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A COMMENTARY ON IMPROVING CLOZAPINE ACCESSIBILITY AND REDUCING TREATMENT COST

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ABSTRACT

Clozapine is vastly underutilized in the United States and many other countries. The most commonly cited reason for this is the requirement for frequent blood monitoring, which continues for the duration of treatment. Despite the notoriety clozapine achieved early in its development, accumulated evidence has demonstrated that close blood monitoring beyond the first year of treatment yields minimal safety benefits. Many health care systems have relaxed clozapine blood monitoring requirements during the COVID-19 pandemic for practical reasons, and this presents an opportunity to implement permanent, long overdue changes in mandated monitoring that reflect what has been learned about the real risk for blood dyscrasias with clozapine.

The COVID-19 pandemic has altered and disrupted established processes and practices in every economy and culture. In the health care sector it has necessitated a rethinking of the ways in which service needs are prioritized, and fresh analyses of the risks and benefits associated with accessing these services. Individuals with very limited financial resources, poor access to health care resources, and fragile social support networks are less likely to avoid infection and more likely to experience its severe sequelae. Many members of our communities who have a serious and persistent mental illness are among those at greatest risk, and an appreciation of this vulnerability has motivated unprecedented adaptations in mental health care practices that aim to balance the risk of infection for clinician and patient against the risks of reducing treatment intensity. One adaptation effected by some health care systems (e.g., New York State Office of Mental Health, 2020 and CareOregon, 2020) in response to the pandemic is a reduction in the frequency of absolute neutrophil count (ANC) and white blood cell (WBC) count monitoring during clozapine treatment. Simultaneously, the United States Department of Health and Human Services Food and Drug Administration (2020) announced that during the public health emergency it is suspending "enforcement action against sponsors or others for accommodations made regarding laboratory testing or imaging study requirements . . . provided that such accommodations were made based on the judgment of a health care professional (p 7)."

In the United States, clozapine continuation is predicated on demonstrating minimum ANC and WBC levels for each prescription renewal; these are measured at weekly intervals for the first 6 months of treatment, then biweekly for the next 6 months, and then monthly for the duration of treatment. A recent survey of 9 countries found that the U.S. blood count monitoring regimen is the most stringent except for Japan, where biweekly determinations continue indefinitely (Nielsen et al, 2016). However, there is accumulating evidence that close monitoring of blood counts beyond the first year of treatment is unlikely to avert agranulocytosis. In a meta-analysis of 108 published studies comprising >450,000 patients, the frequency of mild neutropenia (ANC <1,500/mcL) was 3.8-3.9%, and the frequency of severe neutropenia (ANC <500/mcL) was 0.7-0.9%, depending on the quality of the studies included in the analyses (Myles et al, 2018). That study reported a case fatality rate for severe clozapine-associated neutropenia of 2.8%, and approximately 1 clozapine-induced neutropenia-related death per 7,700 treated persons. Importantly, the incidence of severe clozapine-induced neutropenia after 1 year of treatment is extremely low; 89% of severe neutropenia cases occur within the first year of treatment, and the remaining 11% are distributed in ever-decreasing numbers over subsequent treatment years, with only 4% of cases emerging after 36 months (Myles et al, 2018).

Clozapine is associated with other medically serious adverse effects such as myocarditis, cardiomyopathy, and seizures, but only blood count monitoring is a regulatory mandate. This single-minded focus on the potential for clozapine-induced neutropenia is best understood as stemming from somewhat arbitrary circumstances surrounding its premarketing development. Although chlorpromazine and clozapine were discovered contemporaneously in the 1950s, their subsequent development and implementation trajectories diverged markedly. Whereas chlorpromazine was integrated rapidly into psychiatric practice

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following a series of successful clinical trials in North America, clozapine's pre-marketing evaluations were conducted in Europe and Asia where comparatively less stringent regulatory oversight permitted a series of fatalities to occur in Finland that were linked to clozapine-induced blood dyscrasias, including agranulocytosis (Crilly, 2007). The alarm generated by those fatalities stalled clozapine's FDA new drug application and halted its research and development program, restricting it to compassionate use until 1984 when the FDA invited a new drug application for its use in treatment-resistant schizophrenia (TRS) (Crilly, 2007). Thus, clozapine was quickly branded as significantly more hematologically dangerous than chlorpromazine even though their rates of agranulocytosis and neutropenia are comparable after the first year of treatment (Wiciński and Węclewicz, 2018). A recent meta-analysis comparing neutropenia rates with clozapine and a variety of other antipsychotic agents found no increased risk with clozapine (Myles et al, 2019).

