Sleep Medicine 54 (2019) 1–7

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Suicidal thought and behavior in individuals with restless legs syndrome

Kiran Sai Para [a, 1], Christopher A. Chow [a, 1], Keerthana Nalamada [a], Vikramjeet M. Kakade [a], Priyanka Chilakamarri [a], Elan D. Louis [a, b, c], Brian B. Koo [a, b, *]

[a] Department of Neurology, Yale University, New Haven, CT, USA
[b] Center for Neuroepidemiology and Clinical Neurologic Research, Yale, New Haven, CT, USA
[c] Department of Chronic Disease Epidemiology, Yale School of Public Health, Yale University, New Haven, CT, USA

ARTICLE INFO

Article history:
Received 31 July 2018
Received in revised form
6 September 2018
Accepted 24 September 2018
Available online 11 October 2018

Keywords:
Restless legs syndrome
Suicide
Depression

ABSTRACT

Background: Restless legs syndrome (RLS) is associated with an unrelenting urge to move at night, which can cause chronic sleeplessness, depression, and despondency; thus increasing risk of suicide. We aimed to determine frequency of suicidal ideation and behavior in RLS.
Methods: RLS and control participants were recruited through community and RLS Foundation advertisements. RLS diagnosis was confirmed using the Cambridge–Hopkins RLS Questionnaire and severity was assessed using the International RLS Study Group Severity Scale (IRLSS). Lifetime suicidal ideation (plan) and behavior (attempt) was assessed using the Suicidal Behavior Questionnaire-revised. The Brief Lifetime Depression Scale evaluated lifetime depression history. Forward stepwise logistic regression determined the odds of suicidal ideation or behavior.
Results: In this study, 192 RLS and 158 control participants were comparable for age, sex, race, and other potential demographic confounders. In general, RLS was moderate-to-severe (mean IRLSS 26.4 ± 7.5). Significantly more RLS than control participants had lifetime suicidal ideation or behavior (27.1% vs. 7.0%; $p < 0.00001$) or lifetime depression history (65.6%% vs. 22.8%; $p < 0.00001$). The odds of having a lifetime suicidal ideation or behavior was higher in those with RLS [2.80 (1.29,6.11)], even after accounting for depression and other confounders. In RLS, the odds of lifetime suicidal ideation or behavior was increased if there was lifetime depression [7.37 (2.65,20.47)] or if RLS in the past was severe or very severe [2.36 (1.03,5.40)].
Conclusions: Lifetime suicidal ideation or behavior is prevalent in RLS sufferers, and its likelihood is dependent on RLS severity and depression history.

1. Introduction

Restless legs syndrome (RLS) is a chronic sensorimotor disorder characterized by an inescapable urge to move the legs, most often at night, when rest and sleep are most desired. The need to move of RLS appears as the RLS sufferer is at their most tired state, and in the greatest need for rest. At night, uncontrollable urges to move intervene and sleep is foiled, causing chronic and disabling sleeplessness [1,2]. Indeed, quality of life in RLS sufferers is well below population norms in both mental and physical domains, and matches that of patients with other chronic conditions such as diabetes and osteoarthritis [3–5]. Unsurprisingly, major depressive disorder is also very common among those with RLS, with the likelihood of prevalent depression being two-and-a-half to five times more frequent in persons with RLS compared to those without RLS [6–8].

The likelihood of depression and the severity of insomnia both increase as RLS symptoms worsen in severity [9]. One recent study found that the presence of RLS was associated with a greater than fifty-fold increase in the odds of severe depression assessed by the Beck Depression Inventory [10]. Indeed, symptoms of RLS when they are severe can leave the unfortunate RLS sufferer powerless and despondent. Disturbed sleep, insomnia, and depression are well-known risk factors for suicidality [11–13], and a recent

* Corresponding author. 15 York Street, LCI 710, New Haven, CT, 06510, USA. Fax: +203 937 3464.
E-mail address: brian.koo@yale.edu (B.B. Koo).
[1] Co-first authors; these authors contributed equally to the manuscript.

https://doi.org/10.1016/j.sleep.2018.09.019
1389-9457/

longitudinal study highlighted a strong association between sleep disturbances and suicidal risk independent of depression [14]. Given these notable associations, we wished to study whether there is an association between RLS and suicidal thought and behavior. We aimed to determine the frequency of lifetime suicidal ideation or suicide attempts in patients with moderate-to-severe RLS and age-sex matched controls and to identify clinical correlates of suicidal behavior in patients suffering from RLS.

2. Materials and methods

2.1. Participants, recruitment, & assessment of RLS

Patients with RLS were recruited from May 2017 to January 2018 using advertisements on the website and newsletter of the RLS Foundation and through email solicitation to individuals identified with RLS through Research Match. Control participants were recruited through email solicitation to individuals identified through Research Match and the Yale Research Studies Registry, both registries of persons interested in research participation, between May 2017 and November 2017. Both advertisements and emails indicated that the research aimed to study the emotional state of individuals with RLS compared to control participants without RLS through questionnaire. Neither depression nor suicide were mentioned in the advertisement or emails.

