

# Unexpected Falls in Schizophrenia: Clozapine-Induced Negative Myoclonus

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### Abstract

Myoclonus, characterized by sudden involuntary muscle contractions, can occur in a variety of conditions, including as a side effect of clozapine, which is used in the treatment-resistant schizophrenia. This case study describes a 48-year-old female patient who developed negative myoclonus, manifested by knee flexion and falls, after starting clozapine. Despite dose reduction and the addition of valproic acid, symptoms persisted, highlighting the dose-dependent nature of clozapine-induced myoclonus and the need for clinicians to recognise this risk.

Dear Editor

Myoclonus is defined as a sudden, involuntary contraction of a muscle or muscle group. It can be observed in a number of different pathological conditions, including neurodegenerative, systemic metabolic and central nervous system diseases [1]. Negative myoclonus is a motor phenomenon characterized by involuntary contraction due to short, sudden inhibition of muscle activity.

Since there is insufficient evidence supporting antipsychotic polypharmacy in patients with schizophrenia who have not responded to other antipsychotic monotherapy treatments, clozapine monotherapy is recommended for treatment-resistant patients [2]. The presence of serious side effects, including agranulocytosis, myocarditis and seizures, represents a significant limit to its use. Clozapine-induced seizures manifest as either generalized tonic-clonic or myoclonic seizures, which may in turn precipitate the onset of generalized seizures [3].

Clozapine-induced myoclonus may manifest as either spasmodic muscle contractions (positive myoclonus) or a brief delay in muscle activity (negative myoclonus) [4]. Negative myoclonus presents as bending of the knees or folding of the legs. This article presents the case of a 48-year-old female patient with treatment-resistant schizophrenia who developed negative myoclonus with knee-folding attacks following clozapine treatment.

### About Patient

A 48-year-old patient with a four-year history of schizophrenia and a history of significant extrapyramidal system adverse effects associated with low-dose aripiprazole and risperidone treatments was admitted to the psychiatry clinic for the initiation of clozapine treatment. The patient was commenced on a treatment regimen comprising 25 mg of clozapine per day. The dose was titrated with weekly hematological monitoring. Upon increasing the dosage of clozapine to 75 mg/day, pronounced rigidity was observed in both upper extremities. Consequently, the clozapine treatment was terminated. Following the cessation of clozapine therapy, psychotic symptoms manifested an exacerbation, prompting the reinitiation of clozapine treatment at a dosage of 150 mg/day. At a dosage of 150 mg/day, remission of psychotic symptoms was achieved; however, the patient began to experience involuntary and sudden folding of the knees, falling attacks, and difficulty in climbing stairs. A consultation was held with a neurologist, who considered the possibility of clozapine-induced negative myoclonus. No significant pathological findings were identified in the routine whole blood examination, extensive biochemistry analysis or brain MRI. Valproic acid 1000 mg/day was introduced due to the presence of diffuse spike-wave patterns on the electroencephalogram (EEG). Serum valproic acid levels were measured at 95 µg/mL, which is within the

therapeutic range (50-100 µg/mL) commonly associated with effective seizure control and the management of myoclonus. At 150 mg/day of clozapine, the patient experienced persistent and pronounced myoclonic symptoms, which diminished upon dose reduction to 100 mg/day. The patient was discharged with the current treatment plan and referred to an outpatient clinic for follow-up.

### **Discussion**

The aetiology of clozapine-induced myoclonus remains uncertain. Desarkar et al. [5] have proposed that abnormalities in neurotransmitter systems, including the orexin system, may play a role in clozapine-induced negative myoclonus. Other potential mechanisms include the anticholinergic activity of clozapine, as observed in the context of epileptic seizures. Despite the dearth of sufficient studies of sufficient quality, it has been reported that clozapine-induced myoclonus may be dose-dependent [1] or, more likely, serum concentration-dependent [6]. In our patient, a decrease in knee folding was observed after the clozapine dose was reduced, supporting this finding. Although antiepileptic treatment is also recommended for the management of clozapine-induced myoclonus, it is noteworthy that no improvement was observed with valproic acid treatment in this case [2]. This finding suggests that valproate treatment may not prevent clozapine-induced myoclonus, as previously reported in two cases [7, 8]. Although clozapine-induced hypotension is readily identifiable by clinicians, it is also important to consider the potential for falls resulting from clozapine-induced negative myoclonus.

### **Conclusion**

This case study highlights the necessity for the recognition of clozapine-induced myoclonus as a potential cause of falls in patients. Further research is required to investigate effective management strategies, as current standard treatments, such as valproic acid, may not be consistently effective in preventing these symptoms.

Yours sincerely,

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