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Original Article

Restless legs syndrome severity in the National RLS Opioid Registry during the COVID-19 pandemic☆

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ABSTRACT

Objective/background: No research has yet assessed the impact of the coronavirus disease 2019 (COVID-19) pandemic on restless legs syndrome (RLS). We hypothesized that RLS symptom severity would be increased during the COVID-19 pandemic in a sample of patients with diagnosed RLS.

Patients/methods: The National RLS Opioid Registry is a longitudinal observational study of patients using opioid medications for treatment of RLS. Questionnaires assessing RLS symptom severity, medication dosages, sleep disturbance, depression, and anxiety are administered at baseline and at recurring 6-month surveys. Survey responses from the outset of the pandemic in April/May 2020 were compared to responses completed by other participants in January/February 2020 (between-subjects analysis), as well as responses by the same participants at baseline, approximately six months later in September 2020 through February 2021, and approximately one year later in March through June 2021 (within-subjects analyses).

Results: These analyses provide evidence for higher RLS symptom severity scores at the outset of the COVID-19 pandemic in the US. Symptom severity scores were still elevated on subsequent questionnaires completed over six months into the pandemic but had returned towards baseline by the spring of 2021. Participants with increases in RLS severity were significantly more likely than others to see increases in sleep disturbance, depression, and anxiety.

Conclusions: This is the first study demonstrating increased RLS symptom severity during the earliest stage of the COVID-19 pandemic. These findings warrant similar investigations in other patient populations and suggest that clinicians should attend to RLS symptoms during times of socioeconomic and/or political uncertainty.

1. Introduction

Restless legs syndrome (RLS) is a sensory-motor neurological disorder characterized by an irresistible urge to move the legs and leg discomfort [1]. The leg sensations and discomfort associated with RLS lead to high levels of sleep disturbance, daytime somnolence, and emotional distress among sufferers. Sufferers experience high levels of depressive and anxiety symptoms, as well as high rates of major depressive disorder, generalized anxiety disorder, and panic disorder [2–5]. Clinically significant RLS is thought to be present in roughly three percent of the population [6].

The coronavirus disease 2019 (COVID-19) pandemic has had a massive impact on mental health. Cross-sectional studies conducted throughout the world have provided evidence of high levels of depression, anxiety, and psychological distress during the global outbreak [7–9]. Considering the link between RLS and psychiatric illness, it has been speculated that there may have been increases in RLS symptom severity alongside the recent rise in depression and anxiety [10]. However, no studies to date have investigated the link between COVID-19 and RLS.

The National RLS Opioid Registry (or RLS Registry) is a longitudinal observational study following 500 participants who use opioid medications for the treatment of RLS. In the present study, we investigated the levels of RLS symptom severity reported by RLS Registry participants before and during the COVID-19 pandemic.

2. Methods

The National Restless Legs Syndrome Opioid Registry is a longitudinal observational study following 500 individuals using opioid medications to treat RLS [11]. Participants were recruited

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between December 2017 and September 2019 through the Restless Legs Syndrome Foundation and treating RLS providers nationally. Eligible patients were taking an opioid medication daily to treat diagnosed RLS and had a previous therapeutic response to a dopamine agonist medication. All participants provided verbal informed consent, and this study was approved by the Mass General Brigham Institutional Review Board.

At baseline, all participants took part in a 45-min phone interview with a trained research coordinator where their RLS diagnosis was confirmed using the Hopkins Telephone Diagnostic Interview [12]. Participants also completed an extensive online survey using Research Electronic Data Capture (REDCap). The baseline interview and online survey included questionnaires relating to demographics, opioid types and dosages, and opioid use abuse risk factors. Participants were administered several validated questionnaires including the International Restless Legs Syndrome Study Group severity scale (IRLS) [13], the Insomnia Severity Index (ISI) [14], the General Anxiety Disorder-7 scale (GAD-7) [15], and the Patient Health Questionnaire (PHQ-9) [16].

