The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided.

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Consensus statement on the use of clozapine during the COVID-19 pandemic

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With the ongoing coronavirus disease 2019 (COVID-19) pandemic, psychiatrists find themselves in the clinical situation of being asked by patients, family members and patient advocacy societies to help ensure access to clozapine as a medication critical for ongoing patient care. To provide clozapine prescribing guidance and facilitate regulatory agencies modifying laboratory monitoring and/or dispensing requirements, an expert advisory subgroup of the Treatment Response and Resistance in Psychosis working group developed the following background, recommendations and rationale as a consensus statement.

Clozapine is the most effective antipsychotic for reducing positive symptoms, hospital admissions and all-cause mortality in patients with treatment-refractory schizophrenia.[1–3] Owing to the risk of clozapine-associated severe neutropenia, absolute neutrophil count (ANC) monitoring programs are a prerequisite for clozapine dispensation in most jurisdictions globally.[4,5] Region-specific limits on outings and clinical resource constraints during the COVID-19 pandemic may create challenges for patients to access routine clozapine-associated care, including ANC testing required for dispensing. Discontinuing clozapine, especially abruptly, creates significant risk of relapse or exacerbation of severity of illness and needs to be avoided. Given the importance of continued access to clozapine, for the duration of the public health emergency we recommend the following.

Recommendation 1

The frequency of ANC may be reduced to every 3 months, with dispensation of up to a 90-day supply (if it can be safely stored) for people fulfilling all of the following criteria:

- continuous clozapine treatment for > 1 year
- have never had an ANC < 2000/μL (or < 1500/μL if history of benign ethnic neutropenia)
- no safe or practical access to ANC testing

Decisions about ANC monitoring for patients on continuous clozapine treatment for 6–12 months may be made on a case-by-case basis. Irrespective of ANC monitoring, patients on clozapine should continue to receive regular clinical assessments of mental state and review of potential adverse drug reactions, either face-to-face or through telehealth consultations. For patients being initiated on clozapine, adherence to current country-specific protocols for ANC monitoring is suggested for the first 6 months of treatment.

Rationale: Maintaining access to routine ANC monitoring for all patients prescribed clozapine is preferred. However, severe neutropenia (ANC < 500/μL) is rare (9/1000 people started on clozapine), with a case fatality rate of 2.1%.[4] Importantly, severe neutropenia has its peak incidence in the first months after clozapine commencement and declines to negligible levels after 1 year.[4]

Recommendation 2

For patients on clozapine with any symptoms of infection (including those reported for severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], such as cough, fever and chills, sore throat or other flu-like symptoms), an urgent physician assessment including a complete blood count (with ANC) should be obtained. The clinical assessment could take place either in person or by telehealth based on local protocols.

Rationale: Clozapine may be associated with a higher risk of pneumonia, likely due to sialorrhea and aspiration rather than neutropenia.[6] Clozapine-associated neutropenia is thought to occur as a result of selective neutrophil toxicity mediated by clozapine N-oxide metabolites,[7] or an immune response mediated by a hapten-based mechanism,[8] both of which occur early in exposure. There is limited information on the impact of coronaviruses on neutrophils among people taking clozapine; however, viral illnesses are generally associated with neutropenia,[9] and as such severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in some patients may be a cause of neutropenia not etiologically related to clozapine exposure.

Recommendation 3

If patients on clozapine become symptomatic with fever and flu-like symptoms, the emergence of signs and symptoms of clozapine toxicity may require clinicians to reduce the dose of clozapine by as much as a half. Continue the lower dose until 3 days after the fever has subsided, then increase clozapine in a stepwise manner to the pre-fever dose. Where available, clozapine levels help facilitate clinical decision-making, particularly after substantial dosage change, inadequate response or unexpected adverse effects.

Rationale: Clozapine levels can increase with acute systemic infection,[10] leading to symptoms of acute clozapine toxicity, including sedation, myoclonus and seizures. Patients with respiratory infections in or out of hospital may reduce or cease smoking, also leading to raised clozapine levels.[11]

Any decisions about changes to clozapine dose and monitoring should be made as part of a well-documented, informed consultation with patients and family/caregivers.

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