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Restless Legs Syndrome: Associated with Major Depressive Disorder and Anxiety Disorder But Not with Antidepressant Use

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ABSTRACT

Background: The current study primarily aimed to investigate whether the prevalence of restless legs syndrome differs in patients diagnosed with major depressive disorder or anxiety disorder without antidepressant use compared to control group. Secondly, the study sought to examine whether there was a difference in restless legs syndrome prevalence among patients on antidepressant treatment compared to control subjects.

Methods: Five hundred patients who were diagnosed with anxiety disorder or major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)-5 criteria without a history of antidepressant treatment were included in the study (group 1). Group 2 consisted of 500 patients diagnosed with anxiety disorder or major depressive disorder and on antidepressant treatment who were identified as being in complete or partial remission via psychiatric interview based on DSM-5 criteria. Five hundred age- and sex-matched subjects without any mental illness were included in control group (Group 3).

Results: Among all participants, restless legs syndrome was diagnosed in 101 (6.73%) individuals. There were no significant differences in age, gender, smoking status, marital status, and education level between those with or without a diagnosis of restless legs syndrome ($P = .209$, $P = .519$, $P = .227$, $P = .508$, $P = .676$, respectively). Restless legs syndrome was diagnosed in 65/500 (13.0%) group 1 patients, 16/500 (3.2%) group 2 patients, and 20/500 (4.0%) control subjects, with a significant difference among the groups ($P < .001$). The prevalence of RLS diagnosis did not significantly differ among patients receiving different antidepressant drugs ($P = .965$).

Conclusion: Antidepressant use was not found to be a risk factor for restless legs syndrome. Our study presents important data on the close association of anxiety disorder, especially major depressive disorder with restless legs syndrome.

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INTRODUCTION

Restless legs syndrome (RLS) is a sensory and motor disorder characterized by unpleasant sensations and pain, especially in the legs, and an irresistible urge to move them during sleep or rest. Symptoms commonly occur in the evening or at night and decrease with movement and often lead to sleep disturbance.[1] All 5 essential diagnostic criteria published by the International Restless Legs Syndrome Study Group (IRLSSG) should be met to make a diagnosis of RLS.[2] The reported prevalence of RLS in the general population varies between 5% and 15%.[3]

The exact mechanism underlying RLS has not been fully elucidated. However, altered dopaminergic neurotransmission due to central iron deficiency in the brain caused by genetic predisposition has been implicated in the pathophysiology of RLS.[1] On the other hand, certain medical conditions such as iron-deficiency anemia, end-stage renal disease, pregnancy, diabetes, and rheumatic diseases are associated with increased incidence of RLS.[1,3,4]

Restless legs syndrome is classified according to etiology as primary (idiopathic) and secondary RLS. Primary RLS is the form without all the clinical conditions known to cause the secondary form. The primary form constitutes 70%-80% of all RLS cases. More than half of primary RLS cases have a family history.[3]

In addition to medical conditions, it is known that some antihistamines and antipsychotic drugs may potentially cause RLS.[5-7] Cases of antidepressant-induc ed RLS have been previously reported, mainly occurring with selective serotonin reuptake inhibitors (SSRIs) and mirtazapine.[8-10] Although there are many case reports of RLS

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development with the use of antidepressant drugs, studies examining this potential relationship yielded conflicting results. While some studies reported conclusive data on the link between antidepressant use and RLS, others failed to demonstrate a definitive association.[11-13] In one of those studies, the prevalence of RLS was 9.2% among individuals taking antidepressant medications.[12] In another study, the frequency of RLS was 17.3% in 247 patients diagnosed with anxiety disorder or major depressive disorder who were on antidepressant treatment.[14] Contrastingly, 1 study found that SSRIs may reduce RLS symptoms.[15] The major reason for these contradictory results may be the close relationship of RLS with depression and anxiety. In fact, several studies have demonstrated that RLS is strongly correlated with depression and anxiety disorder.[16,17]

Studies showing increased RLS prevalence in anxiety disorder or major depressive disorder as well as case reports suggesting that antidepressants used to treat these conditions may cause RLS point out to the fact that clinicians should consider the possibility of RLS development in patients seeking treatment. The present study was designed with the aim to help clarify contradictory literature data to guide clinicians on the potential clinical implications of this relationship.