At 6-month intervals following completion of the baseline interview and survey, participants were emailed links to surveys which they completed online via REDCap. These follow-up surveys included many of the same questionnaires administered at baseline, as well as questionnaires on RLS medication changes and health changes. In cases where responses where unclear, a study coordinator contacted the participant for clarification. At the time of the data analysis, 480 participants had completed 6-month surveys, 467 participants had completed 1-year surveys, 460 participants had completed 1.5-year surveys, 423 had completed 2-year surveys, 316 had completed 2.5-year surveys, and 195 had completed 3-year surveys.

The current analysis focused on participants' IRLS, ISI, PHQ-9, and GAD-7 scores. IRLS increases of 3 or more points were defined as clinically significant [17]. The four questionnaires were assessed on a continuous scale unless noted otherwise. Items 3 and 8 on the PHQ-9 (insomnia and psychomotor agitation items) and items 4 and 5 (“trouble relaxing”, “restless”) on the GAD-7 were removed for some of the analyses (as indicated in the Results section) as these closely relate to questions asked on the IRLS and ISI. All significant values reported are two-sided and were calculated using the Prism GraphPad 8 software (Version 8.4.1).

The between-subjects analysis focused on the subset of RLS Registry participants who completed surveys in January, February, April, and May 2020. These participants were divided into pre-COVID (January and February 2020) and early COVID (April and May 2020) groups. Depending on when a given participant was enrolled in the RLS Registry, the survey was either a 6-month, 1-year, 1.5-year, or 2-year follow-up assessment. Statistical analyses included Mann–Whitney U tests and Chi-square tests.

In the within-subjects analysis, April and May 2020 follow-up surveys were compared with those participants' baseline surveys. These baseline surveys were also compared to subsequent 6-month surveys, which were completed between September 2020 and February 2021, and to the next iteration of follow-up surveys, which were completed between March and June 2021. January and February 2020 surveys were also compared to subsequent 6-month surveys, which were completed between May and October 2020, and to the next round, which were completed between November 2020 and March 2021. Statistical analyses included Wilcoxon signed-rank tests and Chi-square tests. All correlations were Spearman's correlations.

Logistic regression was performed to identify factors associated with IRLS score increases from baseline to April and May 2020. Independent variables assessed were socio-demographic measures, physical and psychological health characteristics, as well as baseline questionnaire values. Additionally, participant state was included to assess whether geography and associated COVID-19 restrictions were related to increases in IRLS scores. In this regard, participants were characterized as living in a state with many early COVID-19 restrictions or not. Such states were defined based on a list reported by Becker's Hospital Review which ranked the states with the most restrictions in spring 2020, the time that the follow-up surveys of interest were completed: Illinois, Rhode Island, District of Columbia, Massachusetts, Vermont, Hawaii, Washington, New Mexico, New York, and Michigan [18]. The logistic regression analysis was performed using a forward selection method with a threshold of $p < 0.1$, and both age and sex were controlled for. In the regression model, multicollinearity of all covariates was found to be at an acceptable level (variance inflation factors were all <1.2).

Bar graphs were created in Prism GraphPad, and the correlation plot was created using the corrplot package on R (Version 4.1.0).

3. Results

3.1. Between-subjects analysis

We based our analysis on the time of the outbreak in the United States, as nearly all RLS Registry participants reside in this country (98%). We compared surveys completed two months before with those two months after March 2020, the month when the COVID-19 outbreak was declared a national emergency in the US. A total of 153 participants completed surveys during January and February 2020, and 155 completed surveys during April and May 2020. Participants in both groups had been in the RLS Registry for an average of 1.5 years at the time of completion. There were no significant differences between the two groups in terms of baseline characteristics or questionnaire scores except for a slight difference in age (January/February 2020 = 65 years, April/May 2020 = 67 years).

Table 1 compares questionnaire scores for the two groups. The early COVID responses had significantly higher scores on the IRLS and were nearly twice as likely to have an IRLS score of 20 or above (37.7% vs 20.9%; $p < 0.01$) (Fig. 1). ISI and GAD-7 scores demonstrated trend significant differences between the two groups.

