Abstract:
There are very few reports which suggest an association between antipsychotic clozapine low dose and seizure. We report a case in which initial titration of low dose clozapine developed seizure. A 42-year-old female who did not have any history of seizure and had normal blood parameters and normal computed tomography brain at the baseline developed seizure while on clozapine 300 mg/day. Reduction of the dose of clozapine to 250 mg/day led to the return to baseline, with having another episode of seizure on again increasing the dose of clozapine, requiring tablet haloperidol 10 mg/day as an add-on therapy for normalization of behavioral problems. Later, clozapine was maintained on 250 mg/day, with no recurrence of seizure episodes. To conclude, this case report suggests that clozapine can rarely lead to seizure during the initial phase of titration of treatment.

Keywords:
Clozapine, seizure, side effects

Introduction
Clozapine has a unique receptor-binding profile (high dopamine D4 affinity, significant serotonergic, histaminergic, muscarinic, and alpha-adrenergic blocking properties) which makes it superior to other antipsychotics and at the same time leads to the development of various side effects. Weight gain, salorrhea, orthostatic hypotension, agranulocytosis, carditis, hyperglycemia, and bowel infarction are common aspect effects of clozapine. In terms of its impact on seizure, it can change in electroencephalography patterns and induce epileptic seizures and its dose depending incidence is 1.3%–10% throughout treatment. At low dose, the chance of epileptic seizures is extremely rare but with dose step-up and fast dose titration could induce seizure. Clozapine with high dose (≥600 mg/day) was related to larger risk of fits (5%–14%) than dose on medium range (300–600 mg/day; 2.7%–4%) or lower doses (≤300 mg/day; 0.6%–2%). Fast titration dose, neurologic abnormalities, preexistent seizure disorders, and also the association with medications lowering seizure threshold may increase seizure risk.

Different mechanisms are thought of for lowering seizure threshold of clozapine. As hypothesized close association of seizure threshold with mesolimbic structure, Clozapine inhibits dopamine D4 receptor on the cortex and mesolimbic structure, results in high epileptogenicity. Alternative mechanisms are anticholinergic effects of clozapine and its effects on other receptor varieties such as GABA, nicotinic acetylcholine, glutamate N-methyl-D-aspartate receptor, and serotonin 5-HT2A. Here, in this particular case report, a female patient had sudden generalized seizures while on titration with low-dose clozapine molecule. The patient neither had any physical or neurologic comorbidity, family history, nor preexistent seizure disorders.

Case Report
The consent for the study taken from the patient after attaining insight from her illness. Mrs. A 42 Years old illiterate, hailing...
from poor socioeconomic background presented with a long-standing psychotic illness since the age of 20 years. The illness was of insidious onset, precipitated by a psychosocial stressor, and ran a chronic course. The illness was characterized by irritability, smiling to self, muttering to self, history with irregular medication, increased anger outburst without any provocation, both verbally and physically abusive, demanding attitude, wandering behavior, physically assaultive on slight provocation, roaming here and there and without wearing clothes, decreased participation in household activities, repeated handwashing, self-talking, used to urinates and defecates in room, formal thought disorder, and negative symptoms in the form of a sociality, and emotional withdrawal. Her prior treatment history revealed that she had received four adequate trials of antipsychotics (olanzapine, trifluoperazine, haloperidol, and risperidone) with good compliance but without much benefit as she had a history of an irregular medication, which was precipitated by marital disharmony and increased alcohol-consuming habit of her husband, associated with poor socioeconomic background. At the time of admission, she was treated with olanzapine 20 mg and lorazepam 4 mg in divided doses. As her aggressive, assaultive behavior, pulling her own hair, throwing utensils in dining hall, spitting, and disinhibited behavior, was not controlled, she was treated with injection haloperidol 20 mg in two divided doses, but as she is unmanageable, she is planned for electroconvulsive therapy (ECT) with antipsychotics, with a diagnosis of undifferentiated schizophrenia. Her symptoms are partially improved with the 8th dose of ECT, tablet olanzapine 20 mg, and trifluoperazine 15 mg.

After about 2 months as an indoor patient and using a combination of various antipsychotic molecules, as her symptoms are not improved, a proper preclozapine evaluation was done, she was started on clozapine, and the dose of olanzapine was tapered off. Clozapine was started at a dose of 12.5 mg/day, and it was titrated gradually by 25 mg/day on every 3rd day till 100 mg/day with monitoring of total leukocyte count, total platelet count, and orthostatic hypotension. For the next 1 month, her target symptoms have been improved significantly on tablet clozapine 300 mg, which was build up gradually. However, after around 1 month of buildup the dose, she had a sudden, jerky movement of limbs with loss of consciousness, associated with urination in cloths in the evening time. She was managed conservatively, and in view of seizure, the dose of clozapine is reduced to 250 mg. Blood parameters, electrolytes, serum ions, and blood sugar were evaluated and found within normal limits. Computed tomography scan brain revealed no abnormality. She had no prior history of seizures and no family history of epilepsy in her first-degree family tree.

As she has no seizure observed further and her odd behavioral problem persisted, she was again put on clozapine 300 mg by titrating the dose after about 10 days. About 2 weeks of clozapine 300 mg, again, an episode of seizure with loss of consciousness, frothing, and tongue bite was observed, and she was managed conservatively. Her clozapine dose is reduced to 250 mg, and haloperidol 5 mg was added for her behavior disturbance and gradually increase to haloperidol 10 mg subsequently. There was no history of seizure after that, and she was discharged about 1 month back on the same continued medication of clozapine 250 mg + haloperidol 10 mg with a advice on regular follow-up and medication. She was followed up on the outpatient department, and there was no history of seizure after that.

Discussion

A seizure is rare at 250 mg/day clozapine. There is a dearth of studies with low-dose clozapine-induced seizure within the literature. At the oral dose level of 300 mg, a study has been according to tonic–clonic seizures. Kikuchi et al. found electroencephalography (EEG) abnormalities, with an average dose of 305.0 ± 131.7 mg in ten patients in a study of 26 samples with clozapine, and they observed antipsychotic dose to be about 200 mg/day in three of those ten patients. There are also different factors for having seizures despite low doses of clozapine molecule. Some factors such as high doses of antipsychotic medicine, speedy titration with upward dose, a history of head trauma, sudden termination of molecule, sedative properties of medicine, the comorbid organic mental disorders, the EEG abnormalities or previous epilepsy, family history of epilepsy, and substance like alcohol withdrawal accordingly may extend the precipitation of seizures. An generalized tonic–clonic seizure had evolved in our case though she had none of those mentioned risk factors.

The serum levels of clozapine were not calculated here. The relationship among oral clozapine dose, its serum level, and clozapine-induced seizure was represented in this report. In some patients, plasma levels of antipsychotics are observed low though the high oral clozapine dose, drugs interacting with cytochrome P450A2, or person in habits of smoking could fluctuate the plasma levels of molecule. Keeping in a very mind, antecedently inadequate response to other molecules except clozapine, we did not change the molecule clozapine in this case. According to the treating team, it was more appropriate to make prophylaxis of seizure with a plan of antiepileptic medication; however, in our case, the patient is not needed any antiepileptic medication as she maintained well, though sodium valproate is used as a standard molecule for the prevention of clozapine-induced seizures.
It may be insufficient to predict the incidence of seizures\cite{10,21,22} as seizures can be seen even in very low-risk situations such as our patient: (1) EEG monitoring at regular interval, (2) regular study of plasma levels of clozapine, and (3) raising awareness within the families of patients using clozapine would be vital for prevention of the development of seizures. On the first episode of seizure with clozapine, the dose of clozapine should be reduced or using an alternate molecule ought to be most popular. An anticonvulsant drug should be started if a second seizure again occurs.\cite{10}

**Conclusion**

From the existing literature, it can be concluded that seizure is a rare side effect of clozapine on low oral dose, and our case description suggests that clinicians should consider a reduction in the dose of clozapine while managing clozapine-associated seizure, besides using other strategies.