The current study primarily aimed to investigate whether the prevalence of RLS differed in patients diagnosed with major depressive disorder or anxiety disorder who were not receiving antidepressant medications compared to control group. Secondly, the study sought to examine whether there was a difference in RLS prevalence among patients on antidepressant treatment compared to patients not receiving antidepressant treatment and control subjects. The antidepressant treatment group consisted of patients who were identified as being in partial or complete remission following a psychiatric evaluation. The reason for the selection of patients in remission was due to the consideration that ongoing anxiety and depressive symptoms may have contributed to the reports of a link between antidepressants and RLS of the subjects in former studies. For these purposes, the validity of the following hypotheses was tested in our study: (1) the frequency of RLS is higher among patients with anxiety disorder or major depressive disorder not using antidepressant medications compared to healthy controls and (2) RLS is more common in patients in complete or partial remission who are in antidepressant treatment than in control subjects.

MAIN POINTS

- Restless legs syndrome (RLS) has been associated with certain psychiatric disorders including depression and anxiety disorder, and antidepressants are used to treat these conditions.
- Based on the results of our study, RLS is not correlated with age, gender, and smoking.
- Our findings indicate that RLS is closely associated with anxiety disorder, especially major depressive disorder.
- The frequency of RLS did not differ between patients taking antidepressant medications and control group, suggesting that antidepressants are not associated with RLS.
- Patients on dual antidepressant therapy showed a similar frequency of RLS compared to patients on antidepressant monotherapy. Thus, the use of combination antidepressant therapy does not seem to increase RLS frequency.

METHODS

Ethics approval for the study was obtained from the institutional review board of our university (April 19, 2021; no: 2021/12-03). Considering the study that found an RLS prevalence of 17.3% in patients diagnosed with anxiety disorder or major depressive disorder, the minimum sample size was calculated as 443 subjects per group at an alpha = 0.05, power = 0.80, and margin of error = 0.05.[14] Five hundred patients who presented to our psychiatry outpatient clinic between April 2021 and October 2021 and were diagnosed with anxiety disorder or major depressive disorder according to DSM-5 criteria without a history of antidepressant treatment were enrolled in the study consecutively based on the date of presentation (group 1). Other five hundred patients diagnosed with anxiety disorder or major depressive disorder and on antidepressant treatment who presented to our outpatient clinic during the same time period and were identified as being in complete or partial remission via psychiatric interview based on DSM-5 criteria were enrolled in the study consecutively based on the date of presentation (group 2). Complete remission was defined as the absence of signs and symptoms of the illness within the last 2 months. In cases where some of the disease symptoms persist but DSM-5 diagnostic criteria are no longer met, the individual was considered to be in partial remission. Partial remission was also considered for those without any evidence of the disease for less than 2 months.[18,19] Five hundred age- and sex-matched subjects without any mental illness and not receiving antidepressant medications were included in control group (group 3). The control group consisted of healthy volunteers accompanying patients and members of our hospital staff. Face-to-face interviews were conducted with all control subjects and those with symptoms of anxiety or major depression were not included in the study. Written informed consent was obtained from all participants and they were asked to complete sociodemographic data sheet and the Depression Anxiety Stress Scale-21 (DASS-21).

A structured clinical interview for DSM-5 disorders was conducted by psychiatrists on each participant. Following mental, physical, and neurological assessments, 5 essential criteria formulated by the IRLSSG were questioned in all participants for the diagnosis of RLS (Table 1). After the initial assessment, the RLS rating scale developed by IRLSSG (IRLS) was applied to the participants diagnosed with RLS.

Table 1. The Diagnostic Criteria Specified by the International Restless Legs Syndrome (RSL) Study Group (IRLSSG)

1. Generally, the presence of disturbing and unpleasant sensations in the legs and the resulting urge to move the legs (sometimes this impulse can arise without the disturbing sensations, affecting the arms and other parts of the body).
2. Starting and worsening of the urge to move the legs or the disturbing sensations at times of inactivity such as during resting, sitting, or lying down.
3. Partial or complete improvement of the symptoms by movement such as walking or stretching, at least as long as the activity continues.
4. The urge to move the legs and accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or at night compared to daytime.
5. The occurrence of the characteristics above cannot be solely accounted for as symptoms primary to another medical or behavioral condition, such as myalgia, venous stasis, swollen legs, cramps of legs, and habitual leg shaking.