Both participant screening and survey completion was conducted using the electronic questionnaire software (Yale Qualtrics Survey Tool). Potential participants were screened for inclusion/exclusion criteria; and based upon responses to questions, they were either able to proceed and be included in the study or the survey ended and potential participants were excluded. Inclusion criteria were age 18–89 years, ability to read and understand English. Exclusion criteria were chronic psychiatric diseases (other than depression), neurologic diseases (other than RLS), terminal disease, and RLS-like symptoms (for control patients; see below). Participants were screened using the Cambridge–Hopkins RLS Questionnaire, which includes seven questions assessing RLS core features [15]. Potential participants were considered as controls if they answered 'No' to both these questions: (1) 'Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down?' and (2) 'Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down?'. Potential participants were included in the RLS group if they answered 'yes' to the two above questions and they identified that the symptoms (3) occurred with rest, (4) were alleviated by movement, (5) occurred anytime other than the morning, (6) were not alleviated by simple position change, and (7) were not due to leg cramping.

2.2. Patient consents

As the study was conducted via on-line questionnaire, the survey was anonymous (ie, research staff did not know the identity of any participants). Before participants began the study, a description of the study methods as well as its risks were given. The potential participant was informed that the survey was anonymous and thus by proceeding that they understood the study and agreed to participate, thereby provided informed consent. All participants provided online informed consent as approved by the Yale University Ethics Board.

2.3. Assessment of suicidal behavior and depression

Suicidal behavior was assessed using the Suicidal Behavior Questionnaire-revised (SBQ-R) scale [16]. The SBQ-R consists of four questions: (1) Have you ever thought about or attempted to kill yourself? (1 = never, 2 = just had a brief passing thought, 3 = have had a plan at least once to kill myself, 4 = have attempted to kill myself); (2) How often have you thought about killing yourself in the past year? (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = very often); (3) Have you ever told someone that you were going to commit suicide, or that you might do it? (1 = no, 2 = yes at one time, 3 = yes more than once); (4) How likely is it that you will attempt suicide someday? (0 = never, 1 = no chance at all, 2 = rather unlikely, 3 = unlikely, 4 = likely, 5 = rather likely, 6 = very likely). Risk of suicidal behavior was considered high if the total SBQ-R score was $\geq$7, standardly used cutoff in non-clinical samples [16]. Suicidal thought was considered present if there was indication of having had a plan at least once for suicide; and suicidal behavior was considered present if there was endorsement of a suicide attempt [16].

Lifetime depression history was assessed using the Brief Lifetime Depression Scale (BLDS) [17,18]. This scale ascertained whether during a person's lifetime there was a period of at least two weeks, during which certain symptoms were present: (1) felt down, depressed, or hopeless; (2) had little interest in doing things; or (3) were less able to enjoy things. If they answered yes to any one of these questions they were asked if they had also experienced (4) sleep problems, (5) fatigue or tiredness, (6) appetite changes, (7) feelings of being a failure, (8) concentration problems, (9) psychomotor retardation, or (10) passive suicidal ideation. Consistent with the DSM-V depression diagnostic criteria, participants were considered to have a lifetime history of depression if at least five depressive symptoms were present with at least one being depressed mood or anhedonia [17,19].

2.4. Assessment of covariates and RLS severity

Demographic information was collected, including age, sex, race, marital status, education, and income. Information on medical history, medications, and lifetime drug and alcohol abuse history was also collected. Current and past use of dopamine agonist medication was noted. Current usage of medications for RLS was noted including dopamine agonists, alpha-2-δ ligands (gabapentin, pregablin, or gabapentin enecarbil), opiate medication, or benzodiazepines. Education was considered as high if college or graduate school was completed and low if high school or secondary school was completed. For marital status, those that were currently married constituted one group compared to those who were single, divorced, separated, or widowed. For income, those with middle or high income were grouped and compared to those with low income, which was defined as monthly income of $3000 or less. Participants were considered to have a history of drug abuse if there was a period of at least one year in which recreational drugs were used weekly. They were considered to have a history of alcohol abuse if there was a period of at least one year in which alcohol was consumed for $\geq$3 days per week with $\geq$2 drinks per day.

RLS severity was assessed using the International RLS Study Group Severity Scale (IRLSS) [20], which contains 10 items inquiring about different aspects of RLS symptoms, each scored on a zero to four scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe); total score out of 40. For this IRLSS rating, participants were asked to rate their RLS as it has been over the years with the following instructions, "Please rate your RLS as a whole. This includes how your RLS is currently and how it has been over the years, on and off of medication, trying to average how it has been as a whole (good and bad periods of time)." It should be noted that this is an adaptation of the IRLSS and is not validated for use in this manner. Assessing RLS separately, were questions which asked about current and past RLS by the following questions. "How would

you rate your RLS currently?" and "How would you rate your RLS as it has been in the past?" Answer choices included: (a) I have minimal RLS (up to 2–3 times monthly but it does not bother me much); (b) I have mild intermittent RLS (1–2 times weekly and it bothers me slightly); (c) I have moderate RLS (3–4 times weekly and it bothers me moderately); (d) I have severe RLS (3–6 times weekly and it bothers me a lot); (e) I have very severe RLS (4–7 times weekly and it is just about unbearable). RLS participants were asked if they had ever experienced augmentation with the following question, "Have you ever experienced augmentation? Augmentation is a worsening of RLS symptoms over days to weeks which includes one of the following: RLS symptoms occurred earlier in the day/evening, RLS symptoms became more intense, RLS symptoms spread to previously unaffected body parts (like arms), RLS symptoms were more difficult to alleviate with movement." Persons with RLS were also asked the following question, "If you have had suicidal ideation (thoughts of committing suicide) in your lifetime, do you feel that you had these thoughts because of your RLS?"

