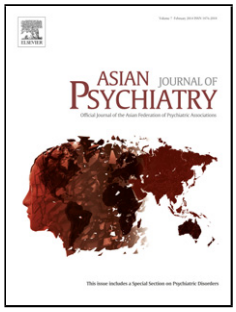

Title: Clozapine withdrawal catatonia, psychosis and associated neuroleptic malignant syndrome

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Clozapine withdrawal catatonia, psychosis and associated neuroleptic malignant syndrome

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Clozapine withdrawal psychosis is a relatively well-recognized phenomenon. However, literature exploring clozapine withdrawal associated catatonia is limited to a few case reports [Bastiampillai, 2009]. We present a case of clozapine withdrawal catatonia, psychosis and associated neuroleptic malignant syndrome (NMS) and discuss its clinical implications.

Mr. C is a 44 year old man, who was well managed on clozapine 200 mg nocte and paliperidone depot 75 mg 4 weekly for schizoaffective disorder with no past history of catatonia. He presented with recent onset atypical chest pain with a raised troponin of 81 ng/L. Clozapine was discontinued abruptly due to suspected myocarditis. Cardiology evaluation definitively excluded myocarditis following normal cardiac investigations. He had received his depot paliperidone two weeks preceding clozapine cessation.

On day seven, following clozapine cessation, he developed autonomic instability and worsening clinical features of mutism, gegenhalten rigidity, perseveration, catalepsy, staring, bizarre mannerisms, stereotypy with head rocking from side to side and diaphoresis. His CK was elevated to 1740 u/L and he was afebrile. This phenomenon of clozapine withdrawal catatonia was initially unrecognised and interpreted instead as solely clozapine withdrawal NMS. Retrospective Bush Francis Catatonia Rating Scale (BFCRS) scored 41 on day nine. Given the diagnosis of NMS, neuroleptics were avoided and Mr. C was managed on Lorazepam 9 mg/day. On retrospective chart review, his catatonic symptoms responded within 72 hours with resolution of mutism, rigidity and autonomic instability with BFCRS reducing to 4.

On day ten, however, clozapine rebound psychosis manifested with auditory hallucinations, labile affect and intrusive behaviour. With suspected diagnosis of NMS, use of any antipsychotics including clozapine was avoided. On day twelve, olanzapine 5 mg was given. However, within 48 hours, he rapidly deteriorated with return of rigidity, bradykinesia, tachycardia and diaphoresis without fever. The severity was such that he was unable to blink to visual confrontation and his CK rose significantly to 6858 u/L. Mr. C was diagnosed to have olanzapine induced NMS and was managed in an ICU setting with benzodiazepines but with minimal response.

Following consultation with the psychiatry team, he was now diagnosed as having clozapine withdrawal psychosis and with caution clozapine was initiated and gradually up-titrated 12.5 mg every 2 days without inducing NMS. Clozapine was gradually increased to 200 mg dose within 4 weeks with complete clinical response and no further complications.

Abrupt cessation of clozapine results in withdrawal symptoms affecting various receptor sites and neurotransmitters [Stahl, 2013]. Case reports of clozapine withdrawal catatonia have been rarely described with onset ranging from immediate to 7 days. It is hypothesised that clozapine has GABA agonist properties and sudden clozapine withdrawal may result in sudden decrease in GABA activity that may contribute to the development of catatonic symptoms in predisposed patients[Bilbily et al, 2017]. In our case, it is noteworthy that olanzapine likely induced severe NMS following period of clozapine withdrawal catatonia. It is also likely that paliperidone may have contributed to the NMS component that accompanied the initial episode of clozapine withdrawal catatonia [Northoff, 2002]. It probably indicates that caution should be exercised with the use of other neuroleptics in a patient undergoing sudden clozapine withdrawal [Kurien et al., 2013].

Clozapine withdrawal psychosis is well recognised and has been documented with onset within 14 days. The mechanism likely relates to loose binding to DA2 receptors, compensatory increases in DA2 following chronic administration, its therapeutic effectiveness with much lower DA2 occupancy (Miller, 2009) and potentially rebound effects from other receptors: mainly cholinergic but to a lesser extent serotonergic, noradrenergic and GABA-ergic receptors (Shields et al., 2012). The main therapeutic strategy to resolve clozapine withdrawal psychosis is reinstatement of clozapine, which was delayed in this case due to concerns about induction of NMS.

Our case highlights the importance of understanding the potentially complex symptom profile following sudden clozapine withdrawal, which can often trigger withdrawal psychosis and rarely also withdrawal catatonia. It is very important to clinically recognise this withdrawal state and reinstate clozapine as quickly as possible, understanding that benzodiazepines could specifically address the with-

drawal catatonia as an adjunctive agent [Daniels, 2009]. Administering other antipsychotics in the setting of clozapine withdrawal will likely not address either clozapine withdrawal psychosis or catatonia and could instead cause clinical deterioration by worsening catatonia or inducing NMS in predisposed patients. [Lee et al., 1997]

A better understanding of clozapine withdrawal catatonia and psychosis may also allow us to better analyse the unique properties of clozapine, with possible suggestion that it could be a GABA agent further supporting the importance of the GABA system in schizophrenia. [O'Connor and O'Shea, 2015]

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References

Bastiampillai T, Forooziya F, and Dhillon R, 2009. Clozapine withdrawal Catatonia; Aust NZ J Psychiatr; 43 (3):283-284.

Biliby J, McCollum B, and de Leon J, 2017. Catatonia Secondary to Sudden Clozapine Withdrawal: A Case with Three Repeated Episodes and a Literature Review. Cas R Psychiat, Article ID 2402731

Daniels J, 2009. Catatonia: Clinical aspects and neurobiological correlates. JNP; 21: pp. 371- 380

Joseph W Y Lee et al, 1997. Clozapine withdrawal catatonia and NMS; a case report. Ann Clin Psychiatry; 9 (3)

Kurien R et al., 2013. Psychotropic discontinuation leading to an NMS-like condition. Prog Neuro- Psychiat

Miller R (2009) Mechanisms of action of antipsychotic drugs of different classes, refractoriness to therapeutic effects of classical neuroleptics, and individual variation in sensitivity to their actions. Curr Neuropharmacol; 7 (4), (302-314), (315-330)

Northoff G. 2002. Catatonia and neuroleptic malignant syndrome: psychopathology and pathophysiology. J Neural Transm; 109: 1453.

O'Connor W. T and O'Shea S.D. 2015. Clozapine and GABA transmission in schizophrenia disease models; establishing principles to guide treatments. Pharmacol Therapeut; 150, pp 47-80.

Shields MK, Bastiampillai T and Mohan T, 2012. Managing clozapine discontinuation- acute and chronic maintenance strategies. Aust NZ J Psychiat; 46 (11), pp 1104-1105

Stahl S. 2013. Essential Psychopharmacology, neuroscientific basis and practical applications, fourth ed.