Restless leg syndrome (RLS) is a common disorder causing sleep impairment. Antipsychotics particularly belonging to the first generation are a common cause of RLS. Whereas, RLS induced by olanzapine is rare, there are only a few cases reported earlier. We report a 38-year-old lady suffering from persistent delusional disorder who was prescribed olanzapine. She developed RLS after initiation of olanzapine which improved when switched over to risperidone. This report will caution clinicians about this side effect of a very commonly prescribed antipsychotic drug.

**KEY WORDS:** Olanzapine, restless legs syndrome

### Introduction

Restless leg syndrome (RLS) is a common disorder characterized by an unpleasant sensation in the legs and a continuous urge to move them. The estimated prevalence of RLS is about 10% in large community-based studies in western industrialized countries.\(^1\) It has multifactorial etiology and commonly can be drug-induced. As early as 1999, it was reported that olanzapine might cause RLS.\(^2\) However, since then few similar cases have been recognized which are summarized in Table 1. Prescribers need to be cautious regarding this drug-induced condition which can be a possible cause of noncompliance to treatment.

### Case Report

A 38-year-old married female without any past or family history of psychiatric or neurological illness and with good premorbid functioning. She was harboring delusion of infidelity against her husband along with disturbed socio-occupational and biological functioning for the past 6 years. There was no history of substance use disorders, except excessive caffeine use, or any high risk sexual behavior. Organic psychiatric disorder or symptoms of schizophrenia were not evident. Detailed general physical examination including neurological evaluation did not reveal any abnormality except mild pallor. She reported regular menstruation and the last childbirth was 10 years back. Mental status examination revealed that she was having an uncooperative and aggressive attitude, delusion of infidelity, impaired judgment, and lack of insight. So, she was admitted to psychiatry ward with a diagnosis of persistent delusional disorder as per International Classification of Diseases, 10th edition. She was started on intramuscular olanzapine 10 mg/day. On investigation, her complete hemogram revealed a Hb of 11.5 gms/dL and a serum ferritin level of 30.2 ngm/ml (normal value for females is 10-291 ng/mL). Other routine hematological and biochemical parameters including blood sugar, renal, liver, and thyroid function were within normal limits. We also planned a vitamin B12 and folic acid estimation which could not be done due to lack of resources.

Within 4-5 days of starting olanzapine, there was a decrease in her aggression and she became cooperative for interviewing. However, she would report that she was having sleeping difficulty due to an itching sensation in both upper and lower limbs at night. She would rub her legs against bedclothes, tie pieces of cloth around her limbs, and ask for limb massage to get relief from such a discomfort. She would have such symptoms for hours after lying down at night. During daytime, she would, however, feel comfortable, relaxed, and was able to sleep. She was evaluated for sleep disorder before this she never had any sleep complaint, neither was there any family history of sleep disorder. During sleep, there was no history of snoring, no abnormal limb or breathing movements. Ear, nose, throat examination was also noncontributory. She was having a thin built and a body mass index of 15.56. As she became
cooperative, she was shifted to oral psychotropics (olanzapine 15 mg/day + clonazepam 1 mg at bedtime). Also oral iron supplementation in the form of ferrous fumarate 350 mg, vitamin B12, and ascorbic acid was started. To improve her sleep, general sleep hygiene practices were initiated, she was prohibited from taking any caffeine beverages at night and the clonazepam was further increased up to 2 mg at bedtime. But there was no improvement in her nighttime symptoms.

In view of her above symptoms and investigations, she was diagnosed to have RLS with an International Restless Legs Scale Score (IRLS) of 24 indicating high severity and olanzapine was considered to be the probable cause. Hence, the olanzapine was decreased to 10 mg/day and oral risperidone 2 mg was added at bedtime. On the next day, the severity of symptoms decreased to a RLS score of 12. No other change in medication was done during this period. So, after 2 days, olanzapine was stopped and risperidone was increased to 6 mg at bedtime. Thereafter, her troublesome symptoms ceased completely. Though she still harbored the delusions yet the conviction decreased and she became more cooperative with her husband and the treating clinician. Then after about a week of uneventful ward stay, she was discharged free of her sleep-related difficulties on clonazepam started and risperidone was increased to 6 mg at bedtime. Thereafter, the treatment continued with the plan to continue her antipsychotic drugs and iron supplementation on an outpatient basis.

Discussion

This patient clearly satisfied all the criteria of RLS as per the International RLS Study Group (IRLSSG), namely, an urge to move the limbs often accompanied by an unpleasant sensation which worsens at rest, inactivity, nighttime, and also this urge is partially or completely relieved by movement.[3] Before a diagnosis of RLS in this patient, we considered its differential diagnosis—being uncooperative due to psychotic state, akathisia, psychogenic cause, and peripheral neuropathy. Lack of symptoms during daytime and a zero score on the Barnes Akathisia Rating Scale ruled out akathisia. The classical presentation and diurnal variation clinched the diagnosis as RLS can be adequately diagnosed by the IRLSSG criteria alone. Sleep laboratory observation could not be done due to lack of this facility in our setup. For a diagnosis of RLS, tests like polysomnography or “suggested immobilation test” lack reliability and are only suitable for special circumstances.[8]

Polysonmography would have been useful in ruling out comorbid periodic limb movement disorder or sleep disordered breathing. The fact that her symptoms persisted even with change of mode of delivery of olanzapine from injectable to oral, the temporal association of symptoms with increasing doses of olanzapine and a high score of +8 on Naranjo Adverse Drug Reaction Probability Scale makes the association of this adverse drug reaction (ADR) with olanzapine highly probable.[9]

The probable reason for RLS was evaluated. Lack of a family history ruled out genetic influences as etiology. Among the major secondary causes of RLS, a relatively low ferritin level (<50 μg/dL) may provide a probable answer as it has been shown that low brain iron leads to altered dopamine metabolism and D2 receptor profile states particularly in substantia nigra and putamen. Other common causes of RLS like parkinsonism, renal failure, and diabetes mellitus were also considered. These were ruled out by physical examination in view of her above symptoms and investigations, she was diagnosed to have RLS with an International Restless Legs Scale Score (IRLS) of 24 indicating high severity and olanzapine was considered to be the probable cause. Hence, the olanzapine was decreased to 10 mg/day and oral risperidone 2 mg was added at bedtime. On the next day, the severity of symptoms decreased to a RLS score of 12. No other change in medication was done during this period. So, after 2 days, olanzapine was stopped and risperidone was increased to 6 mg at bedtime. Thereafter, her troublesome symptoms ceased completely. Though she still harbored the delusions yet the conviction decreased and she became more cooperative with her husband and the treating clinician. Then after about a week of uneventful ward stay, she was discharged free of her sleep-related difficulties on clonazepam started and risperidone was increased to 6 mg at bedtime. Thereafter, the treatment continued with the plan to continue her antipsychotic drugs and iron supplementation on an outpatient basis.

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Table 1:

| Author | Patient profile | Clinical profile (initial IRLS score mentioned) on olanzapine (dose mentioned) | Treatment |
|--------|-----------------|---------------------------------------------------------------------------------|-----------|
| Kraus et al.[7] | 41 year, male, residual schizophrenia | Symptoms of RLS (paresthesia) and periodic limb movement during sleep (PLMS) in legs on 20 mg/day | Olanzapine changed to clozapine for relief of symptoms |
| Kang et al.[7] | 35 year, female, schizophrenia | Tingling sensation and restlessness in legs (IRLS-31) on 20 mg/day | Zolpidem and ropinirole did not control RLS-relieved when drug changed to amisulpiride 1000 mg, 6 mg haloperidol, and finally clozapine |
| | 34 year, male, paranoid schizophrenia | On 15 mg, she developed symptoms in legs (IRLS-27) | Reduction of dose of olanzapine to 10 mg along with benzodiazepines |
| | 28 year, female, paranoid schizophrenia | Tingling sensation and urge to move both legs and arms (IRLS-21) on 20mg/day | Reduction of dose; ropinirole and and clonazepam started |
| | 59 year, male, bipolar I mania | Crawling sensation in legs only (IRLS-35) on 20 mg/day | Stoppage of olanzapine |
| Khalid et al.[8] | 54 year, female, bipolar I mania | Creeping and crawling sensation in the legs (IRLS-36) at 20 mg/day | Resistance to clonazepam 2 mg and ropinirole 3 mg, propoxyphene not tolerated-olanzapine replaced with aripiprazole |
| Aggarwal et al.[7] | 29 year, male, schizophrenia | Unpleasant sensation in calves and burning in the feet on 15 mg/day | Replaced by risperidone 4 mg |
| | 62 year, female, bipolar depression | Feeling twitchy and uncomfortable in the legs on 2.5 mg/day | Olanzapine replaced by quetiapine |
| | 36 year, male, paranoid schizophrenia | Symptoms of RLS in lower limbs at 15 mg/day | Olanzapine replaced by aripiprazole |
| Bet et al.[7] | Male, bipolar I patient | Symptoms of RLS on olanzapine | Pramipexole used to treat RLS associated with olanzapine to precipitate mania |

RLS = Restless leg syndrome, IRLS = International restless legs scale score
and biochemical investigations. Considering other confounding factors, our case scored 14 points which is better than the minimum score of 10 considered by Hoques et al., in his comprehensive review.\[^{[10]}\]

One hypothesis regarding the cause of RLS is thought to be dysfunction of dopaminergic innervations of the spinal cord.\[^{[11]}\] In this regard, it is also interesting to note that though the patient had symptoms on olanzapine, yet she reported no symptoms with risperidone which also has significant anti-dopaminergic activity. As illustrated in Table 1, only two prior cases have been reported where RLS induced by olanzapine was relieved by an antipsychotic with more dopamine antagonist activity like amisulpride-haloperidol combination and risperidone, respectively. This calls for an investigation into the underlying mechanism other than dopamine dysfunction.

Our case had another special characteristic that requires attention-the presence of symptoms in upper limbs. Though such a presentation is common in patients with RLS and even exclusive upper limb variant has been described, yet upper limb involvement is a rare manifestation in drug induced variant of RLS.\[^{[12]}\] Only one such previous case has been described.\[^{[3]}\] This case calls for vigilance by clinicians while prescribing olanzapine, considering the fact that it is a commonly prescribed antipsychotic drug in India.

References
1. Winkelman JW, Finn L, Young T. Prevalence and correlates of restless legs syndrome symptoms in the Wisconsin Sleep Cohort. Sleep Med 2006;7:545-52.
2. Kraus T, Schuld A, Pollmächer T. Periodic leg movements in sleep and restless legs syndrome probably caused by olanzapine. J Clin Psychopharmacol 1999;19:479-9.
3. Kang SG, Lee HJ, Kim L. Restless legs syndrome and periodic limb movements during sleep probably associated with olanzapine. J Psychopharmacol 2009;23:597-601.
4. Khalid I, Rana L, Khalid TJ, Roehrs T. Refractory restless legs syndrome likely caused by olanzapine. J Clin Sleep Med 2009;5:68-9.
5. Aggarwal S, Dodd S, Berk M. Restless leg syndrome associated with olanzapine: A case series. Curr Drug Saf 2010;5:129-31.
6. Bet PM, Franken LG, Klumpers UM. Could pramipexole induce acute mania? A case report. Bipolar Disord 2013.
7. Walters AS, LeBrocq C, Dhar A, Hening W, Rosen R, Allen RP, et al. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs syndrome. Sleep Med 2003;4:121-32.
8. Montplaisir J, Boucher S, Nicolas A. Immobilization tests and periodic limb movements in sleep for the diagnosis of restless leg syndrome. Mov Disord 1998;13:324-9.
9. Naranjo CA, Bustó U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
10. Hoque R, Chesson AL Jr. Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: Literature review, qualitative scoring, and comparative analysis. J Clin Sleep Med 2010;6:79-83.
11. Clemens S, Rye D, Hochman S. Restless legs syndrome: Revisiting the dopamine hypothesis from the spinal cord perspective. Neurology 2006;67:125-30.
12. Munhoz RP, Arruda WO, Telve HA. An upper limb variant of RLS? Report of 2 cases. Clin Neurol Neurosurg 2012;114:265-6.
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