

# “I Stopped Hearing Voices, Started to Stutter” – A Case of Clozapine-Induced Stuttering

Dear Editor,

Clozapine is one of the most efficacious treatments in resistant schizophrenia. With action on multiple neurotransmitter systems, clozapine is attributed with multiple common (e.g., sedation, hypersalivation, tachycardia, constipation, weight gain, and seizures) and rare but serious (e.g., agranulocytosis and myocarditis) adverse effects limiting its clinical usage. There are reports of other rarer side-effects such as gastroesophageal reflux disease, priapism, intertriginous erythema, pulmonary thromboembolism, pseudo-pheochromocytoma, and parotitis.<sup>[1]</sup> Stuttering is one such unusual adverse effect of clozapine.<sup>[2]</sup> In this case report, we describe a rare adverse effect of stuttering related to clozapine.

## CASE REPORT

A 29-year-old engineering graduate presented with auditory hallucinations, negative symptoms, and cognitive deficits for 2 years. Diagnosed with schizophrenia, he failed adequate trials (nearly 4 months each) of risperidone (6 mg/day), aripiprazole (20 mg/day), and amisulpride (800 mg/day) with fair medication adherence. Clozapine was initiated after 4 years of onset of illness and gradually titrated up to 125 mg/day over 1 month. He showed significant improvement, with remission of auditory hallucinations within a few weeks of clozapine monotherapy.

The patient developed stuttering after a few days of optimizing clozapine dose, without any other major clozapine-related adverse events. He and his family members noticed dysfluency in his speech, characterized by frequent repetitions of words that included broken words. However, they ignored it as he was relieved of hallucinations. Over the next 3 years of initiation of clozapine, stuttering became a major concern as the patient procured a job as a lecturer in an engineering college.

A detailed clinical evaluation for any childhood onset developmental disorder, anxiety disorder, sensory deficits such as hearing problems, or focal neurological deficits did not reveal any etiological factor for the speech impairment. Electroencephalogram (EEG) failed to show any significant abnormality.

Clozapine dose was reduced to 100 mg, and on follow-up at first and third-month, significant improvement in his

speech fluency was noted, without any deterioration in clinical status. Hence, re-escalation of dose was not attempted. Naranjo adverse drug reaction scale showed a score of six, suggesting stuttering as a probable adverse effect of clozapine.<sup>[3]</sup>

## DISCUSSION

Stuttering is the frequent repetition or prolongation of sounds or syllables or words, or frequent hesitations or pauses that disrupt the rhythmic flow of speech. Stuttering might interfere in academic and occupational functioning and impact on social functioning secondary to self-image disturbances.<sup>[4]</sup>

Stuttering is generally developmental, but secondary etiologies because of the neurological and psychological insults have also been described. Developmental stuttering is usually seen in children, whereas secondary causes may be seen in any age group.<sup>[5]</sup> There is literature on iatrogenic causation with antidepressants and antipsychotics such as risperidone and aripiprazole.<sup>[6]</sup> Although rarely, clozapine has also been reported to cause stuttering. A retrospective study in Ireland estimated the prevalence of stuttering as 0.92% (6 of 654) in patients treated with clozapine.<sup>[7]</sup>

The mechanism of stuttering is complex and poorly understood. Studies have shown psychological stressors, genetic links with familial inheritance, and lingual and laryngeal muscle pathologies to underlie stuttering. However, the evidence largely suggests a lack of integration of somatosensory, language, and motor regions involving fronto-temporo-parietal networks and subcortical structures.<sup>[5]</sup>

The exact mechanism of antipsychotic-induced stuttering is uncertain. It has been related to the duration of antipsychotic treatment and extrapyramidal side effects including dopaminergic supersensitive states such as tardive dyskinesia and dystonia.<sup>[6]</sup> Clozapine, with its lower dopaminergic affinity, is less likely to be involved in extrapyramidal side effects-related pathogenesis. Apart from dopamine, multiple neurotransmitter systems, including muscarinic and  $\alpha$ -adrenergic receptors, where clozapine exerts its influence have also been implicated.<sup>[8]</sup>

A few studies on clozapine-induced stuttering suggest an association between the stuttering and a

seizure-like activity in EEG and improvement with antiepileptics.<sup>[9]</sup> However, our patient did not have any seizures clinically or electrophysiologically, which was also the case with many other cases reported earlier.<sup>[2]</sup> Hence, the exact mechanism needs further systematic evaluation.

This adverse effect also appears to be dose-dependent, and a modest reduction in dose could be the only strategy needed to manage the stuttering.<sup>[10]</sup> A similar phenomenon was observed in our case, where stuttering was induced at a relatively low dose of clozapine, and reduction of dose led to improvement in stuttering without symptom relapse. We did not do the serum clozapine levels because of lack of facility, which remains a limitation of this report.

It is necessary for clinicians to identify rare but consequential side effects such as stuttering due to clozapine, which could be readily missed/misattributed if not for a comprehensive evaluation. Recognizing and treating such side effects with simple measures like reducing the dose would help in the occupational and social recovery of the patients.

#### 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 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.

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#### Conflicts of interest

There are no conflicts of interest.

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