



## Clinical Study

## Olanzapine-induced restless legs syndrome



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## ABSTRACT

Only nine patients with olanzapine-induced restless legs syndrome (RLS) have been reported in the literature to our knowledge. We describe two patients with olanzapine-induced RLS treated at our hospital and review the nine reported patients. There were five women and six men aged between 28 and 62 years in the overall group. RLS symptoms emerged at olanzapine doses between 2.5 and 20 mg. The symptoms improved in all patients when the dose was reduced and immediately disappeared when the medication was stopped. International Restless Legs Scale (IRLS) scores ranged from 10 to 35. Three patients had a family history of idiopathic RLS. Supplemental drugs were administered to control RLS symptoms in five patients. Ropinirole was effective in one patient, while two patients did not respond to the drug. Propoxyphene effectively relieved symptoms in one patient who did not respond to ropinirole or clonazepam. RLS symptoms did not recur following substitution of other antipsychotic drugs for olanzapine. In conclusion, olanzapine can induce RLS, particularly in patients with a family history of idiopathic RLS. More than half of the patients experienced severe to very severe symptoms. A dose-dependent relationship was observed between olanzapine and RLS symptoms. A gradual increase in dose may prevent olanzapine-induced RLS. The optimal treatment for olanzapine-induced RLS is discontinuation of olanzapine.

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## 1. Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by a strong urge to move the legs during periods of rest or inactivity, which is relieved by movement [1]. As awareness of RLS grows, it has become increasingly clear that certain medications, such as escitalopram, fluoxetine, L-dopa/carbidopa and pergolide, l-thyroxine, mianserin, mirtazapine, olanzapine and tramadol may cause RLS [2]. Nine patients with olanzapine-induced RLS have been reported [3–6]. Here, we report two patients treated in our department and review the nine cases reported in the literature.

## 2. Methods

We report two patients with olanzapine-induced RLS treated in the Neurology Department of our hospital. A literature review was performed using the PubMed database with the search terms

“restless legs syndrome” and “olanzapine” (last performed 1 July 2013). References in the identified papers were scanned for additional relevant articles.

## 3. Results

## 3.1. Patient 1

A 59-year-old woman with tension-type headache and generalized anxiety disorder was admitted to the Neurology Department of our hospital. She was started on olanzapine 2.5 mg per night, lorazepam 0.5 mg per night, and citalopram 20 mg per day. On the second day after admission, olanzapine and lorazepam were increased to 5 mg and 1 mg per night, respectively, because the patient had difficulty falling asleep. On day 4 after admission, lorazepam was switched to clonazepam, 1 mg per night. On the sixth day, the patient experienced an uncomfortable tightening sensation in her legs when in bed. The paresthesia was relieved only by moving her legs and she had to walk around the ward during the night. However, the patient did not experience restlessness or demonstrate objective akathisia during the day. Furthermore,

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symptoms associated with a high dose of olanzapine, in particular parkinsonian signs, were not present. Ibuprofen (400 mg) administration did not control her symptoms. The patient did not have a personal or family history of RLS. Laboratory investigations including serum iron, ferritin, glucose, thyroid-stimulating hormone, and renal function tests were within normal limits. The neurological examination revealed no abnormalities and nerve conduction velocity (NCV) and electromyogram (EMG) were normal. She showed no clinical evidence of sleep apnea syndrome. The symptoms met the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria: (1) an urge to move the limbs with or without sensation, (2) worsening at rest, (3) improvement with activity, and (4) worsening in the evening or night [1]. The patient was diagnosed with RLS associated with olanzapine. Her score on the International Restless Legs Scale (IRLS) [7] was 30. The patient's condition immediately improved following the reduction of olanzapine to 2.5 mg per night, and her IRLS score decreased to 9. Her symptoms disappeared completely after discontinuation of olanzapine. However, the headaches recurred and the patient agreed to try olanzapine manufactured by a different pharmaceutical company. The initial dose was 2.5 mg per night increased to 5 mg per night 2 weeks later. Her headache markedly improved and the RLS symptoms did recur. She reported no RLS symptoms at 3 month follow-up.

