Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Clozapine treated patients and COVID-19: Ensuring continued care through collaboration

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In the United States, the FDA clozapine Risk Evaluation and Mitigation Strategy (REMS) monitoring program's motto on the front page of the website is "No Blood, No Drug." (Clozapine REMS - Home Webpage) Pharmacists in community settings may refuse to dispense clozapine if the absolute neutrophil count (ANC) is not up-to-date within the online REMS program. Those prescribing clozapine must be proactive to coordinate with pharmacies to ensure clozapine therapy continues uninterrupted due to COVID-19 pandemic barriers. Barriers to hematologic monitoring encountered locally or regionally include but are not limited to laboratory closures in areas with limited resources, reduced ability to access transportation, and patient concerns of leaving their residence. Elderly and immunocompromised patients taking clozapine or patients living with elderly or immunocompromised individuals are at potential higher likelihood to defer clinic visits or hospital encounters for hematologic monitoring.

In late 2015, the FDA launched the web-based clozapine program, altering the manner in which clozapine must be monitored and reported. Prior to this, the FDA required each clozapine manufacturer (brand and generic) to manage its own system for hematologic monitoring of patients on clozapine therapy ("Clozapine in Practice: A Toolkit | cpnp.org"). Logic built into the REMS program currently allows for a "grace period" that will give an electronic indication that clozapine is "ok" to dispense for up to 56 days after the time an ANC should have been due. However, the monitoring frequency indicated to the pharmacist at the time of dispensing may change dependent on the last ANC draw date. In a community with a population of approximately 120,000 individuals, pharmacies throughout the city were contacted preemptively to ask how they would handle a patient with delinquent ANC reporting due to a COVID-19 related issue. This was important information for prescribers, such that they may be able to quickly issue new prescriptions to a different pharmacy if patients were unable to be dispensed clozