is a viable response to worsening RLS symptoms with augmentation or tolerance. Tolerance is associated with development of augmentation [6].

Fig. 2. Augmentation classification system.

Subjects enrolled in the study were far more likely to meet Criterion 2 of the NIH criteria than Criterion 1 of earlier onset (30% met Criterion 2 and 5% met Criterion 1). Four subjects (2%) reported earlier onset of symptoms (Criterion 1) without changes in the nature of symptoms (Criterion 2). Among those subjects who met Criterion 2, the proportions reporting each type of symptom change were as follows: symptoms beginning more quickly at rest (79%), shorter duration of treatment effect (71%), increased or new leg cramping or jerking (53%), symptoms spreading to different parts of the body (e.g., arms) (46%), symptoms worsening with dose increase or lessening with dose decrease (30%).

At least one medical, pharmacologic or behavioral change that could exacerbate RLS and thus mimic augmentation was present in 18% of patients overall and in 58% of subjects who met NIH Criteria for augmentation. Rates for each factor at the time of suspected augmentation were as follows: significant decrease in physical activity (33.3%), antihistamine use (22.6%), SSRI use (17.9%), iron deficiency diagnosis (17.9%), SSNRI use (9.5%), frequent blood donations (8.3%), substantial blood loss (6.0%). Per NIH criteria, presence of any medication, pharmacologic or behavioral change that could cause augmentation resulted in the conservative exclusion of these patients from the "definite" clinical indicators of augmentation group because it is unclear whether their symptom change was brought on by the dopaminergic treatment or one of these other factors.

Demographic characteristics were generally consistent between subjects with highly suggestive or definite augmentation of RLS symptoms and no augmentation (Table 1). One exception was age: highly suggestive/definite augmenters were significantly older than non-augmenters (61.4 years, SD: 13.0 vs. 56.0 years, SD: 13.9, $p < 0.05$). Highly suggestive/definite augmenters also reported a significantly longer time since RLS diagnosis than those

Table 1
Subject characteristics overall and by augmentation likelihood.

	Total subjects (n = 266)	Definite/highly suggestive clinical indicators (n = 54)(A)	Possible clinical indicators (n = 148)(B)	No clinical indicators (n = 64) (C)
Gender (% female)	66%	63%	69%	63%
Age in years – mean (SD)	57.6 (13.1)	61.4 (13.0)[BC]	56.9 (12.7)	56.0 (13.9)
Hispanic	3%	0%	3%	5%
Race				
Caucasian	85%	85%	88%	78%
Black or African American	3%	7%[B]	1%	5%
Other	5%	2%	6%	8%
Decline to answer	6%	6%	5%	8%
Years since RLS symptom onset – mean (SD)	9.6 (12.0)	8.6 (12.7)	11.9 (12.9)[C]	5.1 (6.7)
Years since RLS diagnosis – mean (SD)	4.3 (5.1)	4.0 (4.4)[C]	5.4 (6.0)[C]	2.2 (1.9)
Current physician primarily responsible for managing RLS				
Neurologist	32%	41%[C]	38%[C]	13%
Primary care physician (Family practitioner/ internist/general practitioner)	66%	56%	62%	86%[AB]
Sleep specialist	4%	6%	5%	3%
Other	1%	0%	2%	0%
*Current primary RLS treatment***				
Ropinirole	57%	67%	51%	61%
Pramipexole	34%	19%	39%[A]	34%
Levodopa	8%	13%[C]	9%	3%
Frequency of medication administration				
Once daily	67%	30%	69%[A]	95%[AB]
More than once per day	27%	67%[BC]	24%[C]	0%
As needed	5%	4%	6%	5%
Increase in medication dosage *	53	59[C]	74%[AC]	0%
Duration of current primary treatment in years – mean (SD)	2.7 (2.4)	2.9 (2.3)[C]	2.9 (2.0)[C]	1.7 (1.2)
Switched from another DA to current therapy	37%	37%	40%	30%

A/B/C denotes significance testing at 95% CI compared to the column indicated by the letter.
* Note: This variable is included in the augmentation likelihood determination.
** Pergolide use curtailed during this study time by FDA action and availability, the number of patients on pergolide were too few to provide meaningful analyses.

with no indicators of augmentation (4.0 years, SD: 4.4 vs. 2.2 years, SD: 1.9, $p < 0.05$). Overall, subjects reported 4.3 years (SD: 5.1) since RLS diagnosis.

RLS treatment characteristics substantially differed between these two groups (Table 1). Highly suggestive/definite augmenters were significantly more likely to visit a neurologist for their RLS than their non-augmenter counterparts (41% vs. 13%). Those with no indication for augmentation (non-augmentors) were significantly more likely to be currently managed by a PCP (86% vs. 13%). Treatment usage varied significantly, with highly suggestive/definite augmenters reporting greater use of levodopa (13% vs. 3%) and a greater likelihood of split dosing (67% vs. 0%) than non-augmenters. Notably, there was no significant difference between the two groups in terms of likelihood of having switched from another dopamine treatment; however, highly suggestive/definite augmenters were significantly less satisfied with their current RLS treatment than non-augmenters.

3.3. Factors associated with augmentation likelihood

A discriminant analysis was conducted to identify factors significantly associated with no augmentation vs. those with highly suggestive or definite augmentation. For the purposes of this analysis, the definite and highly suggestive groups were combined into one group. The possible group was excluded from the analysis, as the likelihood for presence or absence of augmentation could not be determined. The model developed from this analysis correctly classified the subjects into the no augmentation or highly suggestive/definite augmentation groups for 84.7% of the cases.

Within-group correlations between each variable and the two discriminant functions are outlined in Table 2. Based on the variable coefficients, presence of augmentation is significantly associated with 6 factors. One of these was judged to reflect response to augmentation, i.e., administration of dopaminergic treatment more than once per day. Five factors were considered likely to reflect increased risk of developing augmentation, i.e., more frequent RLS symptoms pre-treatment, greater discomfort with RLS symptoms before treatment, comorbid asthma, older age, and longer treatment duration ($p < 0.05$).

3.4. Effect of duration of dopaminergic treatment on occurrence of augmentation

The logistic regression of occurrence of augmentation vs. the total years of dopaminergic treatment (Fig. 5) showed a significant regression, with a reduction in log likelihood of 9.56%. Accuracy of predicting both augmentation groups was between 70% and 75%. The logistic regression indicated the risk of augmentation was about the same–8% each year–for any duration of treatment up to about 8 years, at which point there is a suggestion of decreased risk. Actual frequencies support the finding that augmentation likelihood increases with increased treatment duration. Fig. 6 shows that the incidence of no augmentation drops from 37% for subjects on treatment less than 2.5 years to 11% among those on treatment for more than 6.5 years.

3.5. Comparison of outcomes between augmenters and non-augmenters

Patient-reported outcomes varied significantly and linearly by likelihood of augmentation. Subjects reporting definite or highly suggestive clinical indicators of augmentation had consistently

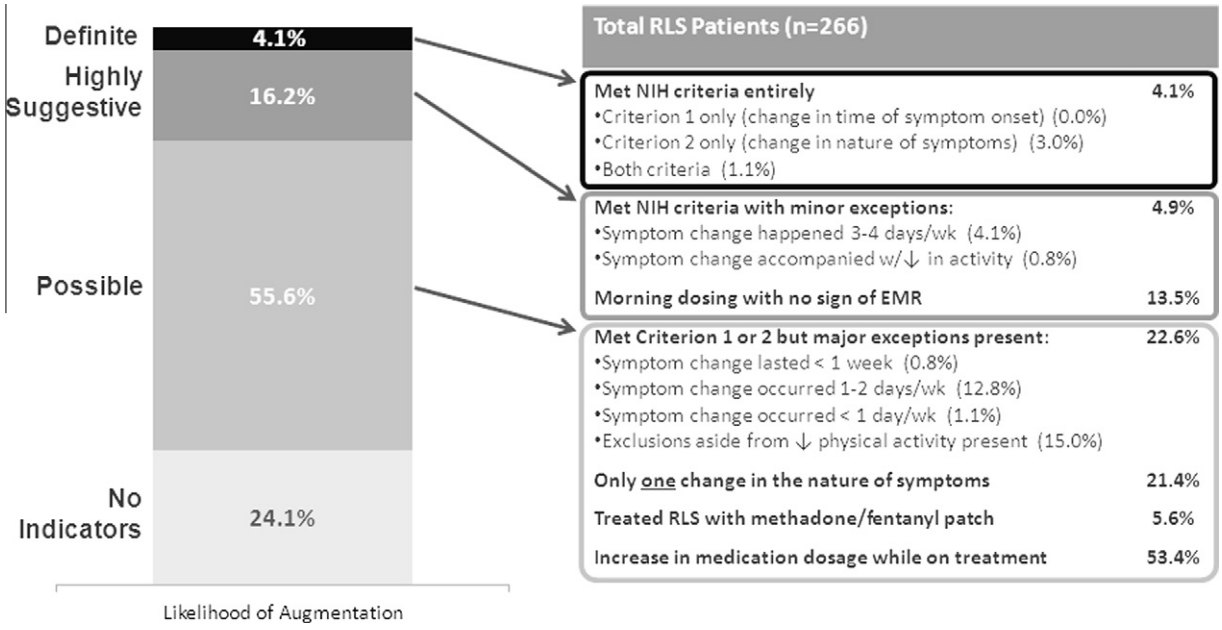


Fig. 3. Clinical indicators of augmentation and augmentation likelihood classification.

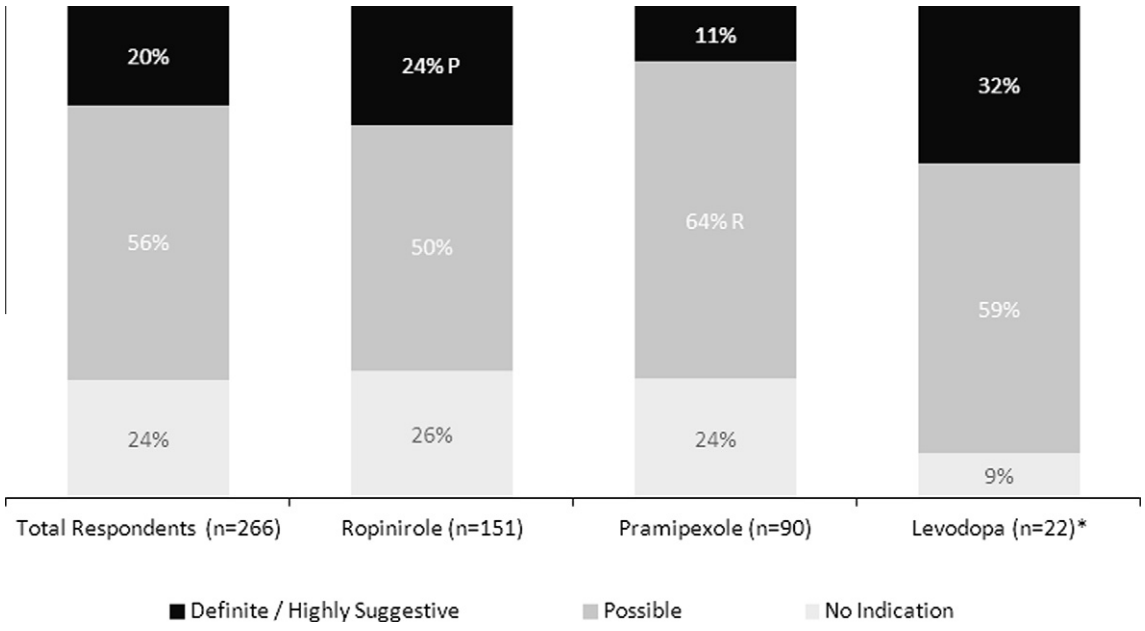


Fig. 4. Augmentation rates by current treatment.

worse outcomes: they were least satisfied with their RLS medication and they reported on their treatment the most severe current RLS symptoms (by IRLS total score), the greatest quality of life impact due to RLS (RLS-QOL summary score) and the most negative sleep status (MOS Sleep Problems Index II). Subjects with no indicators of augmentation scored the best on all outcome measures, while those with possible indicators scored in the middle (Table 3).

4. Discussion

To our knowledge, this is the first published study to attempt to detect symptoms indicating RLS augmentation using a patient-reported self-assessment during actual clinical care in a large sample of patients from multiple medical practices. Recent studies and clinical trials evaluating augmentation, such as Frauscher et al. [12], Högl et al. [4], Trenkwalder et al. [14], Winkelman & Johnston [6], Silber et al. [5], Oertel et al. [13] and Ondo et al. [15] relied on clinical interviews or clinician assessments of patient medical charts either in a controlled clinical study or from a single medical practice. In this study RLS experts identified, before collecting any data, symptoms highly suggestive of augmentation that could be reported by a patient on a questionnaire. The high rate in our population of these symptoms highly suggestive of augmentation could be seen as indicating that the NIH criteria lack sensitivity for diagnosing augmentation, particularly when given as a self-administered survey.

