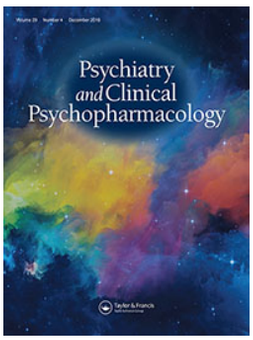

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Is restless legs syndrome related with depression/anxiety disorders or medications used in these disorders? A cross-sectional, clinic-based study

Davut Ocak [a], Vahap Ozan Kotan[b], Salih Cihat Paltun[c] and Makbule Çiğdem Aydemir[d]

[a]Department of Psychiatry, Kahramanmaraş Necip Fazıl City Hospital, Kahramanmaraş, Turkey; [b]Department of Psychiatry, Başkent University Medical Faculty, Ankara, Turkey; [c]Department of Psychiatry, Ankara Numune Training and Research Hospital, Ankara, Turkey; [d]Department of Psychiatry, Ankara University School of Medicine, Ankara, Turkey

ABSTRACT

Objective: The aim of this study is to investigate the frequency and severity of restless legs syndrome (RLS) in patients diagnosed with depression or anxiety disorder and the relationship of RLS with medications used in these disorders and clinical/sociodemographic characteristics of the patients.

Methods: Four hundred and fifty-four consecutive patients who were treated with medication for "Depressive Disorder" or "Anxiety Disorder" in our outpatient clinic were included in the study. Subjects were screened by International Restless Legs Syndrome Study Group (IRLSSG) scale, Hospital Anxiety Depression Scale. Patients who met the criteria of RLS diagnosis due to the RLS screening scale ($n = 104$) were interviewed in detail. Patients' laboratory tests were performed to investigate medical conditions other than antidepressant/antipsychotic use known to be related with RLS and 40 (8.8%) of 104 patients were excluded from the study. The main study group consisted of 414 patients.

Results: The mean IRLSSG score of 64 patients diagnosed with RLS was 18.95 ± 5.11 (min: 7–max: 29), 7.8% of whom had mild and 55.1% had severe RLS. The incidence of RLS in patients receiving antidepressant treatment (*n*: 414) was significantly higher than the general population (15.5%). There were no significant difference neither between diagnostic groups (anxiety/ depression) nor individual antidepressants by means of RLS. Patients receiving combined treatment like SSRI + quetiapine, SSRI + mirtazapine or SSRI + trazodone scored 4.7 times higher on RLS scale.

Discussion: There was no significant difference by means of RLS diagnosis or severity of RLS in patients with a diagnosis of anxiety/depressive disorder. However antidepressant using patients' RLS prevalence was higher than general population's. It was noticed that patients who received combined drug treatment had a 4.7-fold increase in RLS. In conclusion; beginning with as possible as the least number and dose of psychotropic drugs when treating a patient with depression or anxiety disorder does not increase RLS risk as well as providing advantages such as reduced risk of drug interaction and side effects.

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Restless legs syndrome; psychiatric treatments; depression disorder; anxiety disorder; RLS; antidepressants

Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by abnormal sensations, caused by the impulse or need to move legs. Symptoms usually occur at night and often on legs, and rarely on arms symmetrically. RLS should be suspected in patients who have difficulty falling asleep, have difficulty in maintaining sleep and who complain of increased fatigue, concentration impairment and depressive mood during the day. Surveys have shown that RLS affects sleepiness [1], cognitive functions [2,3] and quality of life [4] negatively.