### 3.2. Patient 2

A 51-year-old man with Meige's syndrome and insomnia was admitted to our department. The patient was treated with 2.5 mg olanzapine per night, trihexyphenidyl 2 mg twice daily, and alprazolam 0.4 mg per night. He subsequently reported a tightening sensation in his legs when in bed. As he could not relieve his paresthesia by moving or massaging his legs, he did not find it necessary to walk around. He experienced no additional symptoms associated with olanzapine; in particular, no parkinsonian signs were present. The patient did not have a personal or family history of RLS. Laboratory investigations including serum iron, ferritin, glucose, thyroid-stimulating hormone, and renal function tests were within normal limits. Neurological examination revealed no abnormalities, with the exception of involuntary eyelid and lower mandible movement, and NCV and EMG were normal. He had no clinical evidence of sleep apnea syndrome. He was diagnosed with RLS associated with olanzapine, and his IRLS score was 10. On the third day after admission, olanzapine was stopped, and his RLS symptoms disappeared immediately. The patient was then administered tiapride 0.2 g three times daily and clonazepam 1 mg per night to control the involuntary movement in his eyelids and lower mandible. He reported no RLS symptoms at 6 month follow-up.

### 3.3. Literature review

We found nine previously reported cases of olanzapine-induced RLS in four published English-language studies (Table 1). Patients 1 and 2 are reported in the present study, Patient 3 was reported by Kraus et al. [6], Patient 4 by Khalid et al. [5], Patient 5–8 were reported by Kang et al. [4], and Aggarwal et al. [3] reported Patient 9–11.

### 3.4. Clinical features

The 11 patients included five women and six men aged between 28 and 62 years. Of these, six patients were diagnosed with schizophrenia and three were diagnosed with bipolar disorder at a psychology department. One patient was diagnosed with tension-type headache and generalized anxiety disorder and one with Meige's syndrome in our Department of Neurology. The doses of

olanzapine administered varied; however, RLS symptoms appeared between 2.5 and 20 mg. Patient 4 and 9 were diagnosed with akathisia for the first time, but benztropine, diphenhydramine, atenolol, and lorazepam did not control the symptoms. In two patients (Patient 5 and 8), RLS was initially thought to be psychotic agitation, and the olanzapine dose was increased to control the symptoms. The higher dose aggravated the restlessness; however, the RLS symptoms decreased following a reduction in the dose and completely resolved following the discontinuation of olanzapine. Similarly, RLS symptoms improved in the other patients following a decrease in the dose of olanzapine and disappeared immediately upon discontinuation of the drug. IRLS scores of seven patients varied from 10 to 35: one patient had mild symptoms (0–10), no patient scored in the moderate range (11–20), three experienced severe symptoms (21–30), and three patients had very severe symptoms (31–40). IRLS scores of the other four patients were not provided in the published papers. These findings indicate that more than half of the patients had severe to very severe RLS symptoms. No patient had a prior personal history of RLS, and three patients (Patient 5, 7, and 9) had a family history of idiopathic RLS. All patients met the IRLSSG diagnostic criteria for RLS, and no secondary cause of RLS was identified in any patient.

### 3.5. Drug treatment and replacement

Antipsychotic drugs, such as maprotiline, amisulpride, and mirtazapine, were administered to three patients (Patient 3, 8, 10) simultaneously with olanzapine; citalopram was administered in two patients (Patient 1, 10). We found no evidence of a direct correlation between these drugs and RLS because the symptoms decreased or resolved following the discontinuation of olanzapine. Additional drugs were administered to control RLS symptoms in five patients. Ropinirole was effective in one patient (Patient 7) and had no effect in two patients (Patient 4 and 5). Propoxyphene controlled the symptoms in one patient (Patient 4) for whom ropinirole and clonazepam were ineffective. Gabapentin was not effective in Patient 5. Clonazepam in combination with diazepam and zolpidem moderately alleviated the RLS symptoms in Patient 6. Benzodiazepine was not effective in three patients (Patient 5, 7, and 9).

Two patients (Patient 1 and 9) agreed to retry olanzapine manufactured by a different pharmaceutical company. RLS recurred in Patient 9 but RLS symptoms did not reappear in Patient 1, in whom olanzapine was gradually increased to 5 mg per night following 2 weeks at 2.5 mg per night. In a number of patients, olanzapine was replaced with another antipsychotic drug to control psychotic symptoms, such as tiapride, clozapine, aripiprazole, amisulpride, haloperidol, or quetiapine. RLS symptoms did not recur in these patients during the follow-up period.

## 4. Discussion

Epidemiological studies indicate that the prevalence of RLS in the general population is 1–15% [8–12], and an estimated 3% of the general population have severe symptoms requiring pharmacological treatment [13]. Yet only 6.2% of patients with RLS symptoms who seek medical help reported being diagnosed with RLS [14]. RLS is widely underdiagnosed or misdiagnosed because the disorder is not well understood [15]. Several medications including olanzapine have been reported to induce RLS, but to our knowledge only 11 patients including the two presented here were found to have olanzapine-induced RLS. Thus, it is likely that olanzapine-induced RLS is also underdiagnosed or misdiagnosed, most likely as akathisia or psychotic agitation. Akathisia can be ruled out on the basis of dysesthesia in the legs rather than

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