Unexpected Falls During Clozapine Treatment Explained by Myoclonus

To the Editor: Clozapine is an important tool in the treatment of refractory patients, but clinicians need to be sophisticated in managing its many possible adverse drug reactions.[1] Clozapine can cause falls due to orthostatic hypotension or sedation, particularly in geriatric patients.[2] A less-recognized cause of falls in clozapine patients is myoclonus, which manifests as knee buckling or leg folding.[3–5]Although there are no high-quality studies, clozapine-induced myoclonus can (1) be dose related[6] or, more precisely, serum concentration related; (2) be the first sign of clozapine intoxication; and (3) evolve into generalized tonic-clonic seizures[7] if the dose (or serum concentration) is not reduced.

This case report reminds clinicians using clozapine that myoclonus can be a cause of unexpected falls and supports the concept that myoclonus is a serum concentration–dependent adverse drug reaction that can be safely managed with therapeutic drug monitoring (TDM).

Case report. A 22-year-old white female nonsmoker with a history of treatment-resistant schizophrenia and substance abuse was referred for her fifth admission to a psychiatric hospital. After a brief stay in jail due to public intoxication, she required treatment for auditory hallucinations and thought blocking. Because she had previously failed multiple antipsychotic trials (including single and polytherapy) with oral and long-acting injectable formulations, a clozapine trial was started. Beginning on day 1 of the trial, clozapine was slowly titrated up as olanzapine and haloperidol were discontinued on day 6 and day 56, respectively. Despite no history of prior falls, 4 falls occurred between days 58 and 60 (Table 1). The patient refused vital sign monitoring for 3 days, thus orthostasis was initially considered the cause of the falls. However, when she complied with monitoring, her systolic and diastolic blood pressure were found to be within normal limits (110/92 mm Hg). After the senior author (J.d.L.) described myoclonus as another cause of falls, the second author (J.B.) diagnosed the patient with myoclonus after witnessing a fall with knee buckling (the legs appeared to lose strength, the knees bent, and the patient fell to the floor). Two days later, the patient experienced jerking arm movements, causing her to drop items.

A neighboring university hospital completed most of the laboratory tests, but clozapine TDM using liquid chromatography/mass spectroscopy/mass spectroscopy was performed at a contracted commercial laboratory. Early morning (before medication intake) collections are used as trough clozapine TDM measures in our hospital. We aspire to have at least 5 half-lives with no dose changes to reach drug steady state. Assuming that clozapine's half-life may be up to 24 hours,[6] 5 days may be required to reach steady state, which was reached on days 22, 51, and 92. The TDM on day 64 occurred only 4 days after the last dose change.

Table 1 shows that the patient was taking 1,000 mg/day of valproate, but no valproate concentrations on that dose were measured. On day 62, the valproate dose was increased to 1,500 mg/day, which provided definitive therapeutic concentrations of valproate (ranging from 91–110 µg/mL), but the patient had 2 myoclonic jerks with these therapeutic valproate concentrations with a clozapine dose of 400 mg/day. Conversely, the myoclonic jerks disappeared when the clozapine dose was decreased to 350 mg/day. Therefore, myoclonus occurred despite the patient's use of valproate, with clozapine doses ranging from 500–400 mg/d, while it remitted when the clozapine dose was decreased to 350 mg/day. We followed a guideline[8] that recommends a therapeutic clozapine range of 350–600 ng/mL, thus the clozapine TDM

Table 1. Clozapine Dosing and Therapeutic Drug Monitoring (TDM) in a Patient With Clozapine-Induced Myoclonus

Day	No. of Falls	Clozapine dose (mg/d)	TDM Blood Clozapine Level (ng/mL)			Valproate	
			Clozapine	Norclozapine	Total	Dose (mg/d)	Concentration (µg/mL)
22[a]		100[b]	77[c]	39[c]	116[c]	1,000	
47[d]		500				1,000	
51[e]		500	518[c]	213[c]	731[c]	1,000	
52[e]	1	500				1,000	
58[f]	1	500				1,000	
59[f]	2	500				1,000	
60[f]	1	450				1,000	
61[g]		400				1,000	
62[h]	1	400				1,500	
64[h]	1	400	476[i]	243[i]	719[i]	1,500	93
78[j]		400				1,500	110
85[k]		400				1,250	91
87[k]	1	400				1,250	
88[k]		350				1,250	
92[k]		350	343[c]	225[c]	568[c]	1,500	96
104[l,m]		0				1,500	