Diagnosis of RLS is made by evaluation of the patient's subjective data and the diagnostic criteria developed. RLS can be easily recognized by an evaluation of four questions which can easily be asked in the practice of psychiatric outpatient clinic. Based on the aetiology, RLS is divided into two groups as idiopathic (primary) and symptomatic (secondary). The majority of RLS patients have idiopathic form and this form is early onset [5]. Symptomatic RLS occurs due to medical, neurological or other primer sleep disorder. Iron deficiency, DM, end-stage renal disease, Parkinson's disease may play a role in aetiology. It should not be forgotten that there may be clinical signs of accompanying abnormalities in the symptomatic form of RLS. Besides medical conditions, use of antipsychotics, antihistamines, antidepressants and analgesics have been reported to cause RLS [6–10]. RLS is associated with the use of antidepressant medications, but the number of studies which investigated this relationship is limited in the literature except the case reports [11,12].

A large study of RLS-related factors which conducted with approximately 19,000 subjects in general

CONTACT Davut Ocak ocak.davut@gmail.com

population, investigating association RLS and antidepressant treatments, found that RLS risk was threefold increased in those receiving SSRIs, but not for other antidepressant treatments [13]. Another study reported that 9% of the patients which were included in the study were diagnosed with SSRI-induced RLS [14]. In a study conducted in our country by Odabas and Uca, the prevalence of RLS was found 5.9% among the controls and 9.2% in the patients treated with antidepressants, and the difference between both groups was statistically significant at a limited level [15]. However, some other studies reported that the use of SSRIs to be associated with impairment in preexisting RLS symptoms [16]. Despite all these studies, the number of studies investigating the frequency and severity of RLS in depression and anxiety disorders and the relationship between RLS and psychiatric treatments are still limited in the literature.

In this study, we aimed to investigate the frequency and severity of RLS in patients on medical treatment (depression or anxiety disorder) and the relationship of RLS with medications used in these disorders as well as clinical/ sociodemographic characteristics of the patients. Thus, we have two hypotheses. Our first hypothesis is that the frequency and severity of RLS are increased in patients with anxiety and depression disorder receiving medical treatment. Our second hypothesis is that the frequency and severity of RLS increase with increasing HADS scale scores.

Method

Sample

Four hundred and fifty-four consecutive patients who were diagnosed with anxiety or depression disorder according to Diagnostic Statistical Manual – Fifth Edition (DSM-V) by psychiatry consultants in Ankara Numune Training and Research Hospital Psychiatry outpatient clinic between 1 April 2016 and 31 July 2016 were screened in our study. The individuals accepting to participate in the study were informed, and written informed consents were also obtained from all participants. After a detailed psychiatric, physical and neurological examination, sociodemographic data form and Hospital Anxiety Depression Scale were requested to be filled to evaluate the anxiety and depression severity by the responsible clinician at the first interview in which the patients were evaluated. RLS criteria were investigated according to criteria which were developed by International Restless Legs Syndrome Study Group (IRLSSG) to diagnose RLS. After the first evaluation 104 patients diagnosed with RLS according to IRLSSG criteria. The IRLSSG rating scale was applied to these remaining 64 patients to determine the severity of the disease.

Complete blood count (CBC), liver and kidney function tests, thyroid function tests, vitamin B12, folate, fasting blood sugar, ferritin, iron, iron-binding capacity levels screenings were applied to patients those diagnosed with RLS in the first evaluation. Forty of 104 patients who were diagnosed with RLS were excluded from the study since they were detected to have other medical conditions that could cause RLS. The scales of patients who were excluded from the study according to the results of blood tests were not evaluated in the study. The patients who had comorbid diseases but not diagnosed RLS in order to IRLSSG scale were not excluded from the study. Akathisia was ruled out by the clinician during the clinical evaluation of the patients. The sample consisted of 414 patients after exclusion of 40 patients.

Material

RLS diagnosis was performed under the criteria of RLS proposed by the IRLSSG. The criteria was developed by IRLSSG in 1995 and updated in 2003. Five diagnostic criteria must be met according to IRLSSG.

The demographic data such as age, gender, marital status, educational status, smoking status, comorbid diseases, drug therapies and disorder were obtained from the sociodemographic data form.

The IRLSSG rating scale was applied to these remaining 64 patients to determine the severity of the disease.

