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Case report

Restless arms syndrome with oral olanzapine: case based review

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ABSTRACT

Background: Restless arms syndrome (RAS) is a specific variant of restless legs syndrome (RLS). RAS is characterised by an uncomfortable, painful, burning or uneasy sensation confined to the arm.
Case presentation: We report a case of RAS with oral olanzapine, which improved with medication reduction. In addition, all reported cases of RAS were reviewed to explore the underlying mechanisms, diagnosis and treatment for psychiatric drug-induced RAS. The literature review and new case suggest that iron deficiency may be a predisposing factor for RAS. Psychiatric medications are closely associated with RAS, especially olanzapine, quetiapine, and mirtazapine. Discontinuation is the recommended treatment for psychotropic drug-induced RAS, while α2δ calcium channel ligand drugs and benzodiazepines may be considered.
Conclusion: In conclusion, psychiatrists should be alert to the possibility of RAS when administering psychiatric medications for the first time to psychiatric patients with iron deficiency.

1. Introduction

Restless arms syndrome (RAS) is a specific variant of restless legs syndrome (RLS) that presents as a subjective feeling of uneasiness in the arms, including a feeling of aching, burning and an urge to move the arms. These symptoms are more pronounced at night, occur or worsen at rest, and can be partially or totally relieved by movement [1]. Studies have shown that the arm is the most commonly involved area in RLS, with a prevalence of approximately 17% [2]. However, the incidence of RAS alone is still unknown. Referring to the diagnostic criteria for RLS, RAS can be identified as follows: 1. An irresistible urge to move the arms; 2. Symptoms that begin or worsen during periods of rest or inactivity; 3. Symptoms are partially or totally relieved by movement; 4. Symptoms only occur or are worse in the evening or night compared to during the day; 5. The occurrence of the above features is not solely accounted for as symptoms primary to another medical or a behavioural condition [3]. RAS is a primary disorder that can be secondary to medical activity or medication (including antipsychotics). RLS affects the quality of sleep, decreases the quality of life and may even increase the risk of suicide [1].

2. Case report

The patient is a 48-year-old female. Fourteen years ago, she manifested auditory hallucinations (hearing voices out of thin air) and persecutory delusions (claiming to be victimised). She was diagnosed with schizophrenia. After short-term drug treatment, her symptoms were relieved. However, her condition was unstable due to irregular medication compliance. In 2019, she was hospitalized in another hospital and treated with 20 mg/day of olanzapine. However, as a result of discontinuing her medication, she reappeared with symptoms and was admitted to the hospital. This patient suffered from hypertension for 7 years, uterine fibroid disease for 3 years and iron deficiency anaemia for many years, but none of these were treated formally. Physical examination of the patient on admission was unremarkable. Except for haemoglobin (HGB) 63 g/L (reference range: 115–150 g/L), iron 2.0 μmol/L (reference range: 7.8–32.2 umol/L) and ferritin (FER) 2.0 ng/mL (reference range: 4.6–204.0 ng/mL), the patient's blood biochemistry, liver and kidney function and MRI were normal. She scored 88 points on the Positive and Negative Symptom Scale (PANSS) [4]. On admission, the diagnosis of "paranoid schizophrenia" according to The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) was confirmed, and the patient was treated with olanzapine again. In addition, oral iron was taken to treat iron deficiency anaemia. After ten days of treatment with 20 mg/day of olanzapine, the patient's verbal hallucinations and persecutory delusions disappeared. However, she was still lethargic and delayed sleep. In addition, an uncomfortable sensation emerged in her arms. As such, the medication was adjusted to 20 mg/night of olanzapine, 400 mg/day of amisulpride and 2 mg/night of