Due to the variation in study designs and augmentation assessment criteria, it is difficult to make a direct comparison between

Table 2
Model for factors associated with augmentation.

Functions at group centroids	Function 1
No augmentation	−1.06
Highly suggestive or definite augmentation	1.25
Significant variables ($p < 0.05$)	Discriminant function coefficients
Frequency of medication administration >1 day**	0.807
Greater pre-treatment frequency of RLS symptoms	0.430
Greater discomfort from RLS symptoms prior to treatment	0.419
Comorbid asthma	0.406
Older age	0.289
Total dopaminergic treatment duration for RLS	0.132

** These items were considered likely to indicate response to developing augmentation rather than risk factor for producing augmentation.

the augmentation rates found in this study and other rates reported in the literature. However, patients classified in this study as having definite or highly suggestive clinical indicators of augmentation displayed the primary characteristics of augmentation experiencing either a worsening in the nature of symptoms or a symptom onset earlier in the day (or morning dosing indicating an earlier onset) or both. This study found that 24% of ropinirole users, 11% of pramipexole users and 32% of levodopa users exhibited definite or highly suggestive clinical indicators of augmentation. The 24% rate for ropinirole users is substantially higher than the 3% previously reported by Montplaisir et al. [16]; though that study did not directly seek to assess prevalence of augmentation and collected only spontaneous reports. The 11% rate for pramipexole is lower than the rates of 33% and 32% reported by Silber et al. [5] and Winkelman & Johnston [6], respectively. The rate is slightly higher than the 8.3% found by Ferini-Strambi [17], though the duration of that study was shorter (6 months), reducing augmentation prevalence. Finally, our augmentation rate of 32% for levodopa users was considerably lower than the rate of 73% reported by Allen and Earley [1] or the 60% found by Högl et al. [4]. It is, however, more in line with the rate of 24% found by Trenkwalder et al. [14].

Differences also emerged between this study and other published research on the type of augmentation reported. Subjects who completed this survey were substantially more likely to meet Criterion 2 of the NIH criteria for augmentation diagnosis and few (5% of all subjects) reported symptom onset of 2 or more hours earlier than baseline (Criterion 1). Other studies indicate that the latter–a change in time of symptom onset–is the more common manifestation of augmentation. Earlier onset occurred in 100% of the augmentation sufferers evaluated by Allen & Earley [1] and 48% of augmentation patients studied by Ondo et al. [15]. In this study, however, the dose of medication was both increased for 53% and given earlier in the day for 27% of the patients. These actions would be the expected response to an earlier onset of symptoms during treatment and were thus included in assessment of augmentation likelihood. The earlier onset of symptoms was probably obscured in clinical practice by dose timing changes, but this would have less effect on the other symptoms of augmentation.

This study provides an evaluation of a wide sample of RLS patients for medical practices across the United States, but there was likely some bias introduced into this process that reduces the degree to which this represents the overall population of RLS patients treated with dopaminergics. The doctors and the patients who participated in the survey are potentially biased toward situations where the RLS is more severe and therefore more noticeable. The retrospective self-report may also increase reporting of the more extreme and memorable symptoms. However, the retrospective, patient-reported nature of this study also has the advantage of obtaining direct patient reports over a wide range of treatment conditions and durations. The study did not attempt to detect changes in the time medications were taken. It is possible that physicians managing these patients were sensitive to changes in their patients' symptoms and instructed patients to change time of medication administration or dosage levels to minimize effects of earlier onset of RLS. The frequency of dosage increases (53%) and split dosing (27%) supports this hypothesis.

Prior studies have sought to determine likely causes or risk factors for augmentation [6,12,15,17]. Consensus has been reached on a few factors known to mimic treatment-related augmentation, including SSRI or SNRI use, antihistamine use and iron deficiency (either a result of anemia or substantial blood loss). Therefore, any patients reporting these factors were excluded from the "definite" augmentation category [2,3,18]. Aside from these extrinsic factors, such as contraindicated medications or iron deficiency, data on risk factors of augmentation are not definitive, though some patterns have emerged in the literature [1,4]. The current study found both frequency and degree of discomfort of pre-treatment RLS symptoms increased risk of RLS augmentation, which is consistent with findings by Allen & Earley [1], who determined that more severe baseline RLS sufferers were at higher risk of experiencing augmentation while on treatment. Older age is associated with decreasing dopaminergic function that may increase the risk of augmentation. The longer duration of dopamine treatment probably indicates chronic persistent dopamine stimulation plays a role in altering the dopaminergic system. In this respect the neurobiological changes producing augmentation may have a slow progressive course. If so, there may be early clinical signs of this process that would allow early detection and treatment. It may be, in the future, possible to identify early signs of augmentation. The effect of comorbid asthma increasing the risk of RLS remains somewhat puzzling. A prior study found 4 times more RLS patients than controls used asthma medications [19]. The relationship between asthma and RLS remains unknown, but one interesting factor is the increased risk of childhood asthma reported with anemia [20]. It maybe that the increased comorbid asthma occurs with some chronic iron deficiency and that, as has been previously reported [21], increases the risk of augmentation.