IRLSSG Rating Scale: This scale was developed by the IRLSSG in 2003 and accepted as the gold standard. This scale consists of 10 questions, each graded between 0 and 4. While the first five questions focus on the severity of the symptoms the last five questions are aimed at questioning the effects of RLS on daily life activities or quality of life. The total score reflects the severity of RLS. The maximum score is 40 and it is rated as 1–10 mild, 11–20 moderate, 21–30 and severe and 31–40 very severe [12].

HADS: Developed by Zigmond et al. in 1983 and Turkish validity and reliability were made by Aydemir et al. This scale consists of 14 items, 7 items for depression and 7 items for anxiety levels. Each item had been answered by the patient on a four-point (0–3) response category so the possible scores ranged from 0 to 21 for anxiety and 0 to 21 for depression [17].

In order to perform the study, ethical committee approval of E-16-821 dated 2 March 2016 was obtained for the study.

Statistical analysis

The research data were loaded and evaluated in a computer environment via "SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL)." Descriptive statistics were presented as mean ± standard deviation, frequency distribution and percentage. Pearson Chi-square test and Fisher's exact test were used to evaluate categorical variables. The normal

distribution of variables was examined visually (histogram and probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk Test). Student's *T*-test was statistically significant between the two independent groups for the variables with normal distribution, and among the three independent groups; One-Way ANOVA was applied. The Tukey HSD test was used in post-hoc comparisons to determine the source of the difference when a significant difference was found between the three independent groups. For the variables which are determined as not meeting the normal distribution; Mann–Whitney *U* test was used for statistical significance between two independent groups; The Kruskal–Wallis test was used as a statistical method. Post-hoc Bonferroni correction was performed to determine the source of the difference when a significant difference was found between the independent groups. The relationship between variables was assessed by Spearman Correlation Analysis. The independent effects of some possible predictors on prediction of RLS were determined by Multivariate Logistic Regression Analysis. Model fitting was studied using the necessary residual and fit statistics. Statistical significance level was accepted as $p < 0.05$.

Results

A total of 414 patients with depressive and/or anxiety disorders investigated in this study. The mean age of the patients was 42.13 ± 14.55 (min: 18–max: 83) years. 67.6% of the patients (280) were female and 32.4% of the patients (134) were male. Seventy-three patients had comorbid diseases(45 hypertension, 6 coronary artery disease, 5 migraine, 4 hypercholesterolaemia, 2 asthma, 2 chronic obstructive pulmonary disease, 1 chronic viral hepatitis (HBV), 1 arhytmia, 1 benign prostatic hyperplasia, 1 scoliosis, 1 sjogren, 1 rheumatoid arthritis, 1 polycystic kidney disease, 1 fibromyalgia, 1 gastritis). Ninety-three patients were smokers. One hundred and thirty-eight patients were using combined drug therapy.

There was a statistically significant difference in terms of smoking status and combined drug treatment status among those who were examined with RLS ($p < 0.05$). The percentage of smokers and combined drug treatment among those with RLS was significantly higher than those without RLS (Table 1). Other diseases were found to be not relevant to RLS ($p > 0.05$)

On the other hand, no statistically significant difference was found in terms of age, gender, marital status, education status, presence of additional disease ($p > 0.05$) (Table 1).

There was no statistically significant difference in the prevalence of RLS among patients with an anxiety disorder or depression disorder ($p > 0.05$) (Table 1).

One hundred and thirty-eight of the patients' (33.3%) were receiving two psychotropic medications at the same time (Table 1). The most commonly used second psychotropic medications were quetiapine (29.7%), trazodone (21.0%) and mirtazapine (16.7%).

Sixty-four of the patients were found to have RLS (% 15.5). Mean IRLSSG score of the 64 patients with RLS was 18.95 ± 5.11 (min: 7–max: 29), which was 7.8% mild, 55.1% moderate and 39.1% had severe RLS (Table 2).