Sleep latency and sleep quality were also assessed. Participants were asked the following question, "How long does it usually take you to fall asleep?". Answer choices were (1) 0–15 minutes, (2) 16–30 minutes, (3) 31–60 minutes, (4) 1–2 hours, (5) 2–4 hours, and (6) more than 4 hours. Long sleep latency was considered if answers were 1–2 hours 2–4 hours, or more than 4 hours. Short sleep latency was considered when sleep latency was 0–15 minutes or 16–30 minutes. Participants were also asked, "How would you rate your overall sleep quality?". Potential answers included (1) Very good, (2) Fairly good, (3) Average, (4) Fairly bad, (5) Very bad. In regression models those with fairly bad or very bad sleep quality were compared to those with very good or fairly good sleep quality.

2.5. Statistical analysis and sample size calculation

Characteristics were compared between RLS and control groups using chi-squared (dichotomous variables) and Welch two sample t-tests (continuous variables). In particular, chi-squared testing was performed to compare the frequency of having had a suicide attempt or plan in one's lifetime between those with RLS and controls. A sensitivity analysis was carried out, comparing the frequency of having had a suicide attempt or plan in one's lifetime between those with mild to moderate RLS (IRLSS < 20) and controls.

Logistic regression for the outcome of having had a suicide plan or attempt in one's lifetime was carried out for the overall and RLS groups, separately. Linear regression was also conducted for the outcome of SBQ-R score for the overall and RLS groups, separately. Forward stepwise regression was used with variables entered in the final model if they were associated with suicidal thought or behavior in a separate bivariate analysis (p-value $\leq$0.10), including lifetime depression and having RLS, or if they have clear association with suicide in population studies, including age, gender, race, marital status, education, income, and drug/alcohol abuse history [21]. Sensitivity analysis was carried out using logistic regression for the outcome of having had a suicide plan or attempt in one's lifetime for the overall group in those without depression. Statistical analysis was performed using the R statistical package 3.3.2 (Auckland, New Zealand).

Lifetime suicidal ideation in the general population is about 9.2% [22]. Lifetime depression has been estimated to be two to two-and-a-half times more frequent in persons with RLS than persons without RLS [7,23]; and therefore, we estimated that lifetime suicidal ideation might be two-and-one-quarter times or 20.7% that of the general population. Given a power of 80%, a significance level of 0.05, a population suicidal ideation prevalence of 9.2% and an RLS suicidal ideation prevalence of 20.7% (9.2% $\times$ 2.25), a sample size of 150 in each group was predicted.

3. Results

3.1. Characteristics of RLS and control groups

One-hundred ninety two RLS (162 women, 84.4%) and 158 control participants (131 women, 82.9%) were included in the study. RLS and control groups were comparable for age (p = 0.54), sex (p = 0.71), Caucasian race (p = 0.36), current marital status, education, and income (Table 1). Participants with RLS were significantly less likely than control participants to have a lifetime

Table 1
Demographic features of restless legs syndrome patients and controls.

Demographics	Overall cohort (n = 350)	RLS (n = 192)	Controls (n = 158)	p-value[1]
Age (mean ± SD)	50.5 ± 13.7	51.0 ± 11.9	50.0 ± 15.5	0.54[a]
Sex (female; n, %)	293/350 (83.7)	162/192 (84.4)	131/158 (82.9)	0.71[b]
Race (Caucasian; n, %)	332/350 (94.9)	184/192 (95.8)	148/158 (93.7)	0.36[b]
Marital Status (currently married; n, %)	236/350 (67.4)	134/192 (70.8)	102/158 (64.6)	0.21[b]
Education (finished college; n, %)	330/350 (94.3)	178/192 (92.7)	152/158 (96.2)	0.16[b]
Economic[2]				
High/middle (n, %)	318/350 (90.8)	172/192 (89.6)	146/158 (92.4)	0.36[b]
Low	32/350 (9.2)	20/192 (10.4)	12/158 (7.6)	
Lifetime Depression (n, %)	162/350 (46.3)	126/192 (65.6)	36/158 (22.8)	1.3×10^{-15}[b]
Lifetime Augmentation (n. %)	NA	162/192 (84.4)	NA	NA
Current Dopamine Agonist (n, %)	NA	103/192 (53.6)	NA	NA
Lifetime Dopamine Agonist (n, %)	NA	152/192 (79.2)	NA	NA
Current Alpha-2-δ ligand (n, %)	43/350 (12.3)	43/192 (22.4)	0	<0.00001[b]
Current Benzodiazepine (n, %)	20/350 (5.7)	19/192 (9.9)	1	<0.00001[b]
Current Opiate (n, %)	19/350 (5.4)	19/192 (9.9)	0	<0.00001[b]
Current Antidepressant (n, %)	95/350 (27.1)	82/192 (42.7)	13/158 (8.2)	5.3×10^{-13}[b]
Lifetime Drug Abuse[3] (n, %)	56/350 (16.0)	36/192 (18.8)	20/158 (12.7)	0.12
Lifetime Alcohol Abuse[4] (n, %)	122/350 (34.9)	52/192 (27.1)	70/158 (44.3)	0.0008
Lifetime Suicide plan (n, %)	45/350 (12.3)	39/192 (20.3)	6/158 (3.8)	<0.00001[b]
Lifetime Suicide attempt (n, %)	18/350 (5.1)	13/192 (6.8)	5/158 (3.2)	0.13[b]
Lifetime Suicidal plan or attempt (n, %)	63/350 (18.0)	52/192 (27.1)	11/158 (7.0)	<0.00001[b]
High risk suicide (n, %)	75/350 (21.4)	59/192 (30.7)	16/158 (10.1)	<0.00001[b]