All study subjects were evaluated for the differential diagnosis of other movement disorders and those taking antidepressants were also questioned for akathisia.

Individuals with iron-deficiency anemia, diabetes mellitus, thyroid disease, malignancy, rheumatic disease, Parkinson's disease, multiple sclerosis, cardiovascular disease, kidney disease, and pregnant women were excluded from the study. Individuals diagnosed with alcohol/substance use disorder, schizophrenia, bipolar disorder, and mental retardation were also excluded from the study. Additionally, those taking antihistamines, antiepileptics, and antipsychotic drugs for any reason were not included in the study.

Materials

The RLS diagnosis was made according to 5 essential criteria of the IRLSSG. These diagnostic criteria were developed by the IRLSSG in 1995 and revised in 2003.[2] All 5 criteria have to be met for a diagnosis of RLS. The IRLS was applied to the participants who fulfilled all diagnostic criteria.

Sociodemographic data sheet: Sociodemographic data of the participants including age, gender, marital status, medical history, employment status, smoking, and alcohol and medication use were collected using a study-specific data sheet generated by the study investigators.

RLS rating scale: The IRLS was developed by the IRLSSG for the measurement of the severity of RLS. The scale consists of 10 questions, each assigned a score ranging from 0 to 4 points. Total score reflects the disease severity and maximum possible score is 40. Score interpretation: 0 points: none, 1-10 points: mild RLS, 11-20 points: moderate RLS, 21-30 points: severe RLS, and 31-40 points: very severe RLS.[20]

The Depression Anxiety Stress Scale-21: The DASS-21 is the short form of the DASS-42.[21] The psychometric properties of the Turkish version were demonstrated by Sarıçam.[22] In a community sample, test-retest reliability coefficients were $r=0.68$ for the depression subscale, $r=0.66$ for the anxiety subscale, and $r=0.61$ for the stress subscale. The DASS-21 is a 4-point Likert scale with 7 questions in each subscale to measure the dimensions of depression, stress, and anxiety. Higher scores indicate more severe emotional distress.[22]

Statistical Analysis

Descriptive statistics of the current study were summarized as mean, standard deviation, and minimum-maximum values for numerical continuous variables and as frequency and percentage values for categorical variables. In order to evaluate whether the continuous data showed a normal distribution, kurtosis and skewness values were examined. As a result, it was found that the kurtosis values range from 0.185 (highest) to −1.122 (lowest). For skewness, the values range between 1.006 (highest) and −0.148 (lowest). It has been reported that data are considered to be normal if kurtosis and skewness values fall within the ±2 range.[23] Since the parametric test assumptions were met for numerical continuous variables, the independent samples *t*-test was used to compare the means of 2 independent groups. Mann-Whitney *U* test was used to compare the DASS-21 scale scores between the 2 groups since the standard deviation value was close to the mean value. One-way analysis of variance (ANOVA) was employed for comparisons of numerical continuous variables among more than 2 groups. As the variances for DASS-21 subscale scores were not homogeneous, ANOVA-Welch was used to compare the 3 groups in terms of scale scores. Games-Howell test was used to determine the source of difference among the groups. Categorical variables were compared among the groups using chi-squared test. Fisher-Freeman-Halton test was used when the values were expected to be below 5. A *P* value less than .05 was considered statistically significant.

A logistic regression analysis was performed where the presence of RLS was used as the dependent variable, and major depressive disorder, anxiety disorder, and antidepressant use (divided into 2 groups as major depressive disorder and anxiety disorder in remission) were evaluated as possible risk factors, with the control group included in the model as the reference category. The forward selection (conditional) method was used when performing the logistic regression analysis. Statistical Package for the Social Sciences Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA) was used for the analysis of the study data.