There was no statistically significant difference between the patients with an anxiety disorder or depressive disorder in terms of RLS, RLS severity and IRLSSG score ($p > 0.05$) (Table 2).

Table 1. The distribution of some descriptive and clinical features according to the presence of restless legs syndrome.

	RLS presence		
	No ($n = 350$) *n* (%)	Yes ($n = 64$) *n* (%)	p^b
Age (years), mean ± SD (min–max)	41.95 ± 14.82 (18–83)	43.09 ± 13.09 (19–66)	0.491[c]
Gender			
Female	232 (66.3)	48 (75.0)	0.171
Male	118 (33.7)	16 (25.0)	
Marital status[a]			
Married	216 (61.7)	44 (68.8)	0.284
Single	134 (38.3)	20 (31.2)	
Education status			
Illiterate/elementary	116 (33.1)	19 (29.7)	0.064
Secondary/high School	93 (26.6)	26 (40.6)	
University	141 (40.3)	19 (29.7)	
Smoking status	70 (20.0)	23 (35.9)	**0.005**
Comorbid diseases	64 (18.3)	9 (14.1)	0.415
Drug therapy			
Monotherapy	252 (72.0)	24 (37.5)	**<0.001**
Combined drug therapy	98 (28.0)	40 (62.5)	
Disorder			
Anxiety disorder	203 (58.0)	41 (64.1)	0.365[b]
Depression disorder	147 (42.0)	23 (35.9)	

Note: Mean: average; SD: standard deviation; *n*: number of patients; %: column percentage.
[a]Those who were divorced or widowed combined with the column single la.
[b]Chi-square test.
[c]Mann–Whitney *U* test.

Table 2. The prevalence of RLS and the IRLSSG scale score and the severity of RLS according to the diagnosis of the patients.

	Total	Anxiety disorder	Depression disorder	*p*
RLS ($n = 414$), *n* (%)				
No	350 (84.5)	203 (83.2)	147 (86.5)	0.365[a]
Yes	64 (15.5)	41 (16.8)	23 (13.5)	
RLS severity ($n = 64$), *n* (%)				
Light	5 (7.8)	4 (9.8)	1 (4.3)	0.692[a]
Medium	34 (53.1)	22 (53.7)	12 (52.2)	
Severe	25 (39.1)	15 (36.6)	10 (43.5)	
IRLSSG ($n = 64$), mean ± SD (min–max)	18.95 ± 5.11 (7–29)	19.12 ± 5.03 (8–29)	18.65 ± 5.35 (7–29)	0.822[b]

Note: Mean: average; SD: standard deviation; *n*: number of patients; %: column percentage; RLS: restless leg syndrome; IRLSSG: International Restless Legs Syndrome Working Group Scale.
[a]Chi-square test.
[b]Mann–Whitney *U* test.

In patients with a HADS anxiety subscale score higher than 10, the RLS frequency was significantly higher than those with HADS anxiety subscale score of 10 and below ($p < 0.05$). On the other hand, there was no statistically significant difference between the patients had HADS anxiety subscale scores of 10 and below and those above 10 in terms of RLS severity and IRLSSG score ($p > 0.05$) (Table 2). In patients with a HADS depression subscale score above 7, percentage of RLS was significantly higher than those with a HADS depression subscale score of 7 and below ($p < 0.05$). On the other hand, there was no statistically significant difference between HADS depression subscale score 7 and below and those higher than 7 in terms of RLS severity and IRLSSG score ($p > 0.05$) (Table 3).

There was no statistically significant difference between the patients with mild/moderate RLS and those with severe RLS according to all the drugs used ($p > 0.05$) (Table 4).

The distribution of presence of RLS according to the combination types of SSRI and SNRI group drugs is presented in Table 5.