Despite the consensus among current and widely accepted treatment guidelines regarding its use in TRS, clozapine continues to be substantially underutilized in the United States and in many other countries (Warnez and Alessi-Severini, 2014; Bachmann et al, 2017). The proportion of patients with TRS who receive a trial of clozapine varies by country, with estimates ranging from ~3.5% in the United States to 26% in China and 36-38% in Australia (Wiciński et al, 2017). Even when clozapine is prescribed, its initiation is often delayed for years after the patient has satisfied treatment guideline criteria for eligibility (Howes et al, 2012). For example, one study of clozapine prescribing in New Zealand found that despite a relatively high cross-sectional utilization rate of 32.8%, an average of almost 10 years elapsed between first contact with a clinician and the initial clozapine prescription (Wheeler, 2008). A retrospective study of hospitalized patients treated with clozapine found that they had received an average of 5.7 adequate trials with an average of 4.0 antipsychotic medications prior to clozapine treatment (Taylor et al., 2003). It has been estimated that as many as 5-10 times more patients might benefit from clozapine than are currently receiving it (Stahl, 2014), and there is evidence that clozapine is even less accessible to patients who are female, older, or non-white (Latimer et al, 2013). In contrast to western and European countries, clozapine has been the most commonly used treatment for schizophrenia in China over the past several decades, accounting for up to 60% of all antipsychotic medication prescriptions (Tang et al, 2008). It is interesting to note that in China clozapine is more likely to be prescribed in economically less advantaged communities because of its comparatively low cost (Tang et al, 2008). Clozapine's widespread underutilization outside China has been attributed to a number of factors, but routine blood monitoring is consistently ranked as the most important barrier to clozapine treatment (Farooq et al, 2019).

In response to the logistical challenges of providing continuous clozapine treatment during the pandemic, Siskind et al. (2020) published a consensus statement advocating a temporary relaxation of blood monitoring requirements "for the duration of the public health emergency." Their principal recommendation is to reduce the frequency of ANC monitoring to every 3 months for patients who have been treated continuously with clozapine for >1 year, have never had an ANC <2000 /mcL (or <1500 /mcL if there is a history of benign ethnic neutropenia), and have no safe or practical access to ANC testing. They also recommend urgent medical consultation, including ANC determination, if any symptoms of infection arise, and consideration of reducing the clozapine dosage because clozapine levels can be increased by acute systemic infection. Notably, the need for frequent blood monitoring in perpetuity was questioned long before the pandemic, based on the observation that mortality associated with discontinuing routine ANC monitoring after the first 6 months of clozapine treatment approaches that associated with some other medications and accidental injury (Schulte, 2006). Moreover, the blood monitoring strategies employed in the United States and Europe are not cost-effective (Girardin et al, 2014). These strategies increase quality-adjusted survival by less than 1 day per patient, and for every death avoided by them more than 5,000 patients need to be monitored; compared with no monitoring, their incremental cost-effectiveness ratios are at least US$970,000 per quality-adjusted life-year gained.

The need for close monitoring during the first 6-12 months of clozapine treatment is supported by the evidence, which indicates that neutropenia risk is greatest in the first year, especially in the first 6 months of treatment. In contrast, the requirement for monthly blood monitoring indefinitely after the first treatment year is not evidence-based. Rather, it is the legacy of a singular series of unfortunate events that occurred early in its development and gave rise to a distorted perception of its relative risks, a perception that continues to overshadow its unique and substantial benefits for patients whose response to other antipsychotic medication is unsatisfactory. Monthly blood monitoring after the first treatment year is a barrier to treatment, imposes significant unnecessary direct costs on health care systems and indirect costs on patients, and contributes to inequities in access to health care while providing negligible benefit. The relaxation of clozapine blood monitoring requirements prompted by the pandemic is a convenient inflection point for revising the protocol to be followed once the public health emergency has resolved.

The international expert consensus recommendations of Siskind and colleagues provide a useful framework for a more rational post-pandemic monitoring strategy, for example:

1) weekly WBC and ANC determinations for months 0-6
2) biweekly WBC and ANC determinations for months 7-12
3) if clozapine treatment is continuous for 1 year with no ANC <2000 /mcL (or <1500 /mcL if there is a history of benign ethnic neutropenia), then
   a) quarterly WBC and ANC determinations for treatment years 2 and 3, followed by
   b) annual WBC and ANC determinations thereafter, else
4) if condition 3 is not met, monthly WBC and ANC determinations until it is met
5) at any time, if symptoms of infection arise an ANC should obtained promptly and, if indicated, urgent medical consultation

It will be difficult to overcome the pervasive view that clozapine is unmatched among antipsychotic agents in its potential to harm patients, but it is imperative that the effort succeeds because a more rational blood monitoring strategy has important implications for health care access, equity and costs.

Declaration of Competing Interest

Dr. Gurrera reports no competing interests.

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