Trazodone-Associated Extrapyramidal Syndrome: A Case Report and Review of Literature

Dear Editor,

Drug-induced movement disorders encompass a spectrum of conditions, including drug-induced Parkinsonism (DIP), tardive dyskinesia, tardive dystonia, akathisia, myoclonus, and tremors. Tardive dyskinesia signifies parkinsonian, athetoid, dystonic, and extrapyramidal manifestations resulting from prolonged dopamine receptor blockade, often induced by antipsychotic medications. In contrast, DIP primarily arises from drugs affecting the dopaminergic system.

Trazodone, a potent antagonist of 5-HT2A and 5-HT2B receptors with mild serotonin reuptake inhibition, exhibits additional pharmacological properties, including $\alpha 1$ and $\alpha 2$ adrenergic receptor antagonism, as well as histaminergic H1 antagonism.[1] Trazodone can have a propensity to induce extrapyramidal syndrome, akin to some antipsychotic medications. Here, we present a distinctive case of trazodone-associated movement disorder.

A 67-year-old male sought evaluation at our neurology movement disorders outpatient clinic with a history of action and postural tremors affecting both hands, generalized slowness in activities of daily living, and reduced walking speed, all of which had progressively worsened over the past year. Further

inquiry revealed complaints of progressively worsening restless limb syndrome superimposed on long-standing anxiety. The patient exhibited subtle perioral dyskinesia and lip-smacking movements, which had been present for the past 8–10 months. Medication reconciliation revealed the use of Sitagliptin 50 mg pre-lunch for diabetes, Zolpidem 10 mg once daily, and Trazodone 50 mg once daily for anxiety and depression over the last year. The symptoms had emerged following the initiation of trazodone, and there was a history of increased slowness and drowsiness when trazodone was titrated to 100 mg per day, subsequently reduced to 50 mg per day by the treating physician at that time.

Neurological examination demonstrated intact higher mental function with normal motor strength and cerebellar functions. Extrapyramidal examination revealed perioral dyskinesia with lip-smacking movements, symmetrical postural and action tremors affecting both hands, bradykinesia associated with stooped posture, and a shortened shuffling gait [Video 1: On presentation]. The sensory assessment demonstrated bilaterally decreased sensations of fine touch, temperature, vibration, and joint position below the knees, accompanied by sensory ataxia. Deep tendon reflexes were bilaterally normal at the biceps, triceps, supinator, and knee, with reduced reflexes at the ankle joint. Plantar responses were bilaterally absent, attributed to symmetric small and large fiber distal sensory axonal neuropathy due to diabetes mellitus.

Hematological, hepatic, renal, and thyroid function parameters were within normal limits. Magnetic resonance imaging of the brain revealed no abnormalities. We suspected trazodone-associated extrapyramidal syndrome. Consequently, trazodone was discontinued, and the patient received methyl cobalamin and folic acid for neuropathy. Gabapentin 300 mg/day was initiated for diabetic sensory polyneuropathy, and the ongoing oral hypoglycemic agent was maintained. Follow-up evaluations at 21-day intervals showed marked improvement in the presenting complaints of tardive dyskinesia and extrapyramidal symptoms (tremor and bradykinesia) [Video 1: On follow-up]. No similar episodes were observed following trazodone discontinuation. The Naranjo score for the possibility of adverse drug reactions (ADRs) was 9, confirming a definite ADR related to trazodone exposure.

Trazodone's wide spectrum of pharmacological actions allows for various therapeutic applications, ranging from its use as an atypical antidepressant to off-label use for ameliorating the negative symptoms of schizophrenia, with potential expansion into the realms of chronic pain management and frontal cognitive dysfunction.[2] However, its mixed agonist–antagonist actions on serotonergic and histaminergic receptors[1] render it susceptible to various ADRs, such as cardiac arrhythmias, hallucinations, and delusions.[2] Its interaction with the 5-HT2C receptor remains poorly understood, with reports of agonism, antagonism, and neutral antagonism.[3] Nevertheless, it exhibits a stronger affinity for the 5-HT2C receptors relative to the 5-HT2A receptors.[2] The substantia nigra possesses a high density of 5-HT2C mRNA, alongside a low density of 5-HT2A receptor binding sites.[4] Consequently, it is plausible that trazodone-mediated blockade of the 5-HT2C receptor, leading to indirect dopaminergic inhibition, may elucidate the extrapyramidal features observed in our patient.

Table 1 provides an overview of published cases of Trazodone-induced extrapyramidal syndrome.

In summary, although rare, extrapyramidal manifestations associated with trazodone warrant consideration in the management of major depressive disorders. Particular caution should be exercised when prescribing trazodone to elderly patients and individuals with preexisting Parkinsonism as symptom exacerbation may occur.