RESULTS

This study was conducted with a total of 1500 subjects including 500 patients diagnosed with major depressive disorder or anxiety disorder without a history of

antidepressant treatment (group 1), 500 patients with major depressive disorder or anxiety disorder in complete or partial remission who were currently on antidepressant treatment (group 2), and 500 healthy controls without any psychiatric illness and not on antidepressant treatment (group 3). The mean age of the study sample was 36.87 ± 12.43 years (minimum 18, maximum 80), of whom 979 (65.3%) were female.

There was no significant difference among the groups in age, gender, education level, marital status, employment status, and smoking ($P=.171$, $P=.752$, $P=.265$, $P=.402$, $P=.384$, $P=.254$, respectively). Sociodemographic characteristics of the groups and their mean scores from the assessment scales are shown in detail in Table 2.

In group 1, there were 214 (42.8%) patients with major depressive disorder and 286 (57.2%) patients with anxiety disorder. In group 2, 155 (31.0%) patients had major depressive disorder in complete or partial remission and 345 (69.0%) patients had anxiety disorder in complete or partial remission.

Among all participants, RLS was diagnosed in 101 (6.73%) individuals. There were no significant differences in age, gender, smoking status, marital status, and education level between those with or without a diagnosis of RLS ($P=.209$, $P=.519$, $P=.227$, $P=.508$, $P=.676$, respectively) (Table 3). The depression, anxiety, and stress subscale scores of DASS-21 were significantly higher in the subjects diagnosed with RLS ($P < .001$) Table 3). Of 101 subjects diagnosed with RLS, 29 had mild, 64 had moderate, and 8 had severe RLS symptoms. Those diagnosed with RLS were divided into 3 groups according to disease severity and analyzed with respect to DASS-21 depression, anxiety, and stress subscale scores using one-way ANOVA. No significant difference was found among the groups in terms of DASS-21 scores ($P=.154$, $P=.179$, $P=.764$, respectively).

Restless legs syndrome was diagnosed in 65/500 (13.0%) group 1 patients, 16/500 (3.2%) group 2 patients, and 20/500 (4.0%) control subjects, with a significant difference among the groups ($P < .001$) (Table 4).

Table 2. Comparison of Sociodemographic Characteristics and Scale Scores Among the Groups

	Group 1 (n=500)	Group 2 (n=500)	Group 3 (n=500)	*P*	*P*[d]
Age, years (mean ± SD)	36.12 ± 12.30	37.59 ± 12.63	36.90 ± 12.34	0.171[a]	
Gender					
Male, n (%)	180 (36.0)	169 (33.8)	172 (34.4)	0.752[b]	
Female, n (%)	320 (64.0)	331 (66.2)	328 (65.6)		
Smoking status, n (%)					
Yes	178 (35.6)	159 (31.8)	155 (31.0)	.254[b]	
No	322 (64.4)	341 (68.2)	345 (69.0)		
Marital status, n (%)					
Married	301 (60.2)	313 (62.6)	328 (65.6)	.402[b]	
Single	159 (31.8)	153 (30.6)	144 (28.8)		
Other	40 (8.00)	34 (6.8)	28 (5.6)		
Employment status, n (%)					
Full-time	235 (47.0)	206 (41.2)	227 (45.4)	.384[b]	
Part-time	8 (1.6)	4 (0.8)	5 (1.0)		
Student	80 (16.0)	86 (17.2)	81 (16.2)		
Retired	9 (1.8)	19 (3.8)	17 (3.4)		
Unemployed	168 (33.6)	185 (37.0)	170 (34.0)		
Education level, n (%)					
Primary education	144 (28.8)	148 (29.6)	157 (31.4)	.265[b]	
High school	140 (28.0)	136 (27.2)	157 (31.4)		
University	216 (43.2)	216 (43.2)	186 (37.2)		
DASS-21 (Depression)	7.58 ± 4.75	2.54 ± 1.26	0.85 ± 1.01	<.001[c]	<.001[d]
DASS-21 (Anxiety)	8.25 ± 3.27	2.73 ± 1.00	1.40 ± 1.23	<.001[c]	<.001[d]
DASS-21 (Stress)	8.98 ± 3.05	4.39 ± 1.84	2.43 ± 1.93	<.001[c]	<.001[d]

DASS-21, Depression Anxiety and Stress Scales-21; SD, standard deviation.
[a]One-way ANOVA; [b]Chi-square test; [c]ANOVA-Welch; [d]Post hoc (Games-Howell).
Significantly higher mean scores (group 1 vs. groups 2 and 3 and group 2 vs. group 3). The difference among all groups was highly significant ($P < .001$).
Group 1, patients not using antidepressants; Group 2, patients on antidepressant treatment and in remission; Group 3, controls.

