# Clozapine withdrawal emergent dystonia, oculogyric crisis and rebound psychosis in a single patient

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Abrupt clozapine withdrawal is heralded by both physiological and psychological symptoms requiring urgent management, out of which dystonic reactions have been reported by only two groups to date [Ahmed *et al.* 1998; Mendhekar and Duggal, 2006]. We present here the only case reported in the literature to manifest psychotic decompensation, oculogyric crisis and limb-axial dystonia in a single patient due to abrupt clozapine withdrawal and discuss the putative mechanisms underlying this unique presentation. Early recognition of this syndrome is important as symptomatic treatment alone runs the risk of recurrence of the withdrawal symptoms, as seen in our patient, unless clozapine is reinstituted promptly.

## Case report

Miss 'A' was started eventually on clozapine after sequential trials of trifluoperazine, flupentixol, haloperidol, chlorpromazine and amisulpiride failed to alleviate her schizophrenic symptoms. During her 18 years of diagnosed illness, all these medications were tried for adequate doses and duration, and polytherapy was also tried judiciously. But medication adherence was always erratic and eventual personality deterioration ensued over the years. She now needed assistance even for basic self-care needs and her clinical picture was dominated mainly by negative symptoms. Clozapine was titrated up to 400 mg in divided doses over 4 weeks and some response in self-care and communication was noted.

After 6 months on clozapine, her carer stopped refilling her prescriptions and the patient's self-care and socialization deteriorated further. She was restarted on clozapine and the target doses of 400 mg were achieved over 4 weeks. After 5 days on this dose, the treating team was alarmed by a sudden drop in her consciousness and axillary temperature rise of 101°F with total constipation. An abdominal lump was palpable and, on clinical suspicion of acute intestinal obstruction, all medications including clozapine were stopped considering its strong anticholinergic properties. All routine investigations including creatine phosphokinase (CPK), toxicology, virology and bacteriological scans came out to be within normal range and an abdominal computerized tomography (CT) scan diagnosed a large dermoid cyst.

It was observed that 5 days following discontinuation of medications, the patient became acutely violent, assaultive, talked irrelevantly and showed inappropriate emotional reactions, and had to be calmed down by parenteral benzodiazepines. The very next day, she developed acute oculogyric crisis characterized by uprolling of the eyeballs sustained for 60–90 minutes at a time for 3 times over that day, and profound axial and lower limb dystonia. The dystonia was very severe with the patient shouting continuously in pain and was not able to move at all. Intramuscular promethazine 50 mg was administered and the dystonia disappeared in minutes. Her dystonia recurred the very next day and intramuscular promethazine 50 mg was repeated with prompt response. Detailed neurological examination revealed nothing except the focal dystonias. The treating team considered a diagnosis of clozapine withdrawal emergent dystonia and decided to restart clozapine. Since the re-administration of clozapine, no further recurrence of dystonia was noted and clozapine was uptitrated rapidly to the original doses.

Informed consent was taken from the patient for preparing this report, after assuring anonymity of identification information.

## Discussion

Rebound psychosis after rapid clozapine withdrawal is discussed in length in the literature and mesolimbic dopamine receptor supersensitivity is postulated as the putative mechanism due to relative selectivity of clozapine to the mesolimbic dopamine (DA) receptors [Chouinard *et al.* 1978]. Similarly, the dystonic reactions observed in our patient is also the result of aberrant reactivity of another neurotransmitter system, namely acetylcholine, as implicated in the previous two reports. Clozapine has the highest affinity for acetylcholine receptors among the atypical antipsychotics [Chew *et al.* 2006]. Acetylcholine is excitatory in basal ganglia movement pathways directly via M1 and M4 muscarinic receptors and indirectly via nicotinic acetylcholine receptors. It excites the muscle end plates [Breakefield *et al.* 2008]. That is why we postulate that, after strong and chronic blockade of these receptors, they become upregulated and 'supersensitive', in that when the receptor blockade is withdrawn suddenly, the supersensitive receptors react excessively to acetylcholine and muscle motor endplate hyperactivity results in occurrence of dystonia.

Our case report strengthens the central role of acetylcholine in clozapine withdrawal dystonias. The clinician should be cautious about abrupt withdrawal of clozapine and gradual tapering of the drug with an anticholinergic coverage can save patients from unnecessary suffering.



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## Conflict of interest statement

The authors declare no conflicts of interest in preparing this letter.

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