There was a statistically significant difference in the presence of RLS between SSRI and SNRI combination types ($p < 0.05$). The percentage of patients with RLS using SSRI alone was significantly lower than those of using SSRI + quetiapine, SSRI + mirtazapine and SSRI + trazodone. On the other hand, the percentage of subjects with SNRI + trazodone who had RLS was significantly higher than those using SNRI + quetiapine, SNRI + mirtazapine and SNRI alone (Table 5).

There was no statistically significant difference between the patients who used SSRI + quetiapine and those used SNRI + trazodone combination types, in terms of RLS presence ($p > 0.05$).

According to the results of the analysis; The HADS anxiety subscale scores, smoking status and using combined drug therapy were effective in predicting the presence of RLS (in order, Wald $\chi^2 = 13.644$; $p < 0.001$, Wald $\chi^2 = 7.707$; $p = 0.015$, Wald $\chi^2 = 22.653$; $p < 0.001$). However, the HADS depression subscale score group, gender, alcohol use status, SSRI and SNRI use status were not effective ($p > 0.05$). RLS was 3.3 fold with those HADS anxiety subscale score higher than 10, 2.6 fold with smokers and 4.7-fold those with taking combined medication (Table 6).

Discussion

Sixty-four (15.5%) of the 414 patients examined in our study, were diagnosed with RLS. Frequency of RLS in two epidemiological studies conducted in the general population in Turkey was found to be 3.19% and 3.42% respectively [11]. The prevalence of RLS was found to be higher than the general population's. High prevalence of RLS in our study is thought to be caused by our study sample which was consisted of the population using antidepressant monotherapy or combined drug therapy due to depressive disorder or anxiety disorder or in relation to RLS-depression disorder and RLS-anxiety disorder. The relationship between the use of antidepressant and frequency of RLS is usually written as case reports in the literature

Table 3. Distribution of RLS absence, severity and IRLSSG score according to severity of anxiety and depression.

	HADS anxiety			HADS depression		
	≤10	>10	*P*	≤7	>7	*p*
RLS ($n = 414$), *n* (%)						
No	213 (91.8)	137 (75.3)	<0.001[a]	225 (88.2)	125 (78.6)	0.008[a]
Yes	19 (8.2)	45 (24.7)		30 (11.8)	34 (21.4)	
RLS Severity ($n = 64$), *n* (%)						
Light/medium	11 (57.9)	28 (62.2)	0.746[a]	19 (63.3)	20 (58.8)	0.712[a]
Severe	8 (42.1)	17 (37.8)		11 (36.7)	14 (41.2)	
IRLSSG ($n = 64$), av ± SD	19.00 ± 5.35	18.93 ± 5.06	0.962[b]	18.67 ± 4.72	19.21 ± 5.48	0.677[b]

Note: av: average; SD: standard deviation; *n*: number of patients; %: column percentage; RLS: restless leg syndrome; IRLSSG: International Restless Leg Syndrome Study Group Scale.
[a]Chi-square test.
[b]Student's *T* test.

Table 4. The distribution of severity of restless leg syndrome according to the drugs used by the patients.

Drugs used	Mild/Moderate RLS (*n* = 61)	Severe RLS (*n* = 36)	*p*[a]
SSRI	*24 (57.1)*	*18 (42.9)*	*0.390*
	6 (60.0)	4 (40.0)	*1.000*[b]
Escitalopram			
Fluoxetine	4 (66.7)	2 (33.3)	*1.000*[b]
Paroxetine	5 (41.7)	7 (58.3)	*0.190*[b]
Sertraline	8 (80.0)	2 (20.0)	*0.292*[b]
Citalopram	1 (25.0)	3 (75.0)	*0.291*[b]
TCA	*0*	*1 (100)*	*0.391*[b]
	0	1 (100)	0.391[b]
Clomipramin			
SNRI	*14 (70.0)*	*6 (30.0)*	*0.316*
Duloxetine	8 (61.5)	5 (38.5)	*0.960*
Venlafaxine	6 (85.7)	1 (14.3)	*0.231*[b]
OTHERS	*1 (100)*	*0*	*1.000*[b]
	1 (100)	0	*1.000*[b]
Agomelatine			

Note: *n*: number of patients; %: per cent; RLS: restless leg syndrome; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant; SNRI: serotonin and noradrenaline reuptake inhibitor.
[a]Chi-square test.
[b]Fisher's final test.