3.2. Within-subjects analysis

During early COVID in April and May 2020, IRLS scores were substantially higher than those same participants' baseline values from 6 to 24 months before (Table 2). Over half of participants (51.3%) had an increased IRLS score in spring 2020, and 87.3% of these increasers had a clinically significant elevation. In early COVID, participants were significantly more likely to have an IRLS

Table 1
Comparing surveys completed in January and February 2020 (pre-COVID) to surveys completed in April and May 2020 (early COVID).

	January/February 2020 (n = 153)		April/May 2020 (n = 155)		P-value
	Mean (SD)	Median	Mean (SD)	Median	
IRLS	12.5 (8.8)	12	15.3 (9.4)	15*	**0.007**
ISI	9.7 (6.1)	10	10.8 (6.1)	11	0.10
PHQ-9	4.5 (4.6)	3**	4.6 (3.7)	4	0.27
GAD-7	2.6 (3.2)	2**	2.9 (2.7)	3	0.10

IRLS = International Restless Legs Syndrome Study Group severity scale; ISI = Insomnia Severity Index; PHQ-9 = Patient Health Questionnaire; GAD-7 = General Anxiety Disorder-7 scale. Potentially confounding questions were removed from the PHQ-9 and GAD-7. Bold p-value denotes statistical significance at the $p \leq 0.05$ level. *n = 154, **n = 150.

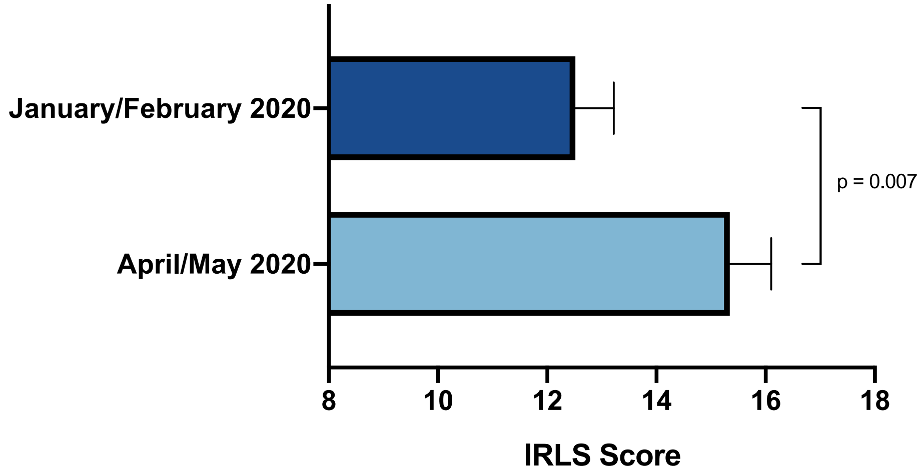

Fig. 1. Title: Between-subjects analysis: Comparing January/February 2020 (n = 153) and April/May 2020 (n = 155) IRLS scores. Caption: IRLS = International Restless Legs Syndrome Study Group severity scale. Error bars represent standard error of the mean. The displayed p-value is from a Mann–Whitney U test.

score of 20 or above (37.7% vs 26.6%; p = 0.04) than at baseline. Participants were also significantly less likely to have no RLS symptoms (as indicated by an IRLS score of 0) in the spring of 2020 (10.4% vs 20.8%; p = 0.01). Item analysis revealed significant increases on the following questions: #4 (Sleep disturbance due to RLS; p = 0.05), #5 (Tiredness during the day due to RLS; p < 0.01), and #10 (Mood disturbance due to RLS; p < 0.01).

Logistic regression analysis revealed that IRLS increases from baseline to April and May 2020 were associated with well-controlled RLS at baseline (IRLS score of 15 or less) (OR 5.21, 2.52–11.28; p < 0.0001). Conversely, living in a state with many COVID-19 regulations was negatively associated with IRLS increases (OR 0.33, 0.12–0.84; p = 0.0237). There was a trend association between IRLS increases and lack of employment (either full-time or part-time) at baseline (OR 2.16, 0.97–4.95; p = 0.06).

