

Clozapine and COVID-19

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We compliment the authors and journal for ensuring the “Consensus statement on the use of clozapine during the COVID-19 pandemic” was published in a timely fashion.¹ Coronavirus disease 2019 (COVID-19) rapidly transformed into a pandemic, challenging medicine in ways initially not imagined; this is certainly the case not only for treatment-resistant schizophrenia and for reasons related to clozapine, but also the patient population.²

Recommendation 1 of the consensus statement speaks to the issue of extending blood monitoring, thereby allowing individuals to stay at home and decrease the risk of exposure to COVID-19 and to the spread of the virus that causes it. The recommendation provides 3 points to guide clinicians in decision making regarding the extension of blood monitoring. The first indicates that individuals on clozapine for 1 year are eligible for extensions up to 3 months, well beyond the monthly monitoring that regulatory guidelines generally require at this point. The authors note that patients on clozapine for 6–12 months should be considered on a “case-by-case basis” and give no recommendation for change during the first 6 months of treatment. As an aside, we believe that all decisions, regardless of clozapine treatment stage and criteria, must be considered on a case-by-case basis.

The consensus statement notes that severe neutropenia (absolute neutrophil count [ANC] < 500/μL) is rare (0.009% of clozapine starts), with a case fatality rate of 2.1%.³ We would add that approximately 88% of clozapine-induced agranulocytosis cases occur in the first 6 months (unpublished data: HLS Therapeutics, 2020), meaning that the risk is considerably diminished by the time individuals are on biweekly monitoring. With these figures as background, we suggest that clinicians give consideration to this group but consider a window that is narrower; e.g., 3–4 weeks. In line with the consensus

statement, we agree that those being monitored weekly continue as is, reflecting the increased risk during this time period.

The second point in Recommendation 1 relates to not extending blood monitoring for anyone who has had an ANC value < 2000/μL (or < 1500/μL if there is a history of benign ethnic neutropenia).¹ To our knowledge, there is no clear relationship between such drops and actual risk of agranulocytosis, which is rare, idiosyncratic and poorly understood.^{3–5} Using this criterion will exclude many individuals who were not at increased risk of agranulocytosis and, for this reason, we argue against it.

Finally, any discussion of clozapine and agranulocytosis risk must be couched in a historical perspective. The reintroduction of clozapine in the 1990s with strict hematologic monitoring reflects a cluster of deaths that occurred in Finland following its initial release,⁶ to this day not well understood but inextricably linking clozapine and agranulocytosis. We are reminded, though, that a relationship between antipsychotics and agranulocytosis preceded clozapine, with reports dating back to the 1950s and chlorpromazine.⁷ Agranulocytosis has since been associated with a variety of antipsychotics as well as other psychotropics,⁴ and its relationship to the former is, perhaps, best captured in a study of clozapine that concluded, “After the first year of treatment, the incidence of agranulocytosis significantly decreased to the order noted with some phenothiazines.”⁸

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The authors respond

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We thank Dr. Remington and Ms. Powell for their thoughtful comments¹ on our consensus statement regarding the adapted monitoring of patients receiving clozapine treatment during the coronavirus disease 2019 (COVID-19) pandemic.² We agree that all decisions regarding frequency of monitoring need to be made on a case-by-case basis in consultation among the treating team, patients and families/carers. In the absence of clear data on the absolute risk of severe neutropenia in the 6–12 months after clozapine commencement, we did not feel that blanket guidance could be

provided at this time. Hence, we have encouraged prescribers, patients and families/carers to reflect on the risks and benefits for individual cases. We hope that the managers of clozapine monitoring programs will provide access to de-identified data on time to severe neutropenia events to allow the Treatment Response and Resistance in Psychosis (TRRIP) working group and other researchers to analyze these data to better inform clozapine monitoring protocols.

The timing of clozapine monitoring varies from country to country.³ As Remington and Powell note,¹ in Canada biweekly monitoring is recommended in the 6–12 months after starting clozapine, while in Australia and other jurisdictions monitoring is required only every 4 weeks after 18 weeks on clozapine. Clinicians in jurisdictions with biweekly monitoring may wish to consider monitoring every 4 weeks after 6 months on clozapine if access to biweekly monitoring is not practical. It is worth noting, however, that even weekly monitoring may not identify all relevant cases of true severe neutropenia because the time from normal absolute neutrophil count (ANC) to the nadir may be less than 1 week.^{4,5}

The threshold for lowest historical ANC of 2000/ μ L (or < 1500/ μ L if history of benign ethnic neutropenia) since starting clozapine was set conservatively, given the absence of specific data to guide this value. The number of patients who may be potentially excluded by this higher threshold is unclear. Information from monitoring systems would be very helpful in establishing the percentage affected. Monitoring system data may also allow ascertainment of a relationship, if any, between episodes of ANC between 1000 and 2000/ μ L and risk of future episodes of ANC < 500/ μ L.

A thorough discussion of the historical background of the hematological adverse effects of clozapine was beyond the scope of the consensus statement. We note that a recent meta-analysis found the risk of neutropenia associated with clozapine was not significantly higher than the risk associated with other antipsychotics.⁶ However, for patients with COVID-19, health care providers would be wise to be vigilant regarding possible effects of antipsychotic drugs beyond clozapine (as well as carbamazepine) on white blood cells.

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