[1] Comparing RLS to Controls; superscript letter after p-value indicates type of test used; [a]Student's t-test; [b]Chi Squared test; [2]For the economic variable, High $\geq$ $6,000 monthly income; Middle = $3,001 to $6,000 monthly income; Low $\leq$ $3,000 monthly income; [3]For History of Drug Abuse: Period of one year when drugs were used weekly, referenced to those that had less than this amount of use; [4]For History of Alcohol Abuse: Period of one year when alcohol was used $\geq$ 3 days per week with $\geq$ 2 drinks per day.

history of alcohol abuse ($p = 0.0008$), but were marginally more likely to have a lifetime history of drug abuse ($p = 0.12$) (Table 1).

3.2. Depression and suicidality in RLS and control groups

Participants with RLS were significantly more likely than control participants to have a lifetime history of depression, a lifetime history of having a suicidal plan or attempt (27.1% vs. 7.1%; $p < 0.00001$), and were at higher risk of suicide (30.7% vs. 10.1%; $p < 0.00001$) (Table 1). Logistic regression models showed that the odds of having had a suicide plan or attempt in one's lifetime was almost three-fold greater in those with RLS compared to controls [OR 2.80 (1.29, 6.11)], even while statistically adjusting for lifetime depression (Table 2). This is after statistically controlling for age, sex, race, marital status, education, income, and drug and alcohol abuse history, which were not associated with the odds of having had a suicide plan or attempt in the overall cohort. Neither self-report sleep latency (short vs. long; OR 1.02 [0.52, 2.00]; $p = 0.95$) nor self-reported sleep quality (poor vs good; OR 1.33 [0.69, 2.54] $p = 0.39$) were associated with the odds of suicidal thought or behavior and including both or either in the model did not appreciably affect the results. Among RLS and control participants without a history of lifetime depression, RLS was not associated with having had a suicide plan or attempt in one's lifetime [OR 1.38 (0.36,5.29)].

Table 2
Associations of suicidal thought or behavior in the overall cohort.

Outcome: Suicide plan or attempt in lifetime			
Cohort	Variable	Odds ratio (95% CI)	p-value
Overall cohort	RLS[a]	2.80 (1.29, 6.11)	0.009[j]
	Lifetime depression[b]	4.65 (2.47, 8.76)	0.0000019[j]
	Age (per one year)	1.00 (0.98, 1.03)	0.89
	Male gender[c]	0.93 (0.39, 2.23)	0.87
	Caucasian[d]	0.85 (0.23, 2.18)	0.82
	Currently single, divorced, widowed[e]	1.12 (0.57, 2.21)	0.74
	High school education[f]	1.54 (0.49, 4.90)	0.46
	Low income[g]	1.39 (0.53, 3.64)	0.51
	Drug abuse history[h]	1.27 (0.61, 2.66)	0.52
	Alcohol abuse history[i]	1.11 (0.58, 2.14)	0.76
Outcome: SBQ-R score (Range 3–18)			
Cohort	Variable	SBQ-R score units (95% CI)	p-value
Overall cohort	RLS[a]	0.75 (0.16, 1.34)	0.01*
	Lifetime depression[b]	2.05 (1.45, 2.64)	5.8×10^{-11}*
	Age (per 10 year)	0.16 (−0.04, 0.36)	0.13
	Male gender[c]	0.25 (−0.49, 0.99)	0.51
	Caucasian[d]	−0.05 (−1.22, 1.13)	0.94
	Currently single, divorced, widowed[e]	0.06 (−0.53, 0.65)	0.84
	High school education[f]	0.45 (−0.68, 1.58)	0.44
	Low income[g]	0.75 (−0.20, 1.70)	0.12
	Drug abuse history[h]	0.11 (−0.62, 0.83)	0.77
	Alcohol abuse history[i]	0.16 (−0.40,0.72)	0.58