Perhaps the most important clinical finding is the link between longer treatment duration and augmentation as has been previously reported [4,18]. The logistic regression for duration of treatment effects showed augmentation occurred at about the same rate for patients at each of the durations of treatment for at least 8 years. These results match those from a 10-year follow up of patients in one clinic that also showed continuing occurrence of augmentation at about the same rate for at least 7 years [7]. Thus the risk of augmentation continues over the first several years of dopaminergic treatment. It may be that dopaminergic treatment serves a patient well for several years before the augmentation becomes a problem but that eventually it will be a problem for many if not most RLS patients.

While debate remains on the prevalence rate and specific risk factors of augmentation, the potential for symptom augmentation to negatively impact patient outcomes is well documented [2,12] and further supported by findings in this study. Patients in this study presenting with definitive or highly suggestive clinical indicators of augmentation were least satisfied with their treatment, reported the most severe RLS symptoms, experienced the greatest degree of sleep disturbance and suffered the most substantial reduction in quality of life due to RLS.

The high IRLS total scores on treatment reported in this study deserve note. It is generally felt that almost all patients show a good response to dopaminergic treatment. In this population, that appears to be true for only the 24% who had no indications of

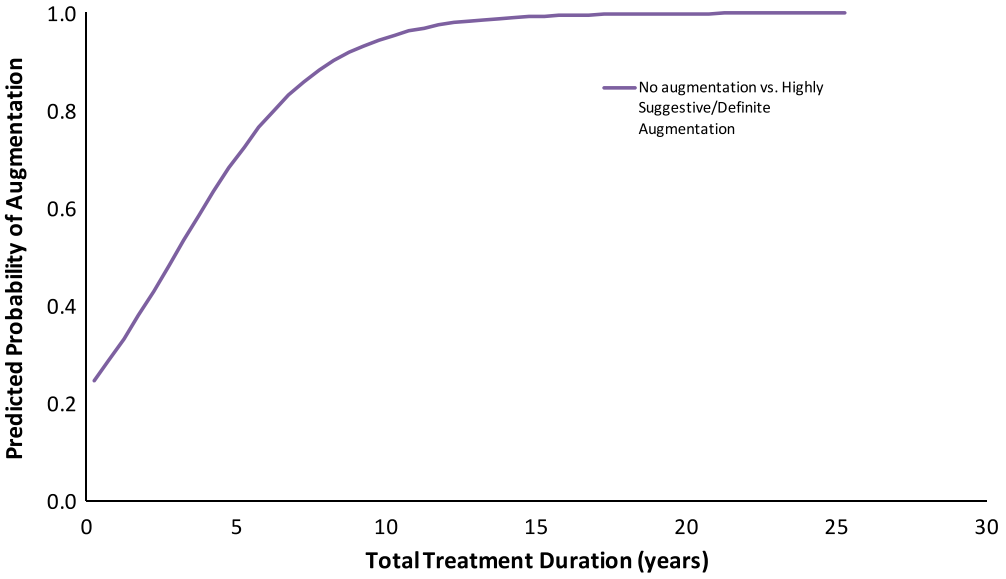


Fig. 5. Logistic regression relating total treatment duration to probability of augmentation. The risk of augmentation was about the same for any duration of treatment up to about 8 years, at which point there is a suggestion of decreased risk.