Both PHQ-9 and GAD-7 scores were also higher during early COVID in April and May 2020 than at baseline. Significant increases were seen on PHQ items #1 (“Little interest or pleasure in doing things”; p = 0.04) and #7 (“Trouble concentrating on things, such as reading the newspaper or watching television”; p = 0.05) and on GAD items #1 (“Feeling nervous, anxious, or on edge”; p = 0.01), 2 (“Not being able to stop or control worrying”; p < 0.01), #3 (“Worrying too much about different things”; p = 0.02), and #7 (“Feeling afraid as if something awful might happen”; p < 0.01).

When comparing pre-COVID January and February 2020 participants' survey responses to their own baseline surveys, there was no change in the IRLS (both 12.5), or on the PHQ-9 or the GAD-7. In fact, there was a significant *decrease* in ISI scores from baseline to January/February 2020. These participants' January and February 2020 surveys were also compared to their own surveys completed during the pandemic both six months and one year later. No significant or trend changes in IRLS, ISI, PHQ-9, or GAD-7 were observed at these later time points.

Fig. 2 shows correlations between the IRLS, ISI, and modified PHQ and GAD questionnaires in terms of changes from participants' baseline scores to their early COVID April and May 2020 scores. Each correlation shown is statistically significant at the p ≤ 0.05 level. The relationship between IRLS and ISI changes was particularly strong: 57.0% of participants with IRLS increases also saw higher ISI scores, compared to just 22.7% of other participants (p < 0.01).

Early COVID April and May 2020 survey responses were also compared to subsequent surveys, which were completed between September 2020 and February 2021. At this later time point, IRLS scores were similar to the early COVID April and May 2020 values and still elevated compared to baseline (n = 149; mean = 15.5; p = 0.03). Modified PHQ-9 (n = 150; mean = 4.4; p = 0.06) and GAD-7 (n = 150; mean = 2.3; p < 0.01) scores were also still higher than at baseline. ISI values remained comparable to baseline (n = 150; mean = 10.8; p = 0.67).

On surveys completed by the same participants in the spring of 2021 (completed between March and June), IRLS scores were no longer elevated compared to baseline (n = 149; mean = 14.4; p = 0.16). Fig. 3 compares IRLS scores at various time points. Participants were also no longer more likely to have an IRLS score of 20 or above (28.2%; p = 0.70). However, scores on the modified PHQ-9 (n = 146; mean = 4.3; p = 0.04) and GAD-7 (n = 146; mean = 2.5; p < 0.01) were still higher in spring 2021 than at baseline.

Table 2
Comparing April and May 2020 surveys to baseline (n = 155).

	Baseline		April/May 2020		P-value
	Mean (SD)	Median	Mean (SD)	Median	
IRLS*	13.6 (9.7)	13	15.3 (9.4)	15	0.06
ISI	11.1 (6.7)	11	10.8 (6.1)	11	0.25
PHQ-9	3.9 (3.5)	3	4.6 (3.7)	4	**0.04**
GAD-7	1.9 (2.1)	1	2.9 (2.7)	3	**<0.01**

IRLS = International Restless Legs Syndrome Study Group severity scale; ISI = Insomnia Severity Index; PHQ-9 = Patient Health Questionnaire; GAD-7 = General Anxiety Disorder-7 scale. Potentially confounding questions were removed from the PHQ-9 and GAD-7. Bold p-values denote statistical significance at the p ≤ 0.05 level.
*n = 154.

4. Discussion

Both the between-subjects and within-subjects analyses show increased levels of RLS symptom severity in April and May of 2020 at the time of early COVID lockdowns. In the between-subjects analysis, the IRLS increase was nearly 3.0 points, which is considered the clinically significant threshold for clinical trial interventions [17]. To the best of our knowledge, this is the first study providing evidence of elevated RLS symptoms during the COVID-19 pandemic. These findings also showed that RLS severity