Reference groups: [a]RLS: referent control group; [b]Lifetime depression: referent no depression; [c]Male gender: referent female; [d]Caucasian: referent other races; [e]Currently single, divorced, widowed: referent currently married; [f]High school education: referent college or graduate school; [g]Low income: referent middle or high income; High ≥ $6,000 monthly income; Middle = $3,001 to $6,000 monthly income; Low ≤ $3,000 monthly income; [h]Drug Abuse history: Period of one year when drugs were used weekly, referenced to those that had less than this amount of use; [i]Alcohol Abuse history: Period of one year when alcohol was used ≥3 days per week with ≥2 drinks per day; * Statistical significance: $p < 0.05$. Forward stepwise regression was used with variables entered in the final model if they were associated with suicidal thought or behavior in a separate bivariate analysis (p-value ≤0.10), including lifetime depression and having RLS, or if they have clear association with suicide in population studies, including age, gender, race, marital status, education, income, and drug/alcohol abuse history [21]

In the overall cohort, linear regression for the outcome of SBQ-R score (range 3–18) showed that SBQ-R score was associated with lifetime depression (2.05 units [1.45, 2.64]; $p = 5.8 \times 10^{-11}$) and the presence of RLS (0.75 units [0.16, 1.34]; $p = 0.01$) (Table 2). This again was after controlling for age, sex, race, marital status, education, income, and drug and alcohol history, which were not associated significantly with SBQ-R score.

In sensitivity analyses, RLS participants with a lifetime history of depression were more likely than control participants with a similar lifetime history of depression to have had a suicide plan or attempt in their lifetime (37.6% vs. 13.9%; $p = 0.007$). RLS participants without depression were not more likely than controls without depression to have had a suicide plan or attempt in their lifetime (7.6% vs. 4.9%; $p = 0.46$). Furthermore, even persons with mild to moderate RLS (IRLSS < 20) ($n = 35$) were significantly more likely than controls without RLS ($n = 158$) to have had a suicide plan or attempt in their lifetime (25.7% vs. 7.0%; $p = 0.001$) and to have had a suicide attempt in their lifetime (11.4% vs. 3.2%; $p = 0.04$).

3.3. Depression and suicidality in RLS group

Of the 192 participants with RLS, 41.1% suffered with RLS for more than 20 years, 22.9% for between 11 and 20 years, 19.8% for between 5 and 10 years, and the remaining 16.2% for less than five years. Participants over their lifetimes rated their RLS as moderate with IRLSS scores of 26.4 ± 7.5 (SD). Current RLS severity ratings were severe or very severe for 66.1%, moderate for 16.7%, and minimal or mild for 17.2%. Past RLS severity ratings were severe or very severe for 68.0%, moderate for 21.0%, and minimal or mild in the remaining 11.0%. Logistic regression models showed that the odds of having had a suicide plan or attempt in one's lifetime was nearly two-and-a-half-fold higher in those that rated their past RLS symptoms as severe or very severe [OR 2.36 (1.03, 5.40)], even after accounting for depression (Table 3).

Covariates of age, sex, race, marital status, education, income, and drug and alcohol abuse history were not significantly associated with the odds of having had a suicide plan or attempt in one's lifetime for persons with RLS. Neither prolonged self-report sleep latency (short vs. long OR 0.84 [0.38, 1.84] $p = 0.66$) nor self-reported sleep quality (poor vs. good OR 1.29 [0.62, 2.68]; $p = 0.49$) were associated with the odds of having a suicide plan or attempt in the past. And including both or either in the logistic regression model did not affect the relationship between the odds of having a lifetime suicide plan or attempt and either lifetime depression history or self-report rating of past RLS symptoms. Other variables which were excluded from the final model because of non-significance were being on a dopamine agonist medication either currently or in the past (current dopamine agonist: OR 1.11 [0.51, 2.40]; $p = 0.8$), being on an alpha-2-δ ligand: OR 1.33 [0.56, 3.15]; $p = 0.52$, being on a benzodiazepine: OR 1.89 [0.64, 5.60]; $p = 0.25$, being on an opiate medication: OR 1.00 [0.30, 3.31]; $p = 0.99$, being on an antidepressant medication: OR 1.41 [0.68, 2.93]; $p = 0.36$, and having experienced augmentation of RLS: OR 0.77 [0.28, 2.12]; $p = 0.62$.

In the RLS cohort, linear regression for the outcome SBQ-R score showed that SBQ-R score was significantly associated only with lifetime history of depression (2.80 units [1.92, 3.68]; $p = 2.9 \times 10^{-9}$). SBQ-R score was not associated with past severe or very severe RLS (0.60 units [−0.28, 1.49]; $p = 0.18$) (Table 3). Of the 52 RLS participants that endorsed having had a suicidal plan or attempt in their lifetime, 12 (23.1%) of them thought that their RLS directly contributed to these episodes.

Table 3
Associations of suicidal thought or behavior in persons with RLS.