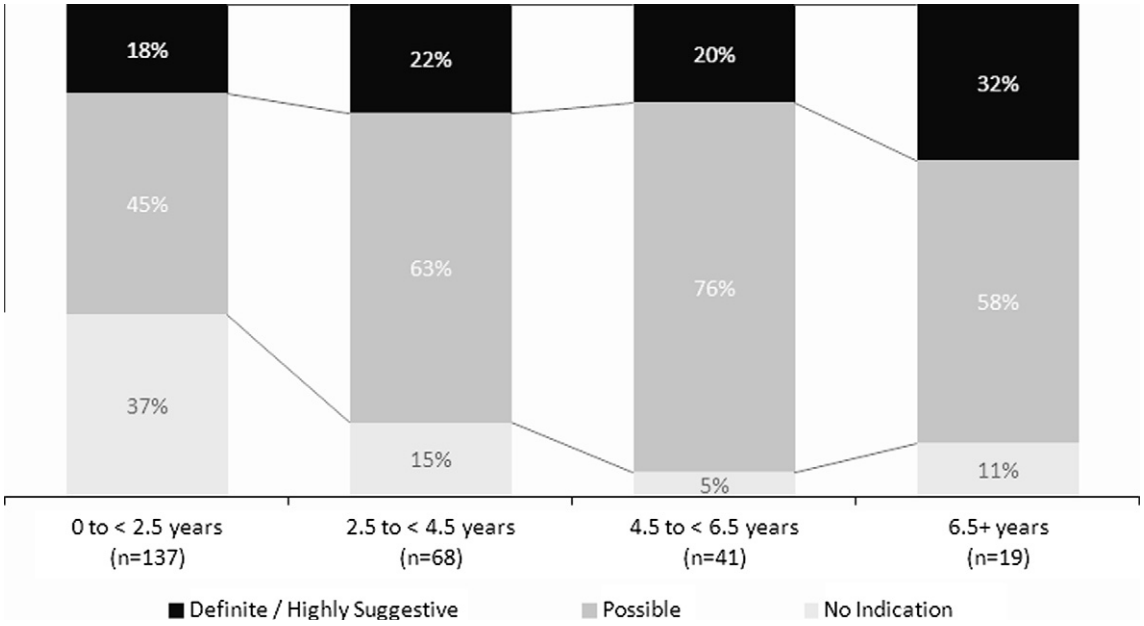


Fig. 6. Augmentation group frequency by total treatment duration.

Table 3
Comparison of treatment satisfaction and patient reported outcomes by augmentation likelihood.

	Total subjects (n = 266)	Definite/highly suggestive clinical indicators (n = 54)	Possible clinical indicators (n = 148)	No clinical indicators (n = 64)
Treatment satisfaction mean (SD)	4.6 (1.4)	4.0 (1.3)	4.6 (1.4)[A]	5.3 (1.1)[AB]
RLS-QOL summary score mean (SD)	77.5 (17.9)	63.9 (20.8)	76.9 (15.5)[A]	90.1 (10.6)[AB]
IRLS summary score mean (SD)	18.2 (9.2)	23.6 (8.4)	18.9 (8.8)[A]	12.0 (7.3)[AB]
Sleep problems index II mean (SD)	33.8 (18.5)	44.9 (18.6)	34.0 (18.2)[A]	24.1 (13.0)[AB]

augmentation. They had an average IRLS of 12, below the usual standard of 15, considered a score indicating need for medication treatment in a clinical trial [16,22]. The groups with indications for augmentation in contrast showed inadequate therapeutic responses with IRLS scores on treatment of 19 (moderate symptoms) for possible augmentation and 24 (severe symptoms) for definite or highly suggestive augmentation. These results suggest that only about one-quarter of the patients in this study are free from the treatment emergent complications associated with augmentation. The other 76% of all patients followed on dopaminergic treatment

showed signs of loss of treatment efficacy if not actual indications for developing augmentation.

5. Conclusions

This study highlights the importance of carefully screening patients for changes in RLS symptoms indicating augmentation for as long as they are on dopaminergic treatment. As findings from this and other studies indicate, physicians should pay close attention to those patients who present with the most severe RLS symptoms prior to treatment initiation. While these patients may require aggressive treatment, they are also likely to be at the highest risk for developing augmentation as a result of that treatment. With 73% of subjects in this study showing at least one possible sign of augmentation, it is important for physicians to recognize the potential for augmentation of RLS symptoms to develop. It can occur at any time even after several years of satisfactory treatment with dopaminergic agents.

Finally, this study provides a framework for a patient-reported assessment of symptoms indicating augmentation, but additional research is warranted to further refine and validate this approach. It maybe possible to develop a patient reported tool for early detection of symptoms of augmentation encouraging earlier intervention to avoid developing its more severe adverse consequences. Since augmentation appears to occur for most patients on dopaminergic medication, there is a compelling need to either learn how to avoid augmentation or to develop well-evaluated non-dopaminergic treatment alternatives for RLS.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2011.03.003.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.sleep.2011.03.003.

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