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lorazepam. However, the patient still had delayed sleep and arm discomfort after 3 days of medication adjustment. The patient complained of delayed sleep onset and sleep maintenance insomnia at night due to discomfort in the arms. These symptoms were characterised as indescribable discomfort in the arms at night and/or in a quiet state, which could be partially relieved by movement. The above symptoms appeared after taking olanzapine and worsened after increasing the dose at night. However, she disclaimed similar discomfort in her legs. The patient did not inform her doctor in time, as she was concerned that she would not be discharged. She had similar discomfort in the past while taking 20 mg/day of olanzapine and needed to take 2 mg/night of clonazepam to help with sleep. Based on these observations, we considered the symptoms to be olanzapine-induced RAS. Laboratory findings showed a serum olanzapine level of 53.5 ng/mL (reference range: 20–80 ng/mL). A score of 34 on the RAS self-rating scale modified from the International Restless Legs Syndrome Study Group Scale (IRLSSG) [5] indicated the symptoms as "Very Severe". Therefore, we reduced olanzapine to 15 mg/night, and the patient's arm discomfort gradually improved. After 3 days of medication reduction, the arm discomfort almost disappeared, with a score of 1 on the RAS self-rating scale and the degree of symptoms were considered "Mild". Therefore, the patient did not consent to polysomnography. At the same time, we reduced olanzapine to 10 mg/night as planned. The patient was discharged without arm discomfort after 30 days of hospitalisation. The patient's arm discomfort, verbal hallucinations and persecutory delusions completely disappeared, with a PANSS score of 53 points and a RAS self-rating scale score of 0 points. The laboratory findings showed serum olanzapine 36.0 ng/mL, HGB 104 g/L, iron 10.9 μmol/L, and FER 9.6 ng/mL. This patient was discharged with 10 mg/night of olanzapine, 800 mg/day of amisulpride and 2 mg/night of lorazepam, while we planned to gradually discontinue olanzapine for outpatient treatment. At the follow-up after 6 months, the patient reported taking the medication regularly, and the arm discomfort had not reappeared.

3. Discussion

This case describes a female with schizophrenia who developed RAS after taking 20 mg/day of olanzapine again. There was no family history of RAS or RLS in the patient. After reducing the dose of olanzapine, her RAS symptoms disappeared. Notably, the patient previously had similar arm discomfort on olanzapine, which required treatment with clonazepam. Unfortunately, her RAS was not confirmed due to a lack of laboratory indications. According to the Naranjo Adverse Drug Reaction (ADR) Probability Scale [6] (Table S1), the relationship between this patient's RAS and olanzapine was "Definite".

Since RAS is a rare variant of RLS, it is difficult to identify clinically [7]. A previous study showed that the variability of RLS is approximately 6.7% [2]. The variant of RLS includes restless arm, restless abdomen, restless genital, restless head syndrome and so on [8, 9]. All analysed RAS cases to date are shown in Table 1 [7,10–19]. These cases ranged in age

Table 1. A review of cases on RAS.

No	Author	Sex	Age	Brain Diseases	Psychiatric Drugs	The onset of RAS	Treatment Strategy	Predisposing Factors
1	Webb, 1976 [10]	M	23	N/A	N/A	N/A	N/A	Spinal cord injury
2	Freedom and Merchut, 2003 [11]	M	77	N/A	N/A	N/A	Clonazepam, gabapentin and ropinirole	Possible beginning peripheral neuropathy
3	Horvath et al., 2008 [12]	M	39	N/A	N/A	N/A	Pramipexole	No
4	Konstantakopoulos et al., 2009 [13]	M	24	Schizophrenia	olanzapine 20 mg/day	24 h after medication	Discontinuation of medication	No
5	Munhoz et al., 2012 [14]	M	47	N/A	N/A	N/A	Pramipexole	No
6	Munhoz et al., 2012 [14]	M	44	N/A	N/A	N/A	Pramipexole	No
7	Ruppert et al., 2012 [15]	F	40	Epilepsy	Oxcarbazepine 600 mg/day	Do not know	Iron supplementation and pramipexole	Periventricular lesions
8	Gupta et al., 2013 [16]	F	28	Depression	Duloxetine 20 mg/day after RAS	N/A	Clonazepam, Duloxetine and Pramipexole	Iron deficiency anemia
9	Ruppert et al., 2015 [17]	M	73	N/A	N/A	N/A	ropinirole; pramipexole; rotigotine; gabapentin; pregabalin	Compression of the ulnar nerves and median nerves; spinal stenosis C3-7 without signs of compression, minor left antero -lateral pontine hypersignal and an état criblé in both insula and Ligamentous nucleus
10	Kim et al., 2017 [18]	M	65	N/A	N/A	N/A	Levodopa	Stroke-related mild hemiparesis and dysesthesia on the right upper extremity
11	Chen et al., 2021 [19]	F	33	Schizophrenia	Amisulpride 600mg/day, quetiapine 100mg/day, venlafaxine 75mg/day, benzhexol 4mg/day	3 days after medication	observation	No
12	Moser and Schwab, 2021 [7]	M	66	N/A	N/A	N/A	Levodopa and benserazide	Mild sleep apnoea syndrome; the lumbar spine and the right shoulder showed age-related degenerative changes, a c6/7 intervertebral disc protrusion and rotator cuff damage of the right shoulder

N/A: Not applicable.

from 23 to 77 years. In contrast to RLS, more male patients (75%) were reported with RAS, which may be due to insufficient case sizes. Similar to RLS, RAS severely affects night time sleep and increases the risk of developing hypertension, cardiovascular disease and impulse control disorders [20]. The suffering caused by such disorders is one of the common reasons psychiatric patients discontinue their medication.