Ethical compliance statement

The authors confirm that institutional review board approval was taken for this work. Verbal and written consent was obtained from the patient for the publication of this case study and accompanying video recording. We affirm that our work aligns with the ethical publication guidelines established by the Journal.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other

Table 1: Review of previous cases of Trazodone-induced extrapyramidal manifestations

Author	Year	Number of cases	Duration of treatment	Symptoms	Neuroradiological imaging	Serum Trazodone level
Demuth *et al*.[5]	1985	1	2 weeks	Tremor, dystonia	Not done	Not done
Kramer *et al*.[6]	1986	1	3 months	Dystonia	Not done	Not done
Albanese *et al*.[7]	1988	1	5 years	Akinesia, rigidity, tremor, gait instability	Not done	Not done
Fukunishi *et al*.[8]	2002	1	18 months	Bradykinesia, cogwheel rigidity, akinesia, gait disturbance	Not done	Not done
Lin *et al*.[1]	2008	1	19 months	Dyskinesia	Normal	Not done
Mayor *et al*.[9]	2015	1	2 days	Cogwheel rigidity	Normal	Not done
Sarwar[10]	2018	1	1 week	Bradykinesia, rigidity, hypomimia, hypophonia	Not done	Not done
Kadota *et al*.[11]	2020	1	1 week	Tardive dystonia	Not done	Not done
Current Case	2023	1	1 year	Tardive Dyskinesia, Tremors, RBD, RLS	Normal	Not done

clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Krushan Yajnik, Nirav Thakar, Harshad Chovatiya[1], Soaham Desai[2]

Department of Medicine, Shree Krishna Hospital and Pramukhswami Medical College, Bhaikaka University, Karamsad, Anand, Gujarat, [1]Department of Neurology, Aster Medcity, Kochi, Kerela, [2]Department of Neurology, Shree Krishna Hospital and Pramukhswami Medical College, Bhaikaka University, Karamsad, Anand, Gujarat, India

Address for correspondence: Dr. Soaham Desai, Department of Neurology, Shree Krishna Hospital and Pramukhswami Medical College, Bhaikaka University, Karamsad, Anand, Gujarat, India.
E-mail: drsoahamdesai@yahoo.com

References

1. Lin CC, Lin PY, Chang YY, Chen CH, Lee Y. Tardive dystonia and tardive sensory syndrome related to trazodone: A case report. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:1609-10.
2. Mittur A. Trazodone: Properties and utility in multiple disorders. Expert Rev Clin Pharmacol 2011;4:181-96.
3. Chanrion B, Mannoury la Cour C, Gavarini S, Seimandi M, Vincent L, Pujol JF, *et al*. Inverse agonist and neutral antagonist actions of antidepressants at recombinant and native 5-hydroxytryptamine2C receptors: Differential modulation of cell surface expression and signal transduction. Mol Pharmacol 2008;73:748-57.
4. Balsara JJ, Jadhav SA, Gaonkar RK, Gaikwad RV, Jadhav JH. Effects of the antidepressant trazodone, a 5-HT2A/2C receptor antagonist, on dopamine-dependent behaviors in rats. Psychopharmacology (Berl) 2005;179:597-605.
5. Demuth GW, Breslow RE, Drescher J. The elicitation of a movement disorder by trazodone: Case report. J Clin Psychiatry 1985;46:535-6.
6. Kramer MS, Marcus DJ, DiFerdinando J, Dewey D. Atypical acute dystonia associated with trazodone treatment. J Clin Psychopharmacol 1986;6:117-8.
7. Albanese A, Rossi P, Altavista MC. Can trazodone induce parkinsonism? Clin Neuropharmacol 1988;11:180-2.
8. Fukunishi I, Kitaoka T, Shirai T, Kino K, Kanematsu E, Sato Y. A hemodialysis patient with trazodone-induced parkinsonism. Nephron 2002;90:222-3.
9. Mayor JS, Pacheco AP, Esperança S, Oliveira e Silva A. Trazodone in the elderly: Risk of extrapyramidal acute events. BMJ Case Repo 2015;2015:bcr2015210726.
10. Sarwar AI. Trazodone and parkinsonism: The link strengthens. Clin Neuropharmacol 2018;41:106-8.
11. Kadota Y, Hori H, Takayama M, Okabe C, Ohara N. Tardive dystonia improved with discontinuation of trazodone in an elderly schizophrenia patient: A case report. Ann Gen Psychiatry 2020;19:1-3.

Submitted: 29-Aug-2023 **Revised:** 01-Oct-2023 **Accepted:** 06-Oct-2023
Published: 30-Nov-2023

Videos available on: https://journals.lww.com/annalsofian

DOI: 10.4103/aian.aian_774_23