

# Can Isolated Head Tremors Be an Extrapyraxidal Symptom Associated with Lurasidone?—A Case Series

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Lurasidone, a new antipsychotic drug, was approved by the US Food and Drug Administration for the acute treatment of adult schizophrenia in 2010, bipolar depression in 2013, adolescent schizophrenia in 2017, and childhood bipolar depression in 2018.<sup>1</sup> It exhibits both antipsychotic and antidepressant properties.<sup>2</sup>

Lurasidone is a full antagonist at D<sub>2</sub>, 5-HT<sub>2A</sub>, and 5-HT<sub>7</sub> receptors.<sup>2</sup> Due to the receptor profile of lurasidone, adverse effects related to muscarinic, adrenergic, and histaminergic receptor blockade are less.<sup>3</sup> Relatively limited extrapyramidal and metabolic side effects were reported with lurasidone than other antipsychotics. Initial studies assessing the long-term safety of lurasidone reported the incidence of tremors as in 2%–2.4%.<sup>4,5</sup>

Isolated head tremor is defined as a head tremor in the absence of voice, jaw, or any arm tremor.<sup>6</sup> From the times of Charcot, isolated head tremors have been considered to be a form of essential tremor (ET).<sup>7</sup> In fact, head/neck tremor is considered to be one of the most

commonly identified clinical features of ET, contrary to Parkinson's disease (PD), in which it is thought to be rare.<sup>6</sup> Also, transient isolated head tremor was found in 10.5% of first-degree relatives of ET patients.<sup>8</sup> Very rarely, head tremors have been reported in PD.<sup>7</sup>

Here, we report three cases of clinically diagnosed isolated head tremors, suggesting extrapyramidal symptoms, that developed after the initiation of lurasidone. We obtained verbal consent from all three patients.

## Case Series

### Case 1

A 38-year-old female, Mrs. JR, presented with a 1-year history of hearing voices, suspiciousness, and beliefs that her thoughts are known to others and 2-month history of excessive speech with increased psychomotor activity, grooming, religiosity, and libido. She was diagnosed to have schizoaffective disorder according to the International classification of diseases Edition 10

(ICD-10). She was premorbidly well-adjusted with no significant past or family history. Her physical examination and laboratory investigations were within normal limits.

She had failed to respond to olanzapine up to 25 mg for 2 months. She did not tolerate quetiapine 200 mg, aripiprazole 2.5 mg, or amisulpride 200 mg as she developed excessive sedation, akathisia, and galactorrhoea, respectively, with them. During the course of her treatment, the patient was also diagnosed with obsessive-compulsive disorder. She had contamination obsessions that she started cleaning the whole ward repeatedly, insisting other patients to clean up the ward and wash their hands frequently, leading to conflicts between her and other patients. She reported that she had repeated thoughts that the surroundings and her hands were unclean, and failing to wash led to severe anxiety. Score on the Yale–Brown obsessive-compulsive scale was 34, and she was started on sertraline 50–100 mg.<sup>9</sup> Also, her psychotic symptoms were prominent. As

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**HOW TO CITE THIS ARTICLE:** Suriya V, Simiyon M, Thilakan P, Topno I. Can Isolated Head Tremors Be an Extrapyraxidal Symptom Associated with Lurasidone?—A Case Series. *Indian J Psychol Med.* 2021;43(6):546–548.

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Submitted: 15 Dec. 2020  
Accepted: 23 Mar. 2021  
Published Online: 2 Jun. 2021



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DOI: 10.1177/02537176211010505

the patient was not willing for clozapine or electroconvulsive therapy (ECT), she was started on lurasidone 40 mg for her distressing psychotic symptoms and the dose was increased up to 80 mg over 2 weeks.

She developed head tremors (no-tremors) in the absence of other extrapyramidal symptoms like rigidity, hand tremor, hypersalivation, reduced arm swing, bradykinesia, or mask-like face. She did not have vocal or jaw tremors. The tremors were found when the patient was sitting or walking, but disappeared when she rested her head. There was no family history suggestive of ET. Magnetic resonance imaging (MRI) of the brain was performed to rule out other reasons for the treatment resistance and the increased sensitivity to antipsychotics, which turned out to be within normal limits. As the patient was embarrassed about the side effects and unwilling to continue lurasidone, it was stopped, trihexyphenidyl 2 mg was started, and her tremors subsided within a week. We observed probable ADR both on the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Center (WHO-UMC) causality assessment<sup>10</sup> and the Naranjo scale.<sup>11</sup>

## Case 2

Mr T, a 39-year-old male and a tailor, presented with a 1-week history of increased psychomotor activity, irritability, violent behavior, increased spending and libido, and overfamiliarity. He was diagnosed to have the first episode of mania without psychotic symptoms, according to the ICD-10. He scored 54 on the Young Mania Rating Scale,<sup>12</sup> indicating severe mania. Furthermore, he had a few dissociative personality traits and occasional alcohol use. His mother had a history suggestive of depression and had committed suicide. His physical examination and laboratory investigations were within normal limits.

He was treated with olanzapine up to 25 mg and sodium valproate 1.5 g and required six sessions of ECT, with which the manic symptoms resolved. He developed side effects such as weight gain and increased sedation. After discharge, while continuing on the above drugs, he developed depressive syndrome (bipolar

depression) with suicidality, hence olanzapine was cross-tapered with quetiapine. We gradually increased the dose to 600 mg.