Predisposing factors of RLS include iron deficiency, renal failure and pregnancy rheumatic diseases [1]. The prevalence of RLS symptoms in iron-deficient individuals is 30% and is approximately 4–6 times higher than that in the general population, depending on sex [21]. Currently, brain iron deficiency (BID) is considered a key initial pathological factor in RLS and is associated with altered iron absorption patterns in the brain [22]. Iron is an important cofactor for tyrosine hydroxylase activity, which is the rate-limiting enzyme for DA production [23]. Previous evidence has shown that BID leads to a hyperdopaminergic and hyper-glutaminergic state. This state determines the dysfunction of cortico-striatal-thalamic-cortical circuits in genetically predisposed individuals, which leads to periodic leg movements (PLMS), one of the important features of RLS [22]. In addition, recent studies have suggested that the enhanced arousal state closely associated with RLS is related to BID. The BID-induced hypoadenosinergic state affects the arousal state by altering the function of the ascending arousal system [22]. Thus, BID provides a pathophysiological mechanism of RLS that links sensorimotor symptoms to the enhanced arousal state. In our case, both serum iron and FER were decreased in the patient. It is noteworthy that this patient did not have arm discomfort prior to taking olanzapine. Therefore, we hypothesized that iron deficiency is likewise a predisposing factor for RAS. However, only case 8 of all reported RAS cases had iron deficiency anaemia, and this patient had normal serum iron levels after continued iron supplementation. Although BID is considered a key initial pathological factor for RLS, it does not explain the variability of RLS. Some theories combine evidence of spinal hyperexcitability and hypothesize that altered triggering mechanisms from dopaminergic supraspinal levels of the lumbosacral segment may be associated with RLS [14, 24]. Therefore, it is possible that RAS is caused by alterations in the cervical medullary segment.

RAS is characterised by an uncomfortable, painful, burning or uneasy sensation in the arm [20]. Similar to RAS, the characteristics of painful peripheral neuropathy, myofascial pain syndromes and fibromyalgia, and akathisia also include subjective feelings of uneasiness [3]. In this case, the patient was taking two antipsychotic drugs, including amisulpride and olanzapine. Meta-analyses showed that the prevalence of individual SGAs producing akathisia ranged from 3.3% to 16.4%, with a relatively higher prevalence of 11.3% for amisulpride [25]. Therefore, it needs to be distinguished from drug-induced akathisia. Akathisia is a movement disorder characterised by a distressing feeling of restlessness or inner tension that is generally associated with antipsychotic medication [26]. In contrast to RAS/RLS symptoms, akathisia does not worsen specifically at night. Moreover, in akathisia, limb movements do not provide, even temporarily, relief from the irresistible urge to move them [1]. In addition, empirical treatments for akathisia (including benztropine, diphenhydramine, and atenolol) do not respond to RLS/RAS symptoms [27]. As the patient presented mainly with arm discomfort rather than internal restlessness, her symptoms worsened during the night and improved with movement. Although we did not use empirical treatment for akathisia, the patient's discomfort was relieved by the reduction of olanzapine and was not worsened by the addition of amisulpride. Therefore, the patient was considered to be suffering from drug-induced RAS rather than drug-induced akathisia.

Evidence from studies has shown that psychiatric medications are strongly associated with the incidence of RLS. The incidence of RLS in patients taking antipsychotic or antidepressant medications is approximately 41.5% [28]. Another study indicated that psychiatric medications that predispose patients to RLS include antipsychotics (olanzapine and quetiapine), antidepressants (sertraline, citalopram, paroxetine, fluoxetine, escitalopram and mirtazapine), and mood stabilizers/antiepileptic drugs (zonisamide and topiramate) [29]. Of all the reported cases of RAS, cases 4 and 11 clearly showed psychiatric drug-induced RAS. These cases implied that the short period (perhaps 3 days) after drug administration may be the peak of RAS onset. In addition, case 7 may be associated with psychiatric drugs, as oxcarbazepine would be used as a mood stabilizer in psychiatry. The patient in our case developed arm restlessness after oral olanzapine. Therefore, we hypothesised that oral olanzapine was a precipitating factor for RAS. A study of drug-induced RLS showed that quetiapine and olanzapine were the antipsychotics that most frequently caused RLS [30]. Olanzapine is a thiophene-like benzodiazepine

