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Is there any association between antidepressants and restless legs syndrome in a large Turkish population receiving mono or combined treatment? A cross-sectional comparative study

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ABSTRACT

OBJECTIVE: Here, we aimed at investigating whether the treatment with antidepressants is associated with restless legs syndrome (RLS) and at determining the effects of mono or combined antidepressant therapy on the patients with RLS.

METHODS: Five hundred and fifty-five patients with RLS receiving mono or combined antidepressant therapy were included in the study group, and 555 individuals with no history of the use of antidepressants constituted the control group. The diagnosis of restless leg syndrome was performed using a questionnaire under the criteria formed by the International Restless Leg Syndrome Study Group.

RESULTS: Both the patients treated with antidepressants in the study group and those in the control group had similar demographic characteristics. The prevalence of RLS was detected as 9.2% ($n = 51$) in the study group treated with antidepressants and as 5.9% ($n = 33$) in the controls. The difference was statistically significant at borderline ($p = 0.053$). While restless leg syndrome was diagnosed merely in 9 (6.8%) of 133 patients receiving combined treatment, 42 (10%) of 422 patients receiving monotherapy were diagnosed with RLS, and the difference was not statistically significant ($p = 0.306$). The frequency of developing restless leg syndrome was found to be significant only in the use of escitalopram ($p = 0.023$), whereas it was found to have a tendency to significant in the use of duloxetine ($p = 0.060$). Among other participants receiving mono or combined treatment, no significant difference was observed.

CONCLUSIONS: The occurrence of RLS can be seen as an adverse effect in the patients receiving mono or combined antidepressant treatment; however, the frequency of restless leg syndrome among those treated with antidepressants is similar to that seen in general population.

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Introduction

The term restless legs syndrome (RLS) was first used to describe emotional symptoms and motor disorders occurring on extremities, especially at rest, by a Swedish neurologist, Karl A. Ekbom in 1945 [1]. RLS is a condition that can coexist with such diseases as depression, anxiety, fibromyalgia, and chronic sleep disorder treated with antidepressants [2]. In addition, it is known that there is a significant association between depression and RLS.



Another factor confounding the association between RLS and depression is also antidepressant medications known to cause some risks for RLS [3]. Several studies reported that antipsychotic, antidepressant, and antihistaminic medications lead to RLS [4–6]. The findings obtained from various case reports and cross-sectional studies demonstrate that RLS can be induced or impaired by antidepressant medications [2]. The

development of RLS due to the use of antidepressant drugs was emphasized in case reports in the literature, but the number of the studies investigating how often RLS develops among the patients receiving antidepressants still remains limited [7].

The aim of the present study is to determine the association between the use of antidepressants and RLS and to investigate the effects of using mono or combined therapy with antidepressants on RLS.

Method

Between the ages of 18 and 70 years, 555 patients receiving mono or combined antidepressant treatment were included in the study group, while 555 individuals not receiving antidepressant drugs were enrolled in the control group. In order to perform the study, an approval was obtained from the local ethics board.

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The individuals accepting to participate in the study were informed, and a written consent was also obtained from each participant. As well as taking history of all participants, physical and neurological examinations were performed.

The demographic data of the participants in both groups, such as age, gender, educational, marital status, employment status and cigarette smoking, and the use of antidepressants were evaluated. The existence of previous RLS, previous treatment regimes due to RLS, and disease period were also investigated in both groups. RLS diagnosis was performed under the criteria of RLS proposed by the International Restless Leg Syndrome Study Group (IRLSSG). The criteria were developed by IRLSSG in 1995 [3] and updated at an international conference at the National Institutes of Health in Washington, DC, in 2003. Currently, the following five diagnostic criteria must be met: (1) the need to move the legs due to accompanied or led by disturbing and unpleasant sensations in the legs; (2) the need to move or disturbing sensations must begin and deteriorate at rest; (3) the need to move or disturbing sensations is relieved partially or totally with movement, such as walking or stretching; (4) the need to move or disturbing sensations becomes worse during the evening or night time, rather than daytime, or occurs only in the evening or at night; and (5) the above-mentioned characteristics cannot be evaluated as associated with only primary symptoms, or other medical or behavioural conditions, such as myalgia, venous stasis, swollen legs, cramps of legs, and habitual leg shaking [8].

The patients in the study group with the history of receiving antidepressant treatment shorter than three months, those diagnosed with RLS before the treatment, and those treated with combined antipsychotic drugs were excluded from the study. In addition, the patients in both groups with diabetes mellitus; diabetic or non-diabetic polyneuropathy; thyroidism; cardiovascular, nephrological, or rheumatological diseases; history of malignancy, pregnancy, and post-partum period; history of schizophrenia, bipolar disorders, and iron deficiency anaemia; and those with a history of using anti-epileptic drugs and alcohol drug abuse were not included in the study.