**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.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Si TM, Zhang YS, Shu L, Li KQ, Liu XH, Mei QY, *et al.* Use of clozapine for the treatment of schizophrenia: Findings of the 2006 research on the China psychotropic prescription studies. Clin Psychopharmacol Neurosci 2012;10:99-104.
2. Welch J, Manschreck T, Redmond D. Clozapine-induced seizures and EEG changes. J Neuropsychiatry Clin Neurosci 1994;6:250-6.
3. Naber D, Leppig M, Grohmann R, Hippius H. Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia—a retrospective study of 387 patients. Psychopharmacology (Berl) 1989;99 (Suppl):S73-6.
4. Kikuchi YS, Sato W, Ataka K, Yagisawa K, Omori Y, Kanbayashi T, *et al.* Clozapine-induced seizures, electroencephalography abnormalities, and clinical responses in Japanese patients with schizophrenia. Neuropsychiatr Dis Treat 2014;10:1973-8.
5. Schuld A, Kühn M, Haack M, Kraus T, Hinze-Selch D, Lechner C, *et al.* A comparison of the effects of clozapine and olanzapine on the EEG in patients with schizophrenia. Pharmacoepidemiol 2000;33:109-11.
6. Landry P. Gabapentin for clozapine-related seizures. Am J Psychiatry 2001;158:1930-1.
7. Devinsky O, Pavia SV. Seizures during clozapine therapy. J Clin Psychiatry 1994;55 (Suppl B):153-6.
8. Günther W, Baghai T, Naber D, Spatz R, Hippius H. EEG alterations and seizures during treatment with clozapine. A retrospective study of 283 patients. Pharmacoepidemiol 1993;26:69-74.
9. Centorrino F, Price BH, Tuttle M, Bahk WM, Hennen J, Albert MJ, *et al.* EEG abnormalities during treatment with typical and atypical antipsychotics. Am J Psychiatry 2002;159:109-15.
10. Bolu A, Akarsu S, Pan E, Aydemir E, Ozgun T. Low-dose clozapine-induced seizure: A case report. Clin Psychopharmacol Neurosci 2017;15:190-3.
11. Ereshefsky L, Watanabe MD, Tran-Johnson TK. Clozapine: An atypical antipsychotic agent. Clin Pharm 1989;8:691-709.
12. Haller E, Binder RL. Clozapine and seizures. Am J Psychiatry 1990;147:1069-71.
13. Lieberman JA, Kane JM, Johns CA. Clozapine: Guidelines for clinical management. J Clin Psychiatry 1989;50:329-38.
14. Hedges DW, Jeppson KG. New-onset seizure associated with quetiapine and olanzapine. Ann Pharmacother 2002;36:437-9.
15. Toth P, Frankenburg FR. Clozapine and seizures: A review. Can J Psychiatry 1994;39:236-8.
16. Ravasia S, Dickson RA. Seizure on low-dose clozapine. Can J Psychiatry 1998;43:4209.
17. Thomas P, Goudemand M. Seizure with low doses of clozapine. Am J Psychiatry 1992;149:138-9.
18. Newton-Howes G. The low down: Clinical response complicated by tonic-clonic seizures on low dose clozapine. Aust N Z J Psychiatry 2009;43:979-80.
19. Güleç G, Kiliç RY. Seizure associated with olanzapine: Case report. Bull Clin Psychopharmacol Turk 2007;17:134-7.
20. Eren I. seizure with clozapine: Olgusunumu.psychiatry 2003;6:119-22.
21. Wong J, Delva N. Clozapine-induced seizures: Recognition and treatment. Can J Psychiatry 2007;52:457.
22. Caetano D. Use of anticonvulsants as prophylaxis for seizures in patients on clozapine. Australas Psychiatry 2014;22:78-83.