Table 5. Distribution of RLS presence according to combination types of SSRI and SNRI combination groups.

	Patients without RLS (*n* = 295) *n* (%)	Patients with RLS (*n* = 51) *n* (%)	p
SSRI combination type			
SSRI + quetiapine	17 (60.7)	11 (39.3)	<0.001
SSRI + mirtazapine	8 (66.7)	4 (33.3)	
SSRI + trazodone	12 (66.7)	6 (33.3)	
Only SSRI	189 (93.1)	14 (6.9)	
SNRI combination type			
SNRI + quetiapine	12 (92.3)	1 (7.7)	0.012
SNRI + mirtazapine	9 (81.8)	2 (18.2)	
SNRI + trazodone	5 (45.5)	6 (54.5)	
Only SNRI	43 (86.0)	7 (14.0)	

Note: *n*: number of patients; %: per cent of line; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin and noradrenaline reuptake inhibitor.

[11,12]. Many case reports point to the possibility of antidepressant-induced RLS [18–24]. A large study of investigating RLS and antidepressant association approximately 19,000 subjects in general population, found that RLS risk increased three-fold in those with SSRI medication but not with other medications [13]. In another study, 9% of the patients included in the study were diagnosed with SSRI-induced RLS. In a study conducted by Brown et al., 45% of patients taking antidepressant medication were found to meet the diagnostic criteria for RLS, but this was considered to be related to primary diseases and medications being used [12]. In the study of Dimmit and Riley, contrary to previous studies, there was no association between antidepressant use and RLS. On the contrary, there was improvement in the prevalent symptoms of RLS with the use of SSRIs [16]. In a study conducted in our country the prevalence of RLS was found as 5.9% among the controls, and 9.2% among the patients being treated with antidepressants and the difference between both groups was statistically significant at borderline [15] ($p = 0.053$).

In our study, there was no significant difference in the presence or severity of RLS in patients with an anxiety disorder or depressive disorder who were under antidepressant monotherapy. Compatibly, in a systematic study conducted by Brown et al., there was no relationship between primary diagnosis and RLS [12].

In patients with a HADS depression subscale score above 7, percentage of RLS was significantly higher than those with a HADS depression subscale score of 7 and below. That can occur due to symptoms quite common in patients with RLS such as depression, sleep disorders, fatigue, sleep deprivation, decreased concentration and psychomotor agitation [25]. In a review by Picchietti and colleagues, symptoms of depression were found to be widespread in individuals with RLS, and complexity of the relationship between RLS and depression symptoms was noted. Possible explanations for the relationship between depression and RLS include: RLS leading to depression, depression leading to RLS, or a third factor leading to both RLS and depression. Another possibility is that symptoms of a disorder are misdiagnosed as the other disorder and therefore a false relationship between the two disorders is being created [26]. RLS can cause depression with negative effects on sleep, wakefulness and energy. Various epidemiological studies have shown that insomnia, hypersomnia and fatigue are independent risk factors for major depression [27,28]. Despite the fact that insomnia, excessive sleeping, and the underlying causes of fatigue are not identified and likely to vary in these studies, each of these symptoms can be seen in patients with RLS. Pain and social isolation, which are common in people with RLS, may also be predictors of depression [29,30]. Finally, RLS can be considered as a nonspecific stress factor that can induce depressive symptoms. Mechanisms are not clear about the etiopathogenesis of RLS in depression. However, depressive symptoms such as sleep deprivation, malnutrition or lack of exercise may predispose the development of RLS [31–33]. However, people with depression may describe symptoms of subclinical or mild RLS more intensely; which may occasionally cause the diagnosis of RLS to be met. The fact that a third factor is associated with both RLS and depression may inadvertently lead to the conclusion that there is a causal relationship between depression and RLS. This factor can range from dopaminergic system dysfunction to genetic associations that can be seen both in RLS and depression [34,35]. Dopaminergic hypofunction may potentially cause symptoms of RLS and depression [36]. The remarkable efficacy of dopamine agonists in treatment of RLS provides inferential support for the

