Case Report
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Potential Effect of Vortioxetine on Restless Leg Syndrome

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Restless legs syndrome (RLS) is a chronic progressive movement disorder characterized by abnormal sensations, especially at rest and at night, as the need and urge to move the lower extremity. It has been reported that RLS severity and frequency increase in patients with anxiety and depression. It has been reported that serotonin-noradrenaline reuptake inhibitors such as venlafaxine and selective serotonin reuptake inhibitors such as citalopram, fluoxetine, paroxetine, and sertraline can cause RLS symptoms. No adverse effects of vortioxetine on RLS have been reported in the literature. In this case series, we report the effect of vortioxetine in patients with RLS with symptoms of depression and anxiety. In this case series, the effect of adding vortioxetine to treatment on RLS symptoms is reported in 7 patients (5 female). After the use of vortioxetine, 5 of 7 patients' symptoms regressed without the need to start a separate drug for primary movement disorder. In conclusion, we believe that studies should be conducted to investigate the efficacy of vortioxetine in the treatment of RLS. Therefore, randomized controlled studies are needed to determine the effect and safety of vortioxetine on RLS symptoms.

KEY WORDS: Restless legs syndrome; Vortioxetine; Depression; Anxiety; Serotonin and noradrenaline reuptake inhibitors.

INTRODUCTION

Restless legs syndrome (RLS) is a chronic progressive movement disorder characterized by abnormal sensations, especially at rest and at night, as the need and urge to move the lower extremity [1]. It has been reported at a rate of 1−15% in the general population, and its prevalence in Turkey has been reported as 3.19% [2,3] It has been reported that RLS may be idiopathic or may occur secondary to various clinical conditions such as iron deficiency, pregnancy, diabetes mellitus, renal failure and rheumatological diseases [1,4,5]. Although the neurobiological mechanism in RLS has not been fully elucidated, dopaminergic agonists' alleviation of RLS symptoms indicates that dopaminergic dysfunction is in the pathophysiology of the disease [6]. The exacerbation of the disease, especially at night with the decrease of dopamine transmission, also supports the dopaminergic effect in its pathogenesis [7-11]. Although the cause is not clear in the majority of RLS patients, it has been reported that depressive mood, anxiety, compulsion, and somatic complaints may be observed [12]. Similarly, it has been reported that RLS severity and frequency increase in patients with anxiety and depression [6,13,14]. It has been reported that serotonin-noradrenaline reuptake inhibitors such as venlafaxine and selective serotonin reuptake inhibitors such as citalopram, fluoxetine, paroxetine, and sertraline can cause RLS symptoms by inhibiting dopamine through their serotonergic effect [15]. No adverse effects of vortioxetine on RLS have been reported in the literature. In this case series, we report the effect of vortioxetine in patients with RLS with symptoms of depression and anxiety.

CASE

In this case series, the effect of adding vortioxetine to

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treatment on RLS symptoms is reported in 7 patients who applied to the neurology clinic of Gazi Mustafa Kemal Hospital with RLS symptoms.

Treatment of vortioxetine was initiated by psychiatry due to depression symptoms accompanying RLS in 5 females aged 36, 45, 47, 52, 61, and two males aged 45, and 64. After three months of follow-ups, five of the patients had improved the RLS severity results. One patient's RLS severity score had no improvement, and one patient discontinued the drug due to nausea side effects. RLS severity score, beck anxiety, and depression scores are available in Table 1. One of our patients stopped pramipexole treatment spontaneously 2 months after starting vortioxetine, and her RLS symptoms did not return in a 1-month follow-up. During the 3-month follow-up, no patient required a dose increase, and no augmentation was observed.

Case 1

A 61-year-old female patient following with RLS. Despite using pramipexole 1 × 1 mg and gabapentin 1 × 600 mg, RLS symptoms persisted. While the patient's pramipexole treatment was effective at the beginning, after a while, gabapentin was added to his treatment as a result of the development of augmentation. However, she complained that the quality of her life was adversely affected, due to her RLS severity. It was also determined that the patient had significant anxiety symptoms during the examination. For this reason, the patient was started on vortioxetine after obtaining a psychiatric opinion. After vortioxetine treatment, the patient's anxiety symptoms significantly improved, but a slight regression was observed in RLS symptoms. No side effects were observed in the vortioxetine treatment.

Case 2

A 52-year-old female patient was followed for 1 year with RLS symptoms with pramipexole and gabapentin treatment. It was also learned that the patient was started on escitalopram and sertraline treatment with the diagnosis of major depression by the psychiatrist but discontinued the drugs due to side effects. It was learned that RLS symptoms also increased during antidepressant use. The patient's major depression was continuing. Therefore, vortioxetine was added to the treatment. On the follow up depressive symptoms improved, but RLS symptoms slightly decreased.

Case 3

A 45-year-old male patient using sertraline, pramipexole, and gabapentin. He was admitted when his RLS symptoms persisted. In the history, it was learned that RLS symptoms were exacerbated after sertraline treatment, and sertraline treatment was switched to vortioxetine. In the follow-up, it was observed that RLS severity improved slightly.

Case 4

A 36-year-old RLS patient was being followed up with pramipexole and gabapentin treatment. For determining that the patient had significant anxiety and depression symptoms during the examination, starting vortioxetine treatment. After the treatment, her depressive symptoms improved, but no recovery of RLS symptoms.