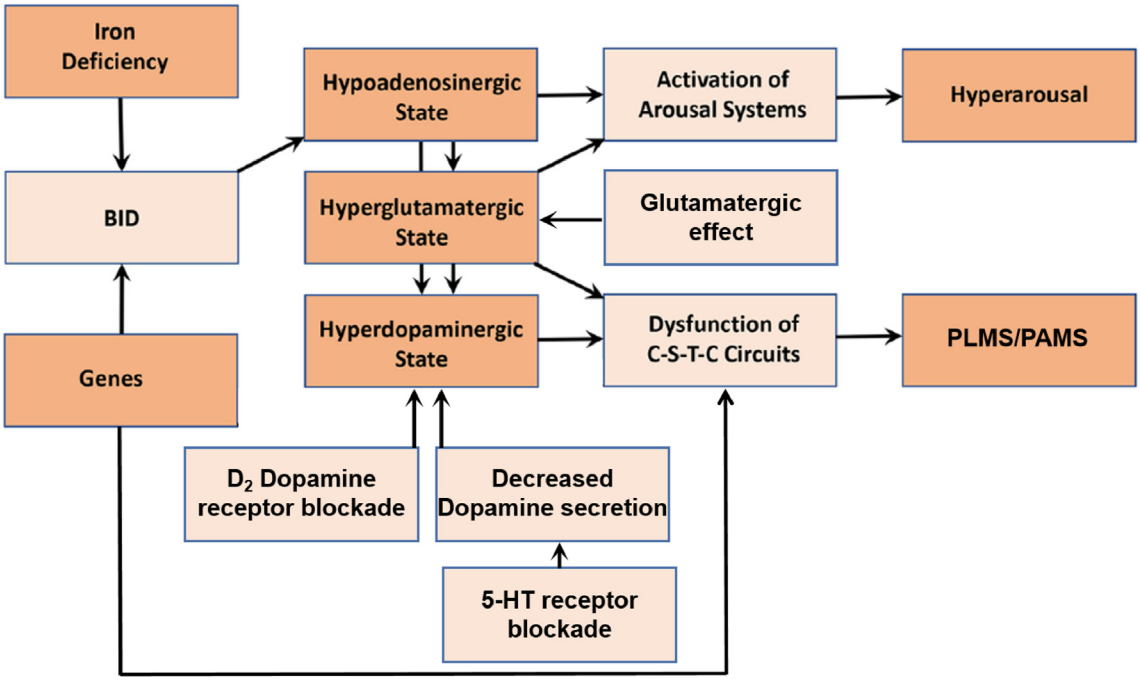

Figure 1. The mechanism of olanzapine induced-RAS (Improvements based on the study of Ferre et al., 2019). PLMS, periodic leg movements; PAMS, periodic arm movements.