Table 6. Independent effects of some possible predators in predicting restless leg syndrome (multivariate logistic regression analysis).

	B	SE	Wald χ^2	sd	OR	%95-CI	*p*
HADS anxiety score							
≤10				*Reference*			
>10	1.155	0.319	13.142	1	3.174	1.700–5.927	**<0.001**
HADS depression score							
≤7				*Reference*			
>7	0.189	0.312	0.369	1	1.208	0.656–2.226	0.543
Gender							
Male				*Reference*			
Female	0.674	0.368	3.356	1	1.962	0.954–4.034	0.067
Smoking status	0.965	0.338	8.130	1	2.624	1.352–5.092	**0.004**
Using alcohol	−0.688	0.496	1.920	1	0.503	0.190–1.330	0.166
Combined treatment	1.409	0.314	20.142	1	4.091	2.211–7.569	**<0.001**
Using SSRI	0.209	0.804	0.068	1	1.233	0.255–5.958	0.794
Using SNRI	0.345	0.841	0.168	1	1.412	0.272–7.342	0.682

Note: regression factor; SE: standard error; OR: odds ratio; GA: confidence interval. Cox and Snell R2: 0.13; Nagelkerke R2: 0.23; Hosmer and Lemeshow, 2: 8.43, $p = 0.393$.

role of dopaminergic abnormalities in RLS. The role of dopamine in depression is less established. Several dopamine-receptor agonists have been shown to be effective in treatment of depression.

The association of depression and RLS can be a product of overlapping symptoms of these two disorders. Four criteria for depression disorder according to DSM-5, can also be seen in RLS as; insomnia or over sleep, fatigue/loss of energy, decrease in concentration and psychomotor retardation or agitation. In this way, an individual with RLS can be diagnosed with depression much more easily in the depression questionnaire. On the other hand, individuals with major depression may be mistakenly diagnosed with RLS in epidemiological studies [37]. Because older depressed patients often become somatized, which can lead to a response to questions about discomfort and discomfort in the legs. These and similar causes reveal the weaknesses of scales for RLS and depression. Studies using Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D) in the literature have shown that depression and anxiety scores are higher in studies investigating the severity of anxiety or depression with RLS. Sevim et al. reported that HAM-D and HAM-A scales were not designed to measure anxiety and depression levels in RLS patients and that sleep-related items were excluded before comparing the total patient and control scores. As well as the fact that Hospital Anxiety Depression Scale (HADS) is a better choice for evaluating anxiety and depressive symptoms in patients with somatic diseases, HADS was also chosen in our study because of the reasons explained above. When we compared the anxiety disorder and depressive disorder groups in our study, we did not find any significant difference between HADS depression and anxiety subscale scores and RLS severity.

In our study, it was seen that RLS increased 4.7 times in the group receiving combined drug treatment. In a study conducted by Çalıkuşu and his colleagues, there was a similar relationship between RLS and combined drug therapy [38]. In addition, Baughman and colleagues found no significant risk of RLS development in patients using combined antidepressants [39]. In another study conducted by Odabas and Uca no statistically significant difference was determined between the groups receiving mono or combined treatment [15].