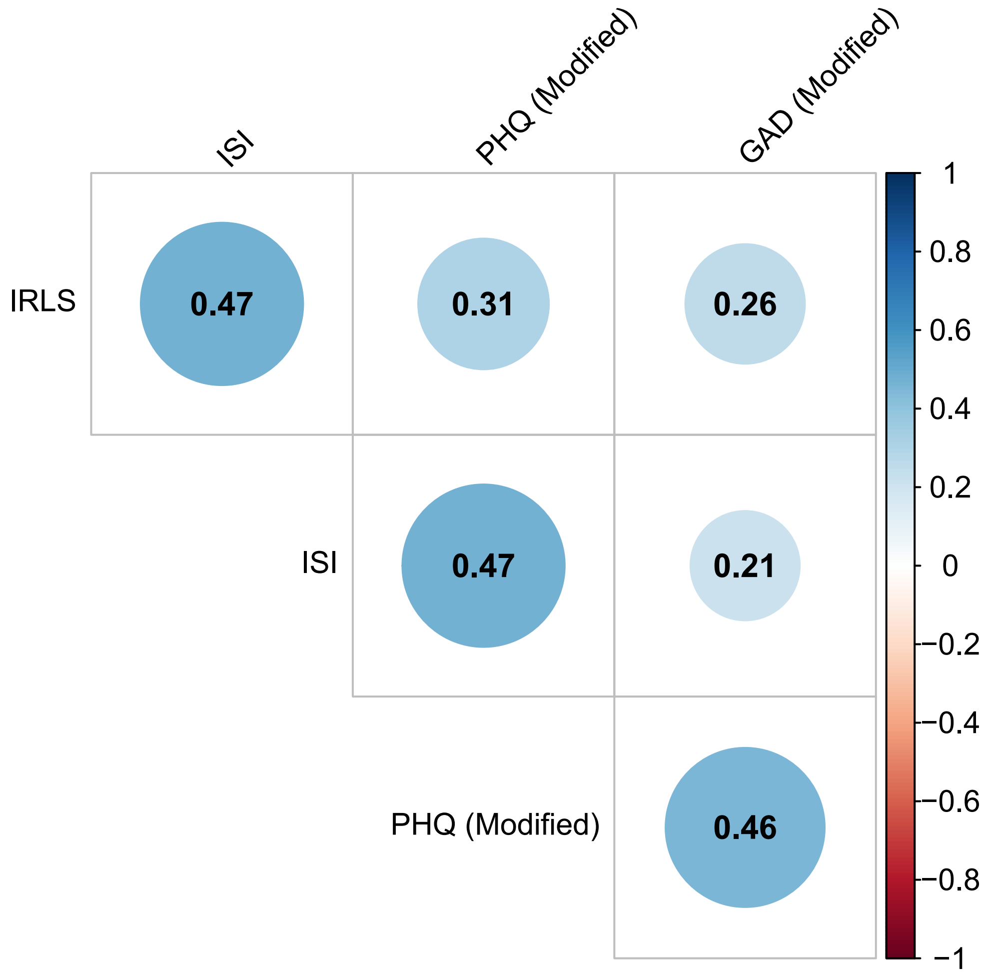

Fig. 2. Title: Correlations between the changes from baseline to April and May 2020 questionnaires (n = 154). Caption: IRLS = International Restless Legs Syndrome Study Group severity scale; ISI = Insomnia Severity Index; PHQ = Patient Health Questionnaire; GAD = General Anxiety Disorder-7 scale. All values shown are Spearman correlation coefficients. All correlations are statistically significant at the $p \leq 0.05$ level.