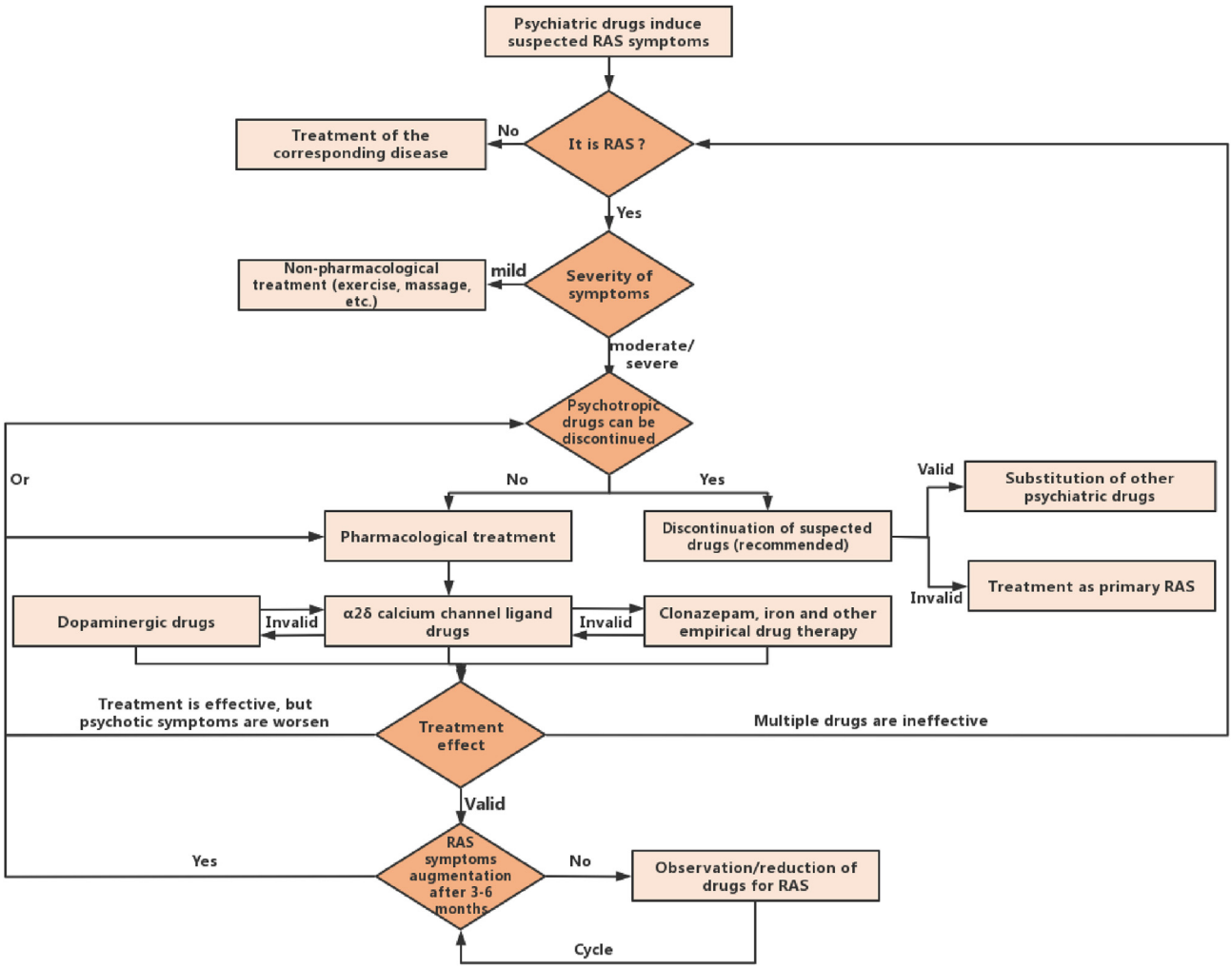

Figure 2. The treatment process of RAS. Mild means a score of 1–10 on the RAS self-rating scale; Moderate means a score of 10–20; Severe means a score of 20 or more. RAS, Restless arms syndrome.

derivative with high affinity for 5-$HT_{2A/2C}$, D_1/D_2, and H_1 receptors and is mainly used for the treatment of schizophrenia. It is metabolised by the hepatic CYP1A2 and CYP2D6 enzymes with a half-life of 21–54 h [31]. The common side effects of drowsiness and weight gain. Currently, olanzapine-induced RLS is mainly explained by the subcortical hypothesis of the hypodopaminergic hypothesis, behind which the hypodopaminergic state of the subcortical dopamine pathway is considered to be the central pathophysiological mechanism of RLS [3, 13]. Studies have shown that olanzapine at 5 mg/day has a mean D_2 occupancy rate of 55%, with a quantitative effect relationship [32]. In addition, dopamine receptor agonists are effective in the treatment of RLS [3, 33], making this hypothesis more reliable. On the other hand, some studies have shown that glutamate receptor action may affect sleep [22]. The glutamatergic effect of olanzapine may be one of the reasons for the enhanced arousal state [31]. Thus, this evidence can be interpreted as indicating two distinct, interacting mechanisms underlying olanzapine-induced RLS symptoms. In all reported cases of RAS, cases 2, 3, 5, 6, 7, 8, 9, 10 and 12 had recovered/improved RAS symptoms after the use of dopamine agonists. Therefore, RAS may have the same pathogenesis as RLS. On the other hand, RAS induced by quetiapine with low dopamine receptor occupancy may be difficult to explain by the hypodopaminergic hypothesis [19]. Therefore, 5-HT alterations are considered an alternative or complementary hypothesis to the pathophysiological mechanisms of drug-induced RAS [34]. 5-HT could lead to increased DA secretion and mediate DA release [35]. On the other hand, olanzapine has a strong antagonistic effect on 5-$HT_{2A/2C}$, with a 90% occupancy of 5-HT_2 receptors at 5 mg/day [32]. Therefore, olanzapine-induced alterations in 5-HT may also be one of the causes of RAS. The mechanism of olanzapine-induced RAS is shown in Figure 1.

