Clozapine Withdrawal–Induced Catatonia

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Catatonia is a complex disorder involving altered motor activity, emotional responses, and involuntary physiological functions, often presenting in the setting of severe psychiatric conditions. While benzodiazepines are typically effective with treatment, catatonia triggered by abrupt clozapine discontinuation poses distinct treatment challenges due to its complex neurochemical effects on dopamine, glutamate, and γ-aminobutyric acid (GABA) pathways.[1,2] This report describes a patient with treatment-resistant schizophrenia who developed persistent catatonia after sudden cessation of clozapine, highlighting the challenges in management and the potential role of clozapine reintroduction.

Case Report

Mr A, who presented with a history of treatment-resistant schizophrenia and unspecified mild intellectual disability, was admitted to the hospital for acute safety concerns due to command auditory hallucinations, disorganized behaviors, and nonadherence to prescribed medications. Upon admission, he exhibited tachycardia and signs of a subclinical urinary tract infection. The patient's confusion, tachycardia, and diaphoresis were initially suspected to result from cholinergic rebound following abrupt discontinuation of clozapine. However, despite treatment with fosfomycin and a repeat urinalysis indicating resolution of bacturia, the patient was still confused and tachycardic. His clinical presentation included severe psychosis, disorganized thought processes, and pronounced catatonia characterized by echolalia, waxy flexibility, verbal perseveration, intermittent catalepsy, and mitgehen.

Initial management included lorazepam and olanzapine, which were titrated to lorazepam 14 mg and olanzapine 22.5 mg. However, Mr A's catatonic symptoms and psychosis were refractory to this regimen. Clozapine was reintroduced after both olanzapine and lorazepam were down titrated. Olanzapine was formally discontinued, but lorazepam was continued at a much lower dose during clozapine therapy. Clozapine was titrated gently per recommendations, which can be found in the package insert or on the US Food and Drug Administration site.[3] Once clozapine reached 300 mg daily, the patient's symptoms began to improve. His catatonic and psychotic symptoms gradually resolved. A further decrease of lorazepam was trialed; however, a resurgence of catatonic symptoms necessitated increasing the lorazepam dose to resuppress the catatonia. By day 40, Mr A's thought processes and behaviors showed marked improvement, although mild disorganization persisted as a likely baseline state.

Discussion

Mr A's case underscores the complexity of managing catatonia and psychosis in the context of abrupt clozapine discontinuation. Withdrawal from clozapine, which modulates dopaminergic, glutamatergic, and GABAergic pathways, has been associated with catatonia and psychotic exacerbation, likely due to abrupt neurochemical dysregulation.[1] The patient's initial presentation with tachycardia, diaphoresis, and acute confusion supports the potential role of cholinergic rebound in his clinical deterioration, a phenomenon observed with clozapine withdrawal.[4]

Lorazepam is a first-line treatment for catatonia, but Mr A's symptoms showed only partial response, consistent with the limited efficacy of benzodiazepine monotherapy in clozapine withdrawal–induced catatonia.[5] Reintroduction of clozapine was pivotal in breaking his persistent catatonic state, despite high-dose lorazepam. This outcome highlights clozapine's unique pharmacologic role, potentially restoring balance in dopamine, *N*-methyl-D-aspartate, and GABA receptor signaling disrupted during withdrawal.[2]

Mr A's improvement with combined lorazepam and clozapine therapy underscores the safety and efficacy of this approach. However, the re-emergence of catatonic symptoms on day 40, after lorazepam was further decreased, necessitated an additional lorazepam increase, reflecting the potential for fluctuating catatonic presentations and the need for tailored therapeutic strategies that may include concurrent clozapine and benzodiazepines.

This case adds to the growing evidence supporting clozapine's role in managing catatonia, particularly in patients with treatment-resistant psychotic disorders. Future studies are needed to better elucidate the mechanisms of clozapine withdrawal–induced catatonia and optimize treatment strategies for refractory cases.

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