Outcome: Suicide plan or attempt in lifetime			
Cohort	Variable	Odds ratio (95% CI)	p-value
RLS cohort	Lifetime depression[a]	7.37 (2.65, 20.47)	0.0001*
	Severity RLS past[b]	2.36 (1.03, 5.40)	0.04*
	Age (per one year)	1.01 (0.98, 1.05)	0.38
	Male gender[c] (ref female)	1.07 (0.40, 2.88)	0.89
	Caucasian[d] (ref other race)	2.07 (0.22, 19.8)	0.53
	Currently single, divorced, widowed[e]	1.37 (0.62, 3.05)	0.44
	High school education[f]	1.30 (0.52, 3.28)	0.57
	Low income[g]	1.78 (0.56, 5.63)	0.33
	Drug abuse history[h]	0.94 (0.39, 2.26)	0.89
	Alcohol abuse history[i]	1.66 (0.76, 3.65)	0.21
Outcome: SBQ-R rcore (Range 3–18)			
Cohort	Variable	SBQ-R rcore units (95% CI)	p-value
RLS cohort	Lifetime depression[a]	2.80 (1.92, 3.68)	2.9×10^{-9}*
	Severity RLS past[b]	0.60 (−0.28, 1.49)	0.18
	Age (per 10 year)	0.13 (−0.22, 0.48)	0.38
	Male gender[c]	0.25 (−0.94, 1.44)	0.68
	Caucasian[d]	0.56 (−1.49, 2.61)	0.60
	Currently single, divorced, widowed[e]	0.37 (−0.55, 1.29)	0.43
	High school education[f]	0.74 (−0.89, 2.38)	0.37
	Low income[g]	0.89 (−0.56, 2.36)	0.23
	Drug abuse history[h]	−0.21 (−1.29, 0.86)	0.70
	Alcohol abuse history[i]	0.34 (−0.61, 1.30)	0.48

Reference groups: [a]Lifetime depression: referent no depression; [b]Severity RLS past: self-report moderate, severe, or very severe referenced to minimal or mild; [c]Male gender: referent female; [d]Caucasian: referent other races; [e]Currently single, divorced, widowed: referent currently married; [f]High school education: referent college or graduate school; [g]Low income: referent middle or high income; High ≥ $6,000 monthly income; Middle = $3,001 to $6,000 monthly income; Low ≤ $3,000 monthly income; [h]Drug Abuse history: Period of one year when drugs were used weekly, referenced to less than this use; [i]Alcohol Abuse history: Period of one year when alcohol was used ≥ 3 days per week with ≥ 2 drinks daily; * Statistical significance: $p < 0.05$.

4. Discussion

The main findings of this study demonstrate that lifetime suicidal ideation and suicide attempts are highly prevalent among persons with largely moderate-to-severe RLS, occurring in more than one-quarter of persons with RLS compared to less than one-tenth of age, sex, and demographically comparable controls without RLS. While suicidal thought or behavior was highly associated with a lifetime history of depression, the suicidal outcome was also independently associated with having RLS in the overall cohort. Furthermore, among the RLS cohort, those that rated their RLS symptoms in the past as severe or very severe had nearly two-and-a-half times the odds of having had a suicide plan or attempt in their lifetime (but not with the SBQ-R score considered continuously), and this association was not attenuated when accounting for self-reported sleep quality, a factor with a known association with suicidal behavior [24]. These findings have population relevance, as the suicide rate in the U.S. has steadily increased from 1999 to 2014, especially for women in whom the suicide rate increased by 45% during this time period [25]. At the same time, RLS is highly prevalent and occurs in 7.6% of U.S. adults to any degree, and in 1.5%–3.1% of U.S. adults to a moderate or severe degree (two or more times weekly) [3,26].

RLS, when severe, is experienced as a relentless urge to move in moments at night when the person and body wish to be calm, rest and then sleep. Needless to say, sleep is often delayed and fragmented considerably as the RLS sufferer may be forced to walk for prolonged periods of time several times on the same night in order to relieve symptoms. In our RLS cohort, as has been found in previous studies, over 20% of RLS sufferers reported that it took longer than one hour to fall asleep and over 5% reported it took two or more hours to fall asleep [27]. Insomnia and difficulty sleeping are well known independent risk factors for suicidal behavior and suicide itself [24,28,29]. Results from our study show that suicidal thought and behavior were associated with RLS even after accounting for depression and sleep problems, suggesting that there may be something about the RLS condition itself that may drive sufferers to think about and in some circumstances attempt suicide. It is also possible that there are factors associated with RLS that are driving this increased risk for suicidal thought and behavior. These factors may include psychoactive medications, including benzodiazepines, opiate, dopamine agonists, or alpha-2-δ ligands, impulsive behavior, or augmentation. We did include these factors which did not show association with suicidality; however, it is very possible that these statistical adjustments were inadequate to capture real life interactions. The suicide literature demonstrates rapid progression from first-onset suicidal ideation to plan and attempt within the same year [30]; therefore, early identification of suicidal ideation among individuals with RLS should be a critical priority.

While it is unclear why RLS itself would independently increase suicidal behavior, RLS is often described by patients as incontrovertible torture. The word 'torture' was first used by Sir Thomas Willis to describe RLS in his book, The London Practice of Physic, where he states, "Wherefore to some, when being in bed they betake themselves to sleep, presently in the arms and legs, leapings and contractions of tendons, and so great a restlessness and tossings of their members ensue, that the diseased are no more able to sleep than if they were in the greatest Place of Torture." [31] Inherent in the word or experience of 'torture' is a state of helplessness or hopelessness. Indeed, RLS is well known to be associated with depression and poor quality of life, which affects both mental and physical aspects of life [4,7,26].