The RLS management guidelines published by the American Academy of Neurology indicate that in cases of drug-induced RLS, discontinuation of the suspected drug should be the first approach if clinically appropriate [36]. If this is not inappropriate, treatment should be individualized and may include both pharmacologic and nonpharmacologic therapies. Nonpharmacological recommendations consist of exercise, massage, good sleep hygiene and avoidance of caffeine, alcohol, and nicotine before bedtime. Pharmacological recommendations include mainly dopaminergic drugs, such as levodopa and pramipexole, as well as α2δ calcium channel ligand drugs, such as gabapentin, enacarbil and pregabalin. Augmented RLS tends to occur with long-term dopamine use, which is characterized by symptoms appearing earlier in the day, expanding to other parts of the body, and becoming increasingly severe, with a shorter remission period after treatment [37]. Studies have shown that the incidence of augmentation at 6 months of continuous treatment with levodopa is approximately 40%–60% [38, 39]. Since the use of dopaminergic drugs leads to the augmentation and exacerbation of psychiatric symptoms, α2δ calcium channel ligand drugs may be more appropriate for psychotropic drug-induced RLS [40].

Previously, most psychiatric drug-induced RLS was controlled by medication reduction or discontinuation [33]. A case of olanzapine-induced RLS was controlled with propoxyphene [41]. In psychiatry, rapid medication reduction tends to fluctuate during the

acute phase of psychosis. Furthermore, RLS symptoms induced by psychiatric medications are usually moderate/severe and are not suitable for nonpharmacological treatment. Among the previously reported cases of drug-related RAS, case 7 was treated with pramipexole because she was a patient with epilepsy. However, cases 4 and 11 were patients with schizophrenia who received discontinuation and observation treatment, respectively. Although oral iron is one of the treatments for RLS [42], the patient's RAS symptoms did not improve and even worsened after 2 weeks of oral iron therapy in our case. As a result, the patient in our case had to discontinue the suspected drug causing the RAS. However, the patient's symptoms completely disappeared after the dose of olanzapine was reduced to 10 mg/day, suggesting a possible quantitative-effect relationship for olanzapine-induced RAS. This evidence provides a reference for the cross-substitution of psychotropic medications in patients with RAS. Psychiatric drug-induced RLS studies found that haloperidol and trazodone are less likely to cause RLS, and bupropion, valproic acid, and carbamazepine have improved RLS [28, 43], which may be options for psychiatric patients with RLS. In the two previous cases of antipsychotic-induced RAS (Cases 4 and 11), there was no mention of medication substitution. In our case, amisulpride was used for treatment with good efficacy and without RAS, indicating that amisulpride is one of the available options for RAS-susceptible individuals. It is important to note that although antipsychotics can induce RLS symptoms, susceptibility to RLS varies from patient to patient. When a patient develops RLS after taking one psychiatric medication, replacing another medication that probably causes RLS may not result in RLS symptoms [33]. The difference in susceptibility may be attributed to biological factors, including pharmacokinetic factors and genetic vulnerability [41]. This suggests that in clinical practice, after a psychiatric drug induces RLS, substitution of another drug may be attempted, despite the risk of this drug inducing RLS. For the same reason as above, after one psychotropic drug induces RAS symptoms in a clinical practice, substitution of another drug with the risk of RAS may be attempted. Other empirical treatments for RLS include benzodiazepines (clonazepam, the most widely studied), opioids, iron, and anticonvulsants (valproic acid and carbamazepine) [29]. However, when using these drugs or dopaminergic drugs, it is also important to be aware of other adverse effects. The process of RAS treatment is shown in Figure 2.

The main limitation of this report was the lack of polysomnography. Previous studies found that patients with RAS had movements of repeated extension of the small finger, which were similar to the PLMS of RLS [15]. In addition, the absence of intravenous iron therapy and comprehensive monitoring of biochemical indicators of iron were limitations of this report too.

In conclusion, psychiatrists should be alert to the possibility of RAS when administering olanzapine for the first time to schizophrenia patients with iron deficiency, especially in female patients. Although RAS does not lead to serious physical complications in the short term, it can be very bothersome and lead to severe emotional distress and sleep disturbances. Since RAS could be a severely distressing experience for patients, psychiatrists should use treatment measures as early as possible after the onset of drug-induced RAS. In addition, further studies should explore the underlying mechanisms of RAS and strategies for its treatment.

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The authors declare no conflict of interest.

Additional information

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