As he did not improve, we started lurasidone 40 mg and increased up to 60 mg after 1 week, with which he developed head tremors. There was no family history suggestive of ET. He had no other extrapyramidal symptoms or vocal or jaw tremors. The tremors were observed when the patient was sitting or walking, but disappeared when he rested his head. MRI brain was performed to rule out the possibilities of organic causes for his psychiatric condition, considering the abrupt onset, atypical age, and treatment resistance, and it was within normal limits. There was no improvement in his depressive symptoms, and the head tremors were causing significant distress to the patient. Hence, we tapered and stopped lurasidone and started trihexyphenidyl 2 mg, after which the tremors disappeared within a week. We observed probable ADR both on the WHO-UMC causality assessment<sup>10</sup> and the Naranjo scale.<sup>11</sup>

## Case 3

Mr SN, a 34-year-old unemployed male, presented with 10 years of alcohol dependence syndrome according to the ICD-10. He visited the hospital for de-addiction. We also diagnosed him with dissociative personality disorder and nicotine dependence syndrome. His father had a history suggestive of alcohol dependence syndrome. The patient had alcohol withdrawal symptoms in the first week of admission, which subsided with treatment, and laboratory parameters were normal. After detoxification and de-addiction, he was abstinent for 1 month and later developed a depressive syndrome. We started him on sertraline and increased it up to 100 mg, with which he developed hypomania. An additional diagnosis of bipolar affective disorder (II) was made. We started him on quetiapine up to 200 mg, following which he developed severe urinary retention. Hence, quetiapine was stopped, and then his depression relapsed.

Subsequently, lurasidone 40 mg was started and increased gradually up to 120 mg. Within a week of attaining 120 mg, the patient developed head tremors.

He did not have vocal or jaw tremors. He had no other extrapyramidal symptoms such as rigidity, hand tremor, hypersalivation, reduced arm swing, bradykinesia, or mask-like face. The tremors were visible when he sat or walked, but disappeared when he rested his head. After obtaining consent, we examined his parents for ET, and it was negative. The patient was discharged against medical advice as he was unwilling to stay due to repeated conflicts with other patients and staff, with an early follow-up date. Immediately after discharge, he stopped the medications. When he came for a follow-up, the patient and his parents stated that the tremors disappeared after 10 days of stopping the drug. We observed probable ADR both on the WHO-UMC causality assessment<sup>10</sup> and the Naranjo scale.<sup>11</sup>

## Discussion

These three patients in a similar age group had different psychiatric disorders with psychiatric comorbidities. According to our departmental protocol, we conduct a clinical meeting to discuss the various treatment options available for such challenging clinical scenarios. Then, in discussion with the patient and the caregiver, we proceed. In these cases, lurasidone was chosen as an antipsychotic (case 1) for schizoaffective disorder and as an antidepressant (cases 2 and 3) for bipolar depression. None of the patients had a past or family history of similar tremors. A detailed neurological examination did not reveal any other extrapyramidal side (EPS) effects, anteroposterior tremors, cerebellar dysfunction, or abnormal involuntary movements. Even though isolated head tremors are traditionally considered to be components of ET,<sup>6</sup> our patients' presentation suggests the possibility of extrapyramidal system involvement. Two of them responded to the anticholinergic drug. But the tremors disappeared on resting, which is not typical of EPS.

A randomized placebo-controlled trial in patients with schizophrenia found that lurasidone causes a modest increase in EPS.<sup>13</sup> Lurasidone-induced Parkinsonism, severe EPS, and rabbit syndrome had also been reported.<sup>14-16</sup> It was suggested that the high affinity of lurasidone for D<sub>2</sub> receptors in the nigrostriatal tract, in combination with poor anticholinergic

activity, could lead to drug-induced Parkinsonism. Even though earlier studies<sup>4,5</sup> reported fewer EPS with lurasidone, the meta-analysis by Leucht et al.<sup>17</sup> identified that lurasidone was one among the five second-generation antipsychotics with significantly more EPS than placebo (OR = 2.46; 95% CI: 1.55–3.72). Another recent meta-analysis found that the risk ratio for the use of antiparkinson medication for lurasidone-associated EPS was 1.94 (95% CI = 1.42–2.48).<sup>18</sup>

Farde et al. suggested between 60% and 80% of striatal D<sub>2</sub> receptor occupancy for adequate treatment response and a maximum of 80% occupancy for EPS.<sup>19</sup> The D<sub>2</sub> receptor occupancy ratio following the intake of lurasidone at the therapeutic dose of 40–80 mg/day was 60%–80%.<sup>20</sup> Also, it is well established that patients with affective disorders are more prone to EPS,<sup>21</sup> and all these patients had an affective component. We should also keep in mind that these patients were sensitive to the side effects of other antipsychotics as well.

We could not do electrophysiological studies, genetic analysis, or assessment of all the first-degree relatives to rule out other causes. However, clinically, these patients had drug-induced Parkinsonism in the form of isolated head tremors.

## Conclusion

This case series reports the unusual manifestation of an extrapyramidal symptom associated with lurasidone. Causality assessment with both the WHO scale and Naranjo scale of adverse drug reaction probability scale showed probable ADR. Even though there is a growing body of evidence for the increased risk of EPS with lurasidone, clinicians should keep this rare side effect (isolated head tremors) in mind while prescribing the drug. Early recognition and management of this side effect will improve the compliance and the quality of life in patients.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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