Table 3. Distribution of Certain Characteristics in Those Receiving or Not Receiving RLS Diagnosis

	RLS		*P*
	Yes (n = 101)	No (n=1399)	
Gender			
Male (n = 521)	32 (6.1%)	489 (93.9%)	.519[a]
Female (n = 979)	69 (7.0%)	910 (93.0%)	
Smoking status			
Yes (n = 492)	39 (7.9%)	453 (92.1%)	.227[a]
No (n = 1008)	62 (6.2%)	946 (93.8%)	
Marital status (n)			
Married (n = 942)	69 (7.3%)	873 (92.7%)	.508[a]
Single (n = 456)	26 (5.7%)	430 (94.3%)	
Other (n = 102)	6 (5.9%)	96 (94.1%)	
Education level			
Primary education (n = 449)	34 (7.6%)	415 (92.4%)	.676[a]
High school (n = 433)	29 (6.7%)	404 (93.3%)	
University (n = 618)	38 (6.1%)	580 (93.9%)	
Age, years (mean ± SD)	38.37 ± 11.03	36.76 ± 12.53	.209[b]
DASS-21 (D) (median, min-max)	6 (1-15)	4 (0-21)	<.001[c]
DASS-21 (A) (median, min-max)	4 (1-15)	5 (0-17)	<.001[c]
DASS-21 (S) (median, min-max)	8 (2-13)	7 (1-20)	<.001[c]

DASS-21, Depression Anxiety and Stress Scales-21; D, depression; A, anxiety; S, stress; min, minimum; max, maximum; RLS, restless legs syndrome; SD, standard deviation.
[a]Chi-square test; [b]Independent samples *t*-test; [c]Mann–Whitney *U*.

In group 1, RLS was diagnosed in 39 (18.2%) of 214 patients with major depressive disorder and 26 (9.1%) of 286 patients with anxiety disorder and the difference was significant (*P* = .003).

When we analyzed the patients currently receiving antidepressants (group 2) with respect to the drugs used, sertraline (n = 115, 23.0%) was the most common antidepressant, followed by escitalopram (n = 80, 16.0%) and fluoxetine (n = 70, 14.0%). Of the patients taking antidepressant treatment, 324 (64.8%) patients have been receiving antidepressant treatment for less than 6 months and 176 (35.2%) for more than 6 months, and 431 (86.2%) patients were on antidepressant monotherapy and 69 (13.8%) were on dual antidepressant therapy. The most common dual therapy used by the patients was a SSRI in combination with mirtazapine (n = 34, 6.8%). The distribution of antidepressants used by group 2 patients and the prevalence of RLS diagnosis are shown in Table 5. As can be seen from Table 5, the prevalence of RLS diagnosis did not significantly differ among patients receiving different antidepressant drugs (*P* = .965). Restless legs syndrome was diagnosed in 14 of 431 (3.2%) patients receiving antidepressant monotherapy and in 2 of 69 (2.9%) patients receiving dual antidepressant therapy and the difference was non-significant (*P* = .878).

Finally, a logistic regression analysis model was constructed based on the presence of RLS. Group 1 subjects were divided into 2 subgroups according to the diagnosis of anxiety disorder or major depressive disorder. Similarly, group 2 subjects with antidepressant use were divided into 2 subgroups based on the diagnosis of anxiety disorder or major depressive disorder in remission. No change was made for group 3 subjects (controls). The regression analysis showed that patients with major depressive disorder were 5.3 times more likely to be diagnosed with RLS compared to controls. The likelihood of being diagnosed with RLS was

Table 4. Comparison of the Study Groups in Terms of the Presence of RLS

	RLS		*P*[a]	*P*[b]
	No	Yes		
Group 1 n (%)	435 (87.0)	65 (13.0)	<.001	<.001
Group 2 n (%)	484 (96.8)	16 (3.2)		<.001
Group 3 n (%)	480 (96.0)	20 (4.0)		.497

[a]Chi-square test; [b]Comparison with Bonferroni-corrected *P* value of .017 for 3 groups.
Thus, the difference between group 1 and groups 2 and 3 is significant but the difference between group 2 and group 3 is non-significant (*P* values were shown in the respective order).
Group 1, patients not using antidepressants; Group 2, patients on antidepressant treatment and in remission; Group 3, controls; RLS, restless legs syndrome.