Statistical analysis

All statistical analyses were conducted with SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). The prevalence and incidence of RLS were determined with the descriptive statistics. In terms of continuous variables, the differences were compared with the *t*-test. To analyse two or more χ^2 categorical variables and 2×2 categorical variables between the groups, the χ^2 and the Fisher's exact tests were used, respectively. All significance levels were pair-tailed and set at the level of 0.05.

Results

The mean age level of 1110 participants in the study was 40.02 ± 9.75 years. Of all participants, 68.7% ($n = 763$) were women, 66.8% ($n = 741$) were primary school graduates, 19.1% ($n = 212$) were secondary/high school graduates, and 14.1% ($n = 157$) were graduated from colleges.

The demographic characteristics of the study and control groups, such as age ($p = 0.091$), gender ($p = 0.604$), marital status ($p = 0.110$), and cigarette smoking status ($p = 0.672$) were similar and are presented in Table 1.

The average use of antidepressant drugs was 16.55 ± 22.11 months (ranging from 3 to 240 months) in the study group. Four hundred and twenty-two (76.0%) of all patients were monotherapeutically treated with antidepressants, while 133 (24.0%) received combined antidepressant treatment. While the most frequently used antidepressants as monotherapy were sertraline in 126 (22.7%), venlafaxine in 83 (14.9%), and escitalopram in 45 (8.1%) patients, the most frequently used antidepressant drugs given as combined therapy were detected as venlafaxine + mirtazapine in 20 (3.6%) patients, sertraline + opipramol in 20 (3.6%) patients, and sertraline + mirtazapine in 19 (3.49%).

Although the prevalence of RLS was found as 5.9% ($n = 33$) among the controls, the prevalence was determined as 9.2% ($n = 51$) in the patients treated with antidepressants, and the difference between both groups was statistically significant at a limited level ($p = 0.053$). While 42 (10%) RLS cases were diagnosed in 422 patients receiving monotherapy, only nine cases (6.8%) of RLS were detected in 133 patients given combined antidepressant drug treatment, and the difference was not statistically significant ($p = 0.306$).

Among the patients receiving specific drugs, the prevalence of RLS was found to be significantly higher only in those treated with escitalopram compared with the controls ($p = 0.023$). In patients treated with duloxetine, however, the prevalence of RLS showed a significant tendency ($p = 0.060$). Among the patient groups receiving other antidepressant drugs, the prevalence of RLS was not statistically significantly different, compared with the controls. The comparisons of RLS prevalence's for the use of specific antidepressants by the patients and the controls are summarized in Table 2.

The rate of male patients with RLS and receiving antidepressant drug treatment ($p = 0.001$) and the rate of university graduates ($p = 0.001$) were found to be significantly higher, compared with those without RLS. However, the association between the existence of RLS and age was not significant ($p = 0.193$). Even so, while age level was higher among the controls with RLS ($p = 0.027$), no significant association was found between gender ($p = 0.086$) and educational status ($p = 0.940$).

Table 1. The demographic characteristics of the study and the control groups.

		Study group (n = 555) (%)	Controls (n = 555) (%)	p
Age (years)		39.52 ± 10.70	40.51 ± 8.68	0.091 ^a
Gender	Male	169 (30.5%)	178 (32.1%)	0.604 ^b
	Female	386 (69.5%)	377 (67.9%)	
Marital status	Married	413 (74.4%)	441 (79.5%)	0.110 ^c
	Unmarried	105 (18.9%)	80 (14.4%)	
	Divorced	37 (6.7%)	34 (6.1%)	
Employment Status	Employed	223 (40.2%)	223 (40.2%)	1.000 ^b
	Unemployed	332 (59.8%)	332 (59.8%)	
Educational status	Primary School	365 (65.8%)	363 (65.4%)	0.466 ^c
	High School	106 (19.1%)	119 (21.4%)	
	College	84 (15.1%)	73 (13.2%)	
Cigarette smoking	Yes	247 (44.5%)	238 (43.1%)	0.672 ^b
	No	308 (55.5%)	317 (56.9%)	

^at test.^bFisher's exact test.^cχ² test.

Discussion

In our study, the prevalence of RLS was found as 9.2% in the study group, while it was detected as 5.9% in the controls. The difference was statistically significant at borderline. While the prevalence of RLS development was significant only for the use of escitalopram, it was found to be significant in the use of duloxetine. Between other participants receiving mono or combined treatment, no significant difference was found in terms of PLS development. In addition, no statistically significant difference was also determined between the groups receiving mono or combined treatment.

In the literature, there are many case studies demonstrating the development of PLS due to the use of mirtazapine [9–13], venlafaxine [9], paroxetine [11], bupropion [14,15], and duloxetine [16]. However, the mechanism asserting the association between the use of antidepressant and RLS is the hypothesis that especially selective serotonin reuptake inhibitors (SSRIs) decrease the amount of dopamine by

increasing serotonin, and such a change may also lead to RLS [17,18]. Based on the literature, although numerous studies reported the development or exacerbation of RLS due to the use of antidepressant medications, the difference between the study and control groups in our study was at borderline significant levels. These findings suggest that the association between the use of antidepressants and RLS may be limited rather than a definite correlation.