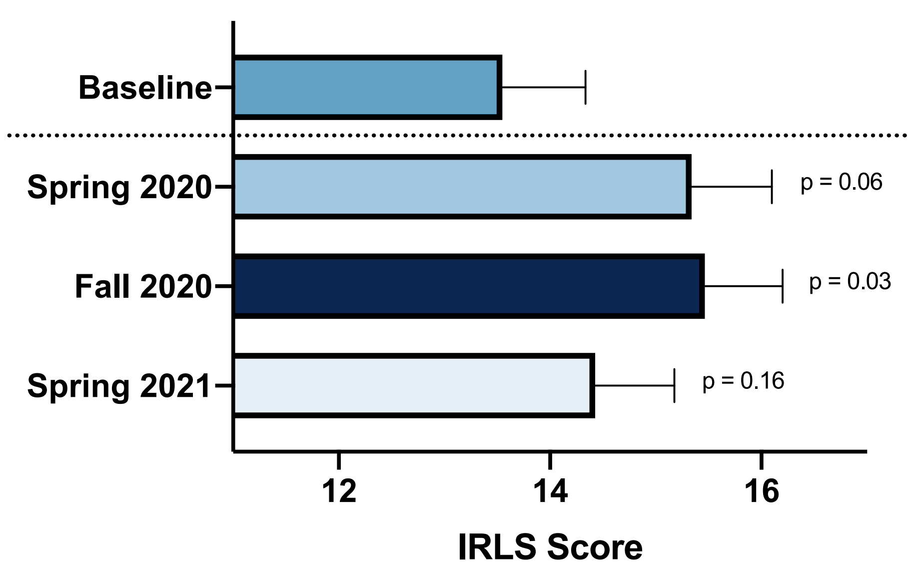

Fig. 3. Title: Within-subjects analysis: Comparing IRLS scores from baseline to various time points. Caption: IRLS = International Restless Legs Syndrome Study Group severity scale. Spring 2020 surveys (n = 154) were completed in April and May, Fall 2020 surveys (n = 149) were completed between September 2020 and February 2021, and Spring 2021 surveys (n = 149) were completed between March and June. Error bars represent standard error of the mean. The displayed p-values are from Wilcoxon signed-rank tests comparing baseline IRLS scores to IRLS scores at the given time point.

scores were still elevated compared to baseline over half of a year into the public health crisis in the United States.

IRLS scores were no longer significantly elevated in the spring of 2021, one year following the initial public health lockdown, suggesting that elevated RLS symptom severity levels may have subsided to some degree as COVID-19 infection rates dropped and public health restrictions were loosened. This finding is consistent with data showing that rates of anxiety and depression dropped during the first half of 2021 [19].

It seems unlikely that the higher IRLS scores seen during early COVID in April and May 2020 can be attributed solely to the passage of time since baseline, as no IRLS increase was seen when comparing pre-COVID January and February 2020 surveys, completed just 3 months earlier, to baseline values. Further against the notion that RLS severity increased over time is our previously published RLS Registry analysis showing no worsening of IRLS scores at 1-year [5], and more recent analysis showing no worsening at 2-years as well (unpublished data; presented at SLEEP 2021).

As this is an observational study, we are unable to definitively conclude that the COVID-19 pandemic caused this observed rise in RLS symptom severity. Numerous potentially stressful events, including the tumultuous 2020 United States presidential race, co-occurred with the COVID-19 pandemic and very well may have contributed to the observed rises in anxiety, sleep disturbance, and RLS symptoms. Similarly, the pandemic produced many social, economic, political, and lifestyle changes, and which of these could have been responsible for changes in RLS severity in our registry population is unknown. Given the geographic diversity of the Registry participants and of the evolving geographic distribution of infections within the US in 2020 and early 2021, it is noteworthy that these associations with the time period of early 2020 are so robust. These data also do not provide any insight into the effect of COVID-19 infection on RLS symptoms; this is a topic that should be investigated in future research.

During the COVID-19 pandemic, and especially during the early months, there were notable decreases in accessibility to primary and specialty care as well as a general fear of making use of medical care. Due to pre-existing opioid-related state legislation, most participants in the RLS Registry were required to meet with prescribers (either in-person or virtually) in order to receive monthly prescriptions and therefore still received care in the early months of the pandemic. However, it is plausible that the quality of this RLS care decreased during this period (e.g. due to transitions to virtual care), resulting in reduced treatment adjustments and thus worse RLS symptoms and IRLS scores. RLS Registry data on RLS medication changes during the pandemic is not yet available for analysis but will eventually provide some insight in this regard.

Notably, individuals who completed surveys in January and February 2020 did not see increases in RLS severity or other mental health questionnaire values on subsequent six-month surveys completed during the pandemic or on the following iteration of surveys 1 year later. We suspect that these findings may be at least partially related to the timing of the surveys. Specifically, these participants' six-month pandemic surveys were mostly completed during the summer of 2020, a time when COVID-19 mortality was low compared to April and May [20]. Additionally, despite the relatively high COVID-19 infection rates in the United States in January and February 2021, there was growing optimism at this point with the beginning of vaccinations.