A statistically significant difference was found in the presence of RLS among the patients treated with combinations of SSRI or SNRI with different drugs in our study. Percentage of RLS in only SSRI-using patients was significantly lower than those using combinations of SSRI + quetiapine, SSRI + mirtazapine and SSRI + trazodone. We found that SSRI + quetiapine combination significantly seems to cause more RLS in our study compared to SSRI monotherapy. This finding seems consistent with the literature. Semiz et al. found that quetiapine increases RLS risk especially among antipsychotics in studies examining RLS association with antidepressant monotherapies and antipsychotic monotherapies [38,40]. Quetiapine and RLS association is frequently encountered in the literature. Quetiapine, which has been used for more than 20 years and licenced for the treatment of depression, is known to have good hypnotic properties. Therefore it is used just before bedtime because of its properties. Quetiapine is observed to be more related to RLS than other second-generation antipsychotics [41–43]. In a review of the relationship between quetiapine and RLS, seven cases were presented and six of them developed RLS with quetiapine + antidepressant drug combination [44]. In one of the cases, quetiapine-induced symptoms were defined as akathisia, but it was reported that the symptoms worsened at nights. Although symptoms of akathisia and RLS seem to overlap. Main symptom of RLS is the problem of moving the limbs that exists at nights. Akathisia continues with intense restlessness throughout the day. The fact that misdiagnosis of quetiapine-induced RLS as akathisia may explain the scarcity of quetiapine-induced RLS cases in the literature.

Quetiapine is an antipsychotic with a high limbic selectivity, loosely bound to dopamine D2 receptors

[44,45]. This receptor profile may explain the appearance of RLS one hour after drug ingestion, as seen in the literature. As well as the antihistaminic effects of quetiapine could cause RLS [41].

On the other hand, the percentage of those with RLS among SNRI + trazodone users was significantly higher than those using SNRI + quetiapine, SNRI + mirtazapine or SNRI only. No significant difference was found in other combinations with SNRIs. SSRI + quetiapine and SNRI + trazodone were the most related combinations with RLS in our study. When we compared these combinations in terms of RLS presence there was no significant difference between them.

In the literature, Çalıkuşu and colleagues found an increased risk of RLS in antidepressants combination with trazodone in their studies. It is explained by the metabolization mechanism of trazodone. Trazodone is metabolized by the CYP450 2D6 and CYP3A4 enzymes in the liver and at the same time limits the activation of the CYP450 2D6 enzyme [38]. Because of this, it is often possible to interact with CYP450 2D6 by altering the metabolism of other antidepressants. Venlafaxine is also metabolized by CYP450 2D6 enzyme and O-desmethyl-venlafaxine followed by 3A4 enzyme. It may be thought that the altered metabolism of drugs in venlafaxine-trazodone combination therapy may lead to an increase in RLS. Furthermore, m-chlorophenylpiperazine, the active metabolite of trazodone, has a strong agonistic effect on the 5HT2A receptors [46]. 5HT2A induces dopamine hypofunction and in this case overlaps with the dopamine hypothesis in the aetiology of RLS. On the other hand, antihistaminic effects of trazodone are also thought to cause RLS [38,46].

To sum up, a systematic, prospective study is needed to examine the relationship between the use of antidepressants and symptoms of a clinical RLS. As a result of our study, it was found that starting the lowest possible number of psychotropic drugs when treating a patient with depression or anxiety disorder did not increase RLS risk as well as providing advantages such as drug interaction and risk of side effects. The priority and prognosis of monotherapy have been observed once again in the treatment. However, when psychotropic combination is used in treatment, clinician should be aware that this combination may increase the risk of RLS, and patients should be evaluated in this respect in the monitoring process. Investigating the frequency and severity of RLS in depression and anxiety disorders and the relationship between RLS and psychiatric treatments needs systematic prospective studies. The fact that our study was single-centred and conducted in a narrow sample. It is not appropriate to generalize the results obtained from this study and the results should be investigated in future studies. These factors can be seen as limitations of our study.

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Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Davut Ocak http://orcid.org/0000-0002-9985-7535

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