Case 5

A 47-year-old female patient following pramipexole treatment for RLS. She started vortioxetine because of the patient's psychiatric symptoms. The patient had not used

Table 1. Patients' clinic features

Case	Age (yr)	Sex	Before vortioxetine			3-month follow-up			Prognosis	Additional treatment
			RLSSS	BDS	BAS	RLSSS	BDS	BAS		
1	61	Female	32	4	30	30	1	9	Partial recovery	Gabapentin, pramipexole
2	52	Female	39	30	45	22	6	43	Partial recovery	Gabapentin, pramipexole
3	45	Male	29	10	13	16	2	6	Partial recovery	Gabapentin, pramipexole
4	36	Female	22	33	35	21	10	7	No recovery	Gabapentin, pramipexole
5	47	Female	26	20	21	-	-	-	Discontinued for side effect	Pramipexole
6	64	Male	39	25	27	24	1	1	Full recovery	Pramipexole
7	45	Female	34	26	31	12	1	1	Full recovery	No treatment

RLSS, Restless Leg Severity Score; BDS, Beck Depression Scale; BAS, Beck Anxiety Scale.

any antidepressants before. The patient dropped out because of nausea and itching.

Case 6

A 64-year-old male patient following with persistent RLS. He before dropped out of gabapentin treatment. Augmentation had developed while still using pramipexole. After the examination had psychiatric symptoms, the patient was started on vortioxetine. He stated that he developed anxiety and depression due to his RLS symptoms. He was started on vortioxetine when he had psychiatric symptoms during the examination. After vortioxetine, the patient's RLS symptoms were almost completely healed, and after 3 months, pramipexole treatment was spontaneously discontinued by patient.

Case 7

A 45-year-old female patient applied to Baskent psychiatry with depressive symptoms. She also has symptoms to meet RLS. She was drug naïve. After the psychiatric evaluation, she wanted to get treatment firstly for depression and refused to use medication for RLS. The patients did not have any other chronic diseases and did not use drugs other than RLS treatment. Each of these patients met 4/4 of the criteria for RLS diagnosis. After the 3-months-follow-up period, she had neither RLS symptoms nor depressive symptoms.

The clinical characteristics of patients are summarized in Table 1.

DISCUSSION

After the use of vortioxetine, 5 of 7 patients' symptoms regressed without the need to start a separate drug for primary movement disorder. It is known that depression and anxiety increase RLS symptoms [3,13,14,16]. In a study comparing more than 2,000 participants in the normal population with 130 patients diagnosed with RLS, a strong relationship was identified between RLS and anxiety disorders (odds ratio = 3.5; 95% confidence interval 1.7–7.1). In a population-based study, patients with RLS exhibited greater anxiety and depression symptoms than control subjects [3]. However, it has been reported that many antidepressants may cause RLS as a side effect. Therefore, psychiatric treatment of patients with depression and anxiety accompanied by RLS a clinical problem.

Vortioxetine is an antidepressant that has recently entered our clinical practice [17]. It has a different and more complex mechanism of action than other antidepressants [17]. Like traditional selective serotonin reuptake inhibitors, it can increase serotonin levels through inhibition of serotonin transporters (SERTs). However, its action on various subtypes of 5HT receptors gives vortioxetine its unique characteristics; Its effect on dopamine, Gaba-aminobuturic acid, Noradrenaline and Acetylcholine has made it accepted as a multimodal antidepressant [17-20]. In animal studies, it has been shown to increase dopamine and noradrenaline, especially in the prefrontal cortex and ventral hippocampus. Findings of studies showing that the drug causes improvement in cognitive functions and low sexual side effects support the increase in dopamine [17,21-23].

The results of animal models of RLS and biochemical, postmortem, and imaging studies in patients with the disease suggest that disruptions in brain iron trafficking lead to disturbances in striatal dopamine neurotransmission [24]. Previous studies have shown that L-dopa can relieve the symptoms by 50% in approximately 90% of patients [25]. For this reason, pramipexole and ropinirole, which act as dopamine agonists, are among the most commonly used treatment options [26,27]. However, recently, considering the risk of long-term dopamine augmentation, there has been an increased interest in gabapentinoids, which are known to be effective by improving somatosensory symptoms on the RLS. Gabapentin and pregabalin has become one of the first-line treatment options [28,29] Considering the efficacy of vortioxetine on both dopamine and gaba , its may have had a positive effect on RLS symptoms.

Two patients' symptoms resolved completely, and one of whose symptoms did not return despite discontinuing pramipexole treatment. Based on the improvement in this case series, it can be thought that vortioxetine is a candidate to be a reliable agent for the treatment of depression and anxiety accompanied by RLS. In a case report in the literature, an increase in RLS symptoms was found after escitalopram was used for major depression. In this case, with the switch to vortioxetine, both the RLS symptoms of the patient improved and her depression was treated. The fact that the RLS symptoms of the cases decreased may be secondary to the treatment of anxiety and depression. However, in one of our cases, the patient was diagnosed with RLS in a detailed anamnesis after he applied to the

psychiatry clinic with depressive symptoms. After the vortioxetine treatment, her depressive and RLS symptoms decreased. Taken together, vortioxetine may be considered a candidate for the treatment of patients with RLS. Although augmentation was not observed in the patients, its effect on augmentation cannot be clearly known since the follow-up is short.

In conclusion, we believe that studies should be conducted to investigate the efficacy of vortioxetine in the treatment of RLS. Therefore, randomized controlled studies are needed to determine the effect and safety of vortioxetine on RLS symptoms.

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■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

Conceptualization: Müge Kuzu Kumcu, Yasemin Hoşgören Alıcı. Data collection and case follow-up: Müge Kuzu Kumcu, Yasemin Hoşgören Alıcı. Writing—original draft: Yasemin Hoşgören Alıcı, Müge Kuzu Kumcu. Writing—review & editing:Yasemin Hoşgören Alıcı, Müge Kuzu Kumcu.

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