Although many of our participants did have worsened RLS severity, it is important to note that many did not have elevated IRLS scores after COVID in 2020. Identifying factors associated with IRLS increases is valuable as it can help clinicians anticipate who may be at risk of elevated RLS symptoms during future lockdowns or other times of socioeconomic uncertainty. We revealed several variables associated with IRLS increases from baseline to April and May 2020. Notably, previous analysis of 1-year RLS Registry follow-up data (in which most responses had been completed before the onset of the COVID-19 pandemic) revealed that a baseline IRLS score of 15 or less was also associated with IRLS increases at this timepoint (unpublished data). This suggests that this subset of participants may be more prone to IRLS increases in general. Given that these participants' baseline IRLS scores were mostly lower than the sample average, this may represent regression to the mean.

Participant state and employment status were both associated with post-COVID IRLS increases in the present analysis, but neither were associated with IRLS elevations in the 1-year pre-pandemic previous analysis. This suggests that these latter two variables are uniquely related to IRLS increases observed during the pandemic. Although many potentially confounding factors are present, it is conceivable that the lower risk of IRLS increases observed in participants living in states with more early COVID-19 restrictions is related to the fact that these individuals felt safer with such regulations in place. Similarly, while it is not immediately clear why those who were unemployed at baseline saw a higher risk of IRLS increase, it is worth noting that most unemployed participants were likely retired; although the baseline demographic questionnaire did not explicitly inquire about retirement status the average RLS Registry participant was 65 years old at entry into the study [11].

The National Opioid RLS Registry is not representative of all RLS patients. For example, the Registry is comprised almost entirely of elderly individuals. This lack of age diversity is a limitation of this data, and it is unclear whether these results are generalizable to younger patients with RLS. However, previous research has shown that older individuals have been particularly psychologically resilient during the COVID-19 pandemic; compared to those in younger age groups, these individuals have not described nearly as large elevations in psychological distress [21]. It is possible that younger individuals saw even larger increases in RLS symptom severity in conjunction with their greater increases in depression and anxiety; future research could address this issue. In addition to being mostly elderly, RLS Registry participants all use the same class of RLS medications and tend to be white and well-educated. Thus, these findings should be corroborated in patients who do not use opioid medications for RLS, as well as in patients of color and individuals with lower education levels.

In the within-subject analysis, changes in IRLS were strongly correlated with changes in ISI scores. This is unsurprising considering that RLS symptoms are known to severely disrupt sleep, and that sleep deprivation worsens RLS [22]. Changes in IRLS were also significantly correlated with changes in both PHQ-9 and GAD-7 scores, providing further support for the associations of RLS to both depression and anxiety. Notably, particularly strong associations were also seen between changes in sleep disturbance and depressive symptoms, and depressive symptoms and anxiety symptoms. Although this research revealed a number of associations between changes in RLS severity, depression, anxiety, and sleep disturbance, these are cross-sectional data and cannot establish causal relationships between these different symptoms.

In conclusion, this study provides the first evidence of increased RLS symptom severity during the COVID-19 outbreak. Elevated RLS severity scores were strongly associated with increases in sleep disturbance, as well as depressive and anxiety symptoms. These data suggest that clinicians should attend to RLS symptoms during the current pandemic and in future instances of socioeconomic and/or political uncertainty. Future studies need to confirm these findings in other populations of patients with RLS.

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Conflict of interest

John Winkelman receives royalties from UpToDate; consultation fees from Emalex, Noctrix, Disc Medicine, Avadel, and CVS; and research support from Merck, American Regent, NIH, the RLS Foundation, and the Baszucki Brain Research Fund. All other authors report no disclosures.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2022.01.011.

Abbreviations

GAD-7	General Anxiety Disorder-7 scale
IRLS	International Restless Legs Syndrome Study Group severity scale
ISI	Insomnia Severity Index
PHQ-9	Patient Health Questionnaire
REDCap	Research Electronic Data Capture
RLS	Restless legs syndrome
OR	Odds ratio

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