[a]Other scheduled oral medications included docusate sodium 200 mg/d, glycopyrrolate 2 mg/d, haloperidol 15 mg/d, and trazodone 100 mg/d.
[b]On this day, the clozapine dose was increased to 150 mg/d after a TDM blood drug level was collected.
[c]Trough and steady state concentrations collected at least 5 days after a dose change.
[d]Other scheduled oral medications included docusate sodium 200 mg/d, glycopyrrolate 5 mg/d, haloperidol 15 mg/d, and trazodone 100 mg/d.
[e]Other scheduled oral medications included docusate sodium 200 mg/d, glycopyrrolate 5 mg/d, haloperidol 10 mg/d, trazodone 100 mg/d, and polyethylene glycol 3350 at 17 g/d.
[f]Other scheduled oral medications included docusate sodium 200 mg/d, glycopyrrolate 6 mg/d, trazodone 100 mg/d and polyethylene glycol 3350 17 g/d.
[g]Other scheduled oral medications included docusate sodium 200 mg/d, glycopyrrolate 2 mg/d, trazodone 100 mg/d, polyethylene glycol 3350 at 17 g/d, and 1% atropine ophthalmic solution administered sublingually 3 drops/d.
[h]Other scheduled oral medications included docusate sodium 200 mg/d, glycopyrrolate 2 mg/d, trazodone 100 mg/d, and 1% atropine ophthalmic solution administered sublingually 3 drops/d.
[i]Trough concentrations collected 4 days after a dose change.
[j]Other scheduled oral medications included docusate sodium 200 mg/d, trazodone 100 mg/d, trihexyphenidyl 2 mg/d, and 1% atropine ophthalmic solution administered sublingually 3 drops/d.
[k]Other scheduled oral medications included docusate sodium 200 mg/d, haloperidol 20 mg/d, trazodone 100 mg/d, trihexyphenidyl 4 mg/d, and 1% atropine ophthalmic solution administered sublingually 3 drops/d.
[l]Other scheduled oral medications included docusate sodium 200 mg/d, haloperidol 20 mg/d, trazodone 100 mg/d, and trihexyphenidyl 2 mg/d.
[m]Two unremitting clozapine adverse drug reactions were present: severe sialorrhea unresponsive to 3 treatments (oral glycopyrollate, oral trihexyphenidyl, and sublingual atropine) and frequent constipation (in spite of docusate sodium and polyethylene glycol 3350). Then, when a trend toward neutropenia (absolute neutrophil count 1,270/µL) appeared, clozapine was stopped. Clozapine provided some benefits: the psychotic symptoms improved more than with prior antipsychotic treatments and the patient gained some insight, but she continued to report hearing voices and to be observed responding to internal stimuli.

associated with myoclonus in this patient did not appear high, as the clozapine concentration was approximately 500 ng/mL, and the total concentration was around 700 ng/mL. The only available clozapine TDM on a 350-mg/day dose that did not cause myoclonus provided clozapine and total concentrations of 343 and 568 ng/mL, respectively. On day 104, although myoclonus was no longer present, clozapine was finally discontinued after its risks were considered greater than its benefits.

Wong and Delva[9] recommended lowering the clozapine dosage when myoclonus is present and described valproate as the most common antiepileptic drug used for clozapine-induced seizure. This case and 2 prior cases[4,10] suggest that (1) valproate treatment may not protect from clozapine-induced myoclonus and (2) clozapine-induced myoclonus may disappear after reducing clozapine dosage/concentrations. On the other hand, myoclonus occurred without abnormally high serum clozapine concentrations only in this case.

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