Persons experiencing suicidal ideation or who have attempted to commit suicide are more likely than other depressed individuals without suicidal behavior to have a hopeless future orientation [32,33]. Hopelessness has not been directly studied among persons with RLS. In our study, as we evaluated for depression, participants were asked if at any time in their lives, did they have a period lasting for more than two weeks in which they felt down, depressed, or hopeless. Among RLS participants, 63.9% answered affirmatively to this question compared to 29.3% of control participants without RLS. Of course, this question does not solely inquire about hopelessness, but it presumably captured some persons who have felt this way. In the clinical experience of the authors (BK), it is not uncommon for persons with RLS to describe feelings of hopelessness and helplessness. It will be important to specifically delineate feelings of hopelessness and helplessness in future studies of RLS.

It is very important to note that the majority (84.4%) of persons with RLS in this study had experienced augmentation in their lifetime. This is likely to be higher than in the general RLS population. While the lifetime prevalence of augmentation among RLS sufferers is not known, the incidence of augmentation has been estimated to be about 9% per year [34]. So the lifetime prevalence of augmentation in persons on a dopamine drug for over five years may in fact be quite high. Consideration must also be made with regard to the many psychoactive medications used to treat RLS which may lead to depression and even suicidal ideation. These include benzodiazepines, alpha-2-δ ligands, and opiate medications. None of these medications when entered into the regression models was however

associated with suicidality. There are other important limitations to consider in our study. These include the cross-sectional design of the study which makes it difficult to make arguments about cause and effect. It is significant to note that many of the RLS participants were members of the RLS Foundation, who may on average have had RLS that is more severe than what may be on average encountered in the community. Lifetime IRLSS scores were 26.6 ± 7.6. For this reason there may have been sampling bias. We did perform sensitivity analyses which showed that lifetime suicidal thought and behavior even in persons with mild to moderate RLS (IRLSS < 20) was significantly higher than in controls without RLS. We were underpowered to assess suicidality in RLS and control participants without depression which did not show a significant difference, although the direction of greater suicidality occurred in the RLS group. Definitions for alcohol abuse, drug abuse, and income were our own. In addition, we were not able to assess completed suicide as this was a self-report study. The strengths of our study include the use of validated scales to assess suicidal thought and behavior and the inclusion of over 150 participants in each group which provided ample power to make comparisons regarding suicidal thought and behavior. We also had comprehensive assessments of sociodemographic information and detailed assessment of RLS severity.

While our survey was able to establish a strong association between RLS and suicidal thought and behavior, it also serves as a launching point for more in-depth study of this link. The relationship among RLS, depression, and suicidal thought/behavior appears complex and is likely to be influenced by poor sleep, medications, socioeconomics, and personality traits. In the RLS group, severity of RLS was associated with lifetime occurrence of a suicide plan or attempt, but not with suicide risk as estimated by the SBQ-R score considered continuously. This report adds to existing literature which demonstrates that RLS is not simply an annoyance, but can seriously affect quality of life and health. In robust population studies, RLS has been linked to overall poor life quality, cardiovascular disease, and even mortality [3,9,35,36]. Now suicidal thought and behavior can be added to this unfortunate list of ill—health associations of RLS. Future studies will need to confirm this relationship and determine which factors, including those that are RLS-specific, like dopamine medications and the presence of augmentation, may be temporally associated with suicidal thought and behavior.

Study funding

None.

Acknowledgements

The authors would like to acknowledge the RLS Foundation and the help they provided in identifying participants with 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: https://doi.org/10.1016/j.sleep.2018.09.019.