Table 5. Comparison of RLS Prevalence Among Patients Receiving Antidepressant Treatment by Medication (n = 500)

	RLS			
Medication	n	Yes (%)	No (%)	*P*
Sertraline	115	3 (2.60)	112 (97.40)	.965[a]
Escitalopram	80	3 (3.75)	77 (96.25)	
Fluoxetine	70	3 (4.28)	67 (95.72)	
Paroxetine	59	2 (3.38)	57 (96.62)	
Citalopram	36	1 (2.77)	35 (97.23)	
Venlafaxine	33	1 (3.03)	32 (96.97)	
Duloxetine	23	1 (4.34)	22 (95.66)	
Vortioxetine	15	0 (0.00)	15 (100.0)	
SSRI + mirtazapine	34	1 (2.94)	33 (87.06)	
SNRI + mirtazapine	7	0 (0.00)	7 (100.0)	
SSRI + trazodone	28	1 (3.57)	27 (96.43)	

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norad renaline reuptake inhibitor; RLS, restless legs syndrome.
[a]Fisher–Freeman–Halton.

Table 6. Logistic Regression Analysis Model for Restless Legs Syndrome

	B	SE	95% CI	Odds	*P*
Control group (group 3)[a]					
Major depressive disorder (not on antidepressant treatment)	1.677	0.289	3.03-9.42	5.34	<.001
Anxiety disorder (not on antidepressant treatment)	0.875	0.307	1.31-4.38	2.40	.004
Antidepressant use (major depressive disorder in remission)	0.392	0.412	0.65-3.32	1.47	.342
Antidepressant use (anxiety disorder in remission)	0.699	0.445	0.20-1.18	0.49	.116

[a]Reference category.
Compared to controls, patients with major depressive disorder were 5.34 times more likely to develop RLS and patients with anxiety disorder were 2.4 times more likely to develop RLS.
RLS, restless legs syndrome; SE, standard error.

2.4 times greater among patients with anxiety disorder than in control subjects. However, the risk of developing RLS was not different in patients with anxiety disorder or major depressive disorder in partial or complete remission who were receiving antidepressant treatment than in controls (Table 6).

DISCUSSION

In the present study, 6.7% of all subjects were diagnosed with RLS. The frequency of RLS was 13.0% in patients with anxiety disorder or major depressive disorder without antidepressant use, 3.2% in patients in partial or complete remission who were on antidepressant treatment, and 4.0% in control subjects. The prevalence of RLS diagnosis did not significantly differ among patients receiving different antidepressant drugs. In addition, the RLS prevalence was similar in patients using antidepressant monotherapy or dual therapy.

As a result of our study, the first hypothesis was confirmed: the frequency of RLS was higher among patients with anxiety disorder or major depressive disorder not using antidepressant medications compared to healthy controls. However, RLS was not more common among patients in remission using antidepressants compared to controls, and therefore, the second hypothesis was rejected.

In the general population, the reported prevalence rates vary from 4.6% in the United Kingdom, 8% in France, and up to 13% in Germany.[24] In our study, the prevalence of RLS among control subjects was lower than that observed in the general population. This is most probably related to the fact that the presence of medical conditions associated with RLS was considered an exclusion criterion when forming the control group. Although medical conditions were excluded from the control group, 4% of them still had RLS, probably because these individuals had primary RLS.

