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Letter to the Editor

# A case of clozapine induced agranulocytosis 25 years after starting treatment: Effective use of lithium for augmentation in rechallenge

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*Letter-to-the-Editor,*

Clozapine remains the only FDA approved treatment for drug refractory schizophrenia. However, its use can be limited by the risk of neutropenia and agranulocytosis. Susceptibility to these hematologic derangements may be secondary to amino acid changes in the major histocompatibility complex (Goldstein et al., 2014). Guidelines for patients taking clozapine who experience neutropenia (absolute neutrophil count (ANC) <0.5 thou/μL) state clozapine should be discontinued and rechallenge considered only if the benefits are determined to outweigh the risks (Clozapine REMS, 2019). Furthermore, rechallenge after neutropenia may be more successful than after agranulocytosis (Manu et al., 2012). The decision to rechallenge clozapine should include a review of treatment adjuncts such as lithium to provide the best chance of a positive outcome.

Several mechanisms by which lithium supports neutrophil production have been demonstrated including enhancement of granulocyte colony stimulating factor (G-CSF) production (Richman et al., 1981) as well as by its trophic effect on neutrophil production via an increased CXCL12 gradient (Kast, 2008). G-CSF itself is a cytokine which acts to directly stimulate proliferation and terminal granulocytic differentiation of hematopoietic precursors through multiple pathways (Lally et al., 2017; Kaushansky, 2006). Up to 38% of patients who experience a first dyscrasia with clozapine will experience a second if rechallenged. The second dyscrasia is often more severe, prolonged, and occurs more rapidly than the first (Dunk et al., 2006). While there have been no randomized controlled trials examining lithium's effectiveness for clozapine induced agranulocytosis (CIAG), several reviews and case studies have indicated this may be an effective treatment (Kanaan and Kerwin, 2006; Meyer et al., 2015). Here we describe a case of clozapine rechallenge with G-CSF followed by lithium maintenance in a patient who experienced agranulocytosis decades after starting clozapine.

Mr. H is a 53-year-old Caucasian man with a history of schizophrenia, treated with clozapine since 1990. Clozapine had allowed Mr. H to live in a supervised residence, largely independent in activities of daily living, and without psychotic symptoms. Approximately 25 years after first starting clozapine, Mr. H was admitted to an inpatient psychiatric unit with symptoms of decreased self-care and increased internal preoccupation after being switched from clozapine to olanzapine two weeks prior to presentation. This switch was made as an outpatient after his ANC dropped precipitously, finally reaching 0.34 thou/μL on the day of admission (Fig. 1), without any noted anteceding medical event while taking clozapine 400 mg daily. The patient's family had noted a decrease in Mr. H's self-care: taking fewer showers, not answering phone calls, aimless walking, and denying the existence of his brother all beginning after the switch from clozapine to olanzapine. On admission Mr. H endorsed "worrying about everything" and increased "nervousness." He denied acute suicidal or homicidal ideation, auditory or visual hallucinations, or substance use. Psychiatric evaluation was significant for limited memory regarding the two weeks prior to presentation, with tangential and vague responses, thought blocking, and disorganization. While admitted, olanzapine was increased from the outpatient dose of 15 mg nightly to 20 mg. Complete blood counts were collected daily. Approximately 10 days after admission, the ANC had risen to an average value of 1.0 thou/μL. Delusions and internal preoccupation persisted and thus a clozapine rechallenge was considered. Hematology was consulted and concluded that his presentation was consistent with CIAG. Following informed consent, a one-time dose of filgastrim 480 μg was administered intramuscularly. Within 2 days, his ANC rose to 10.8 thou/μL and then returned to an average of 2.9 thou/μL after seven days. Four days later, clozapine was restarted at 25 mg daily and titrated concomitantly with a taper of olanzapine. As clozapine dosing reached 200 mg daily, his ANC was measured to be 2.1 thou/μL. Lithium was started at 150 mg daily as an adjunct to support the ANC following rechallenge. Two serum lithium levels collected at 5 days as well as 4 months after initiation were found to be <0.19 mmol/L. Titration of clozapine continued with slow but consistent improvements in symptoms towards his pre-hospitalization baseline. ANC maintained an average of 3.0 thou/μL following discharge.

Clozapine induced agranulocytosis is a rare but life-threatening adverse reaction. It is important to consider that the greatest risk for blood dyscrasias occurs during the initiation of clozapine, however agranulocytosis may occur at any time during the course of treatment. When a rechallenge is indicated, lithium can be effective in maintaining an appropriate ANC. Chronic use of lithium carries its own risk of kidney and thyroid damage, as well as potentially masking a further worsening agranulocytosis. Careful monitoring should be continued throughout treatment for signs of emerging illness. For drug refractory patients at risk for stopping clozapine due to agranulocytosis, adjunctive lithium offers the possibility for successful clozapine rechallenge.

## Contributors

All authors treated the patient. ACM managed the literature review and wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

## Declaration of Competing Interest

The authors declare no conflicts of interest.

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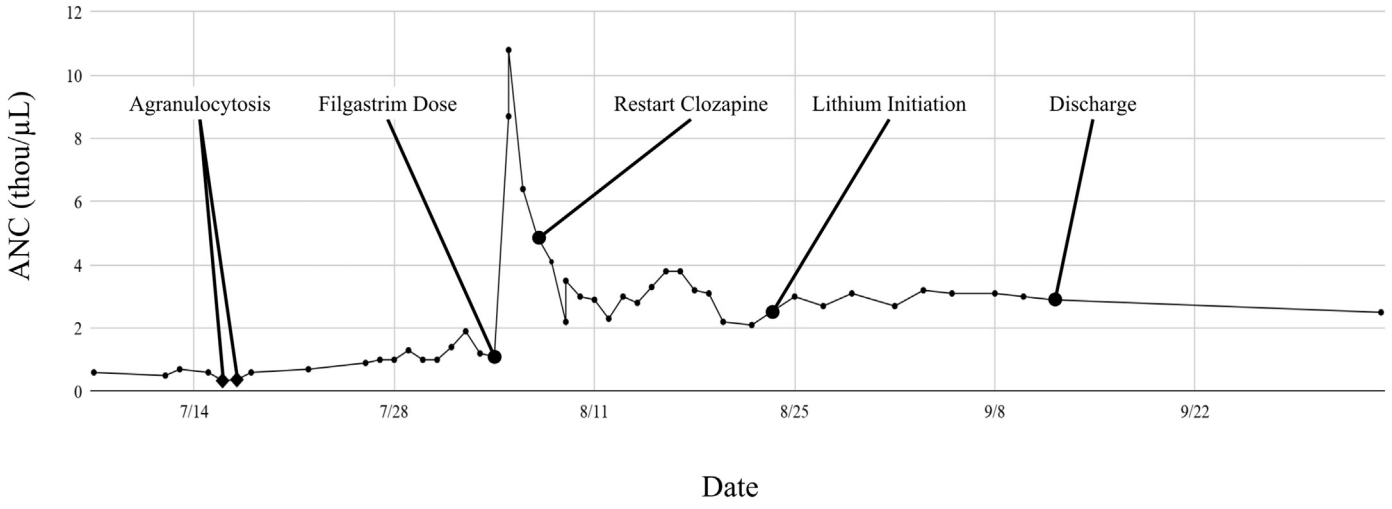


**Fig. 1.** Absolute neutrophil count vs. time. Onset of agranulocytosis is noted followed by subsequent administration of filgastrim, restarting of clozapine, and initiation of lithium.

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