References

[1] Earley CJ, Silber MH. Restless legs syndrome: understanding its consequences and the need for better treatment. Sleep Med 2010;11:807–15.
[2] Durgin T, Witt EA, Fishman J. The humanistic and economic burden of restless legs syndrome. PloS One 2015;10, e0140632.
[3] Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165:1286–92.
[4] Fuhs A, Bentama D, Antkowiak R, et al. Effects of short- and long-term variations in RLS severity on perceived health status – the COR-study. PloS One 2014;9, e94821.
[5] Didriksen M, Allen RP, Burchell BJ, et al. Restless legs syndrome is associated with major comorbidities in a population of Danish blood donors. Sleep Med 2018;45:124–31.
[6] Ulfberg J, Nystrom B, Carter N, et al. Prevalence of restless legs syndrome among men aged 18 to 64 years: an association with somatic disease and neuropsychiatric symptoms. Mov Disord Off J Mov Disord Soc 2001;16:1159–63.
[7] Winkelmann J, Prager M, Lieb R, et al. "Anxietas tibiarum". Depression and anxiety disorders in patients with restless legs syndrome. J Neurol 2005;252:67–71.
[8] Lee HB, Hening WA, Allen RP, et al. Restless legs syndrome is associated with DSM-IV major depressive disorder and panic disorder in the community. J Neuropsychiatry Clin Neurosci 2008;20:101–5.
[9] Winkelman JW, Redline S, Baldwin CM, et al. Polysomnographic and health-related quality of life correlates of restless legs syndrome in the Sleep Heart Health Study. Sleep 2009;32:772–8.
[10] Cho CH, Kim L, Lee HJ. Individuals with restless legs syndrome tend to have severe depressive symptoms: findings from a community-based cohort study. Psychiatr Invest 2017;14:887–93.
[11] Beck AT, Steer RA, Beck JS, et al. Hopelessness, depression, suicidal ideation, and clinical diagnosis of depression. Suicide Life Threatening Behav 1993;23:139–45.
[12] Bolton JM, Belik SL, Enns MW, et al. Exploring the correlates of suicide attempts among individuals with major depressive disorder: findings from the national epidemiologic survey on alcohol and related conditions. J Clin Psychiatr 2008;69:1139–49.
[13] Horesh N, Rolnick T, Iancu I, et al. Anger, impulsivity and suicide risk. Psychother Psychosom 1997;66:92–6.
[14] Bernert RA, Hom MA, Iwata NG, et al. Objectively assessed sleep variability as an acute warning sign of suicidal ideation in a longitudinal evaluation of young adults at high suicide risk. J Clin Psychiatr 2017;78:e678–87.
[15] Allen RP, Burchell BJ, MacDonald B, et al. Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey. Sleep Med 2009;10:1097–100.
[16] Osman A. The Suicidal Behaviors Questionnaire-Revised (SBQ-R): validation with clinical and nonclinical samples. Assessment (Odessa, Fla) 2001;8:443–54.
[17] Bruce DG, Davis WA, Cetrullo V, et al. Clinical impact of the temporal relationship between depression and type 2 diabetes: the Fremantle diabetes study phase II. PLoS One 2013;8, e81254.
[18] Whitworth SR, Bruce DG, Starkstein SE, et al. Lifetime depression and anxiety increase prevalent psychological symptoms and worsen glycemic control in type 2 diabetes: the Fremantle Diabetes Study Phase II. Diabetes Res Clin Pract 2016;122:190–7.
[19] Association AP. Diagnostic and statistical manual of mental disorders (5th edition). Washington, D.C. 2013.
[20] Validation of the international restless legs syndrome study group rating scale for restless legs syndrome. Sleep Med 2003;4:121–32.
[21] Nock MK, Borges G, Bromet EJ, et al. Suicide and suicidal behavior. Epidemiol Rev 2008;30:133–54.
[22] Bromet EJ, Nock MK, Saha S, et al. Association between psychotic experiences and subsequent suicidal thoughts and behaviors: a cross-national analysis from the World health organization World mental health surveys. JAMA Psychiatr 2017;74:1136–44.
[23] Cho SJ, Hong JP, Hahm BJ, et al. Restless legs syndrome in a community sample of Korean adults: prevalence, impact on quality of life, and association with DSM-IV psychiatric disorders. Sleep 2009;32:1069–76.
[24] Goldstein TR, Bridge JA, Brent DA. Sleep disturbance preceding completed suicide in adolescents. J Consult Clin Psychol 2008;76:84–91.
[25] Curtin SC, Warner M, Hedegaard H. Increase in Suicide in the United States, 1999-2014. NCHS data brief. 2016. p. 1–8.
[26] Allen RP, Bharmal M, Calloway M. Prevalence and disease burden of primary restless legs syndrome: results of a general population survey in the United States. Movement disorders. Off J Mov Disord Soc 2011;26:114–20.
[27] Hening W, Walters AS, Allen RP, et al. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Med 2004;5:237–46.
[28] Agargun MY, Kara H, Solmaz M. Sleep disturbances and suicidal behavior in patients with major depression. J Clin Psychiatr 1997;58:249–51.
[29] Fujino Y, Mizoue T, Tokui N, et al. Prospective cohort study of stress, life satisfaction, self-rated health, insomnia, and suicide death in Japan. Suicide Life Threatening Behav 2005;35:227–37.
[30] Kessler RC, Borges G, Walters EE. Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. Arch Gen Psychiatr 1999;56:617–26.

[31] Willis T. The London Practice of physic. London, England: Bassett and Crooke; 1685.
[32] Hintikka J, Viinamaki H, Koivumaa-Honkanen HT, et al. Risk factors for suicidal ideation in psychiatric patients. Soc Psychiatr Psychiatr Epidemiol 1998;33:235–40.
[33] Kienhorst CW, de Wilde EJ, Diekstra RF, et al. Differences between adolescent suicide attempters and depressed adolescents. Acta Psychiatr Scand 1992;85:222–8.
[34] Silver N, Allen RP, Senerth J, et al. A 10-year, longitudinal assessment of dopamine agonists and methadone in the treatment of restless legs syndrome. Sleep Med 2011;12:440–4.
[35] Winkelman JW, Shahar E, Sharief I, et al. Association of restless legs syndrome and cardiovascular disease in the Sleep Heart Health Study. Neurology 2008;70:35–42.
[36] Li Y, Wang W, Winkelman JW, et al. Prospective study of restless legs syndrome and mortality among men. Neurology 2013;81:52–9.