While some studies investigating the use of antidepressants and RLS reported no the association between both conditions [5,19,20], other stated a significant association between the two [10,14]. In several studies, the use of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, bupropion, venlafaxine, duloxetine, and mirtazapine was reported to increase the risk of RLS [10,21–23].

In the study performed by Çalikuşu et al., RLS was reported to occur in 17.3% of the patients receiving mono or combined antidepressant treatment. The same study also emphasized that SSRIs were the most frequently used antidepressants in the patients diagnosed with RLS, and escitalopram, trazodone, and venlafaxine were among the most frequently used antidepressants [7]. In another study compiled by Bhanu et al., it was emphasized that especially the use of mirtazapine among other antidepressant medications showed a higher association with RLS and periodic limb movements. In the same study, it was also reported that venlafaxine may increase RLS and periodic limb movements, but sertraline, fluoxetine, and amitriptyline may lead to periodic limb movements that do not disrupt sleep and are not clinically meaningful [2]. In our study, the association between the use of antidepressants and RLS was only significant for escitalopram and when the use of duloxetine was investigated, we found a level close to significance. As different from these findings, no significant association was found between the use of other antidepressants and RLS in our study.

In many studies investigating RLS frequency, the prevalence of RLS was reported to range between

Table 2. The prevalence rates of antidepressant use and restless leg syndrome (n = 555).

	n	Prevalence of RLS n (%)	p ^a	OR (95% CI)
Sertraline	126	13 (10.3)	0.113	1.82 (0.93–3.57)
Citalopram	35	1 (2.9)	0.713	0.46 (0.06–3.50)
Paroxetine	38	4 (10.5)	0.285	1.86 (0.62–5.56)
Fluoxetine	43	5 (11.6)	0.181	2.08 (0.77–5.64)
Escitalopram	45	7 (15.6)	0.023	2.91 (1.21–7.02)
Venlafaxine	83	6 (7.2)	0.624	1.23 (0.50–3.04)
Duloxetine	34	5 (14.7)	0.060	2.73 (0.99–7.50)
Maklobemid	16	1 (6.2)	1.000	0.14–8.23
Sertraline + Mirtazapine	19	0 (0)	0.618	–
Venlafaxine + Mirtazapine	20	2 (10.0)	0.350	1.74 (0.39–7.83)
Mirtazapine + Paroxetine	18	1 (5.6)	1.000	0.93 (0.12–7.21)
Escitalopram + Mirtazapine	7	1 (14.3)	0.355	2.63 (0.31–22.54)
Sertraline + Trazodone	18	1 (5.6)	1.000	0.93 (0.12–7.21)
Venlafaxine + Trazodone	18	2 (11.1)	0.302	1.97 (0.44–8.96)
Duloxetine + Trazodone	15	1 (6.7)	0.607	1.13 (0.14–8.86)
Sertraline + Opipramole	20	1 (5.0)	1.000	0.83 (0.11–6.41)

Note: Risk estimate for prevalence rate of RLS in the patients receiving specific antidepressant drugs compared with the control group.

^aStatistical value for comparisons of prevalence rate of RLS between patients receiving specific antidepressant drugs and the control group. CI: confidence interval; OR: odds ratio; RLS: restless leg syndrome.

nearly 10% and 15% in societies [24]. In epidemiological studies, the prevalence rates of RLS were stated to be 13% in Germany, 8% in France, and 4.6% in Britain [25]. However, in two studies performed in Turkey, the prevalence of RLS was found as 3.19% and 3.4%, respectively [7]. While the prevalence of RLS was detected as 9.2% in the patients receiving antidepressants in our study, the rate of RLS was found to be 5.9% in the controls and the result was evaluated as borderline significant in the patients treated with antidepressant medications, as consistent with the findings of other studies performed in Turkey.

Although the prevalence of RLS was reported to be observed at equal level in both genders and can sometimes display familial characteristics, the rate was reported to be seen nearly twice more frequently among women [26]. Though its pathophysiological mechanisms still remain unclear, RLS is seen as a risk factor for female gender [27]. The rates of male gender and university graduates were significantly higher among the patients with RLS and receiving antidepressants than those without RLS in our study. Even so, age level was found to be higher in the controls with RLS, but no significant association was determined between gender and educational status.

It is known that there is a significant association between depression and RLS [3]. In our study, psychiatric diagnoses were not investigated through structured interviews, and because our study was a cross-sectional study, it is difficult to detect the association between depression and RLS. This can be seen as a limitation of our study. As other limitations, familial history was not assessed, and no occupational differentiation was made in our study. The unequal number of the patients receiving mono or combined therapy should also be considered another limitation and the present study cannot represent all antidepressants.

The findings obtained in our study suggest that the use of antidepressant medications may have a limited association with RLS, but the risk may increase in male gender and among those with higher socio-cultural background.

Disclosure statement

No potential conflict of interest was reported by the authors.

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