No significant difference was found between those receiving or not receiving a diagnosis of RLS in terms of age, gender, education level, marital status, employment status, and smoking history in our study. Consistently, RLS was not found to be associated with age and gender in 2 studies from Turkey.[11,12] In 1 of these studies, a link between smoking and the presence of RLS was demonstrated.[11] However, in a study from Canada involving 2019 subjects, smoking was not reported to be associated with RLS.[25]

The prevalence of RLS was similar in patients on antidepressant treatment and control subjects in our study, suggesting that antidepressants may not be implicated in the development of RLS. This finding is inconsistent with the data from several previous reports. In a Turkish study involving 414 patients receiving antidepressant therapy, the incidence of RLS was 15.5%, which was much higher than that observed in the general population.[11] In another study, borderline significance was found in the association between the development of RLS and antidepressants in 555 patients taking antidepressant therapy compared to control group.[12] One study in the general population reported a 3-fold higher RLS prevalence in SSRI users than in non-SSRI users.[26] Also a study using the world pharmacovigilance database found an association between SSRIs and all movement disorders, including RLS.[27] In contrast, antidepressant use was not associated with RLS in a study that reviewed medical records of 10 875 patients who were prescribed antidepressants and RLS treatment for the first time.[13] On the other hand, contrary to all literature data reported to date, SSRI use was suggested to reduce the symptoms of RLS.[15]

Unlike many other studies, no association was found between antidepressant use and RLS in the present study, which may be primarily related to methodological differences. In our study, the antidepressant treatment group consisted of patients in partial or complete remission. Higher RLS frequency in patients using antidepressants as reported by other studies may be due to ongoing symptoms of depression and anxiety in those patients. A close association of RLS with anxiety and depression symptoms was demonstrated in former studies.[16,17] In a study examining the relationship between antidepressants and RLS, 414 patients were divided into 2 groups, and patients with a Hospital Anxiety Depression Scale depression subscale score of ≤7 showed a significantly lower RLS prevalence compared to patients with a score greater than 7.[11]

In a study involving 112 patients diagnosed with RLS, the 1-year prevalence of major depression disorder was found to be 33%.[28] Although the close relationship between depression and RLS is known, the underlying mechanism has not been fully elucidated. Possible mechanisms include the

occurrence of depression as a result of RLS, predisposition to develop RLS due to depression, and the presence of a third factor causing both RLS and depression. Another factor that should be taken into account is the possibility of misdiagnosis of one condition in the presence of the other due to a number of overlapping symptoms.[29] Sleep disturbance, tiredness, decreased concentration, and psychomotor agitation are common symptoms of both diseases.[17] Additionally, sleep disruption, decreased energy, and pain associated with RLS may predispose to depression. Studies have shown that insomnia, daytime sleepiness, fatigue, and pain are risk factors for depression. Thus, RLS may be directly causing depression.[17,30] On the other hand, in a study, patients diagnosed with RLS accompanied by depression and those with RLS without depression were compared. According to the results of the study, there was no difference between 2 groups in terms of RLS symptoms and RLS severity. In addition, no difference was found between the groups in terms of sleep disturbance and insomnia severity. The results of this study indicate that insomnia and psychological effects caused by HBS do not directly lead to the development of depression.[28] In patients with depression, longer sleep latency, and decreased movement due to fatigue may lead to a predisposition to develop RLS.[17,31] Another possibility is that a common factor might be involved in the development of both RLS and depression. Dopaminergic dysfunction in the central nervous system may explain the coexistence of both conditions. It is known that RLS symptoms respond very well to low doses of dopamine agonists.[1] On the other hand, metoclopramide (a dopamine receptor antagonist) and antipsychotic drugs may potentially aggravate RLS symptoms.[6] Although the role of dopamine in depression is unclear, decreased dopamine receptor sensitivity and reduced dopamine turnover have been observed in depression.[32] Adding dopamine agonists to the treatment regimen was shown to ameliorate depressive symptoms in patients with treatment-resistant depression.[33]

Anxiety disorders are known to cause RLS symptoms, although this link has been investigated to a lesser extent compared to depression. Higher rates of anxiety were found in patients with RLS in comparison to control group. The same study also reported a correlation between anxiety symptoms and RLS severity.[34] In another study, panic disorder was 4 times more common in RLS patients than in control subjects.[35] In line with the literature data, patients with major depression and anxiety disorder were significantly more likely to receive an RLS diagnosis than healthy controls in our study. With this finding, our study corroborates the close relationship of RLS with both major depressive disorder and anxiety disorder. Additionally, when we divided group 1 patients according to their diagnoses, patients with major depressive disorder showed a significantly higher frequency of RLS compared to those with anxiety disorder. Based on the results of the regression analysis, the likelihood of developing RLS was 5.34 times higher in patients with major depressive disorder and 2.4 times higher in patients with anxiety disorder compared to controls. These results show that RLS is more strongly correlated with major depressive disorder than anxiety disorder. In contrast, in a sample of 414 patients, Ocak et al[11] reported that the RLS prevalence was not different when compared between patients with major depressive disorder and patients with anxiety disorder.

There are many case reports of RLS induced by, especially, SSRIs and mirtazapine.[8,9] Antidepressants are thought to induce RLS symptoms by causing increased serotonergic and noradrenergic activity, as well as decreased dopaminergic activity.[36,37] Another possibility is the occurrence of RLS via histamine receptor blockade with certain antidepressants such as mirtazapine.[9,36] In many case reports of RLS induced by antidepressants, RLS symptoms occurred within the first week after starting antidepressant treatment.[38,39] Some antidepressants are known to increase anxiety symptoms at the initial phase of antidepressant therapy. Considering the relationship between RLS and anxiety, RLS symptoms seen in the first week after the initiation of antidepressant treatment in previous case reports may be related to anxiety as a drug side effect.

In our study, the distribution of RLS according to the antidepressants used was examined in group 2 patients who were currently on treatment. No difference was found in the prevalence of RLS among patients using different antidepressants. In addition, the use of dual antidepressant therapy did not seem to be a risk factor for the development of RLS. Similarly, the prevalence of RLS in patients receiving combination antidepressant treatment (6.8%) was not different from that observed in control group (5.9%) in one study.[12] On the other hand, in another study, RLS was diagnosed in 4 of 12 patients taking mirtazapine in combination with an SSRI and 6 of 18 patients using trazodone in combination with an SSRI. Thus, one-third of the patients receiving these combination therapies were diagnosed with RLS in that study.[11] However, since the severity of major depression or anxiety disorder symptoms in those patients is not known, it is difficult to conclude that there is a clear link between combination antidepressant treatment and RLS based on these results.

Our study has a number of important limitations. First of all, this study had a cross-sectional design which might have affected our results. That is, some patients developing RLS while taking antidepressant drugs might have discontinued their medications or switched to another antidepressant treatment without side effects. This might explain the low prevalence of RLS in patients receiving antidepressant treatment. Secondly, laboratory investigations were not performed on the study subjects, and only previous

medical history and medical records of the subjects were taken into account at the time of enrolment. Another limitation of our study is that the diagnosis of complete or partial remission in group 2 subjects was based on clinical interview alone, with no use of any additional tools. Unfortunately, the DASS-21 scale used in our study does not have a cut-off score to determine disease severity. Moreover, Structured Clinical Interview for DSM-5 (SCID-5) were not employed in our study due to large sample size, which may be considered an important limitation. Family history of RLS was also questioned but the unavailability of adequate information precluded our ability to make a meaningful assessment of family history. This may be considered as another limitation of our study. Lastly, the distribution of antidepressants used by group 2 patients was not homogeneous due to a lower number of some antidepressant drugs.

Despite the aforementioned limitations, we believe that our study provides valuable data which could make important contributions to the literature. The major strength of our study is the inclusion of a large number of subjects, which makes it one of the studies with the largest sample size in this research area conducted to date, apart from some community-based studies. Another strength of the study is that only patients in partial or complete remission were included through face-to-face interviews among patients receiving antidepressant medications. This is an important feature of our study which differentiates it from previous studies.

In conclusion, the data from our study indicate that antidepressant use does not seem to be a risk factor for the development of RLS, which is in contrast with many previous reports. However, our study presents important data on the close association of RLS with anxiety disorder, especially major depressive disorder. Nevertheless, since this was a cross-sectional study, we think that the results of our study should be interpreted with caution and need to be confirmed by prospective studies.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Sanko University (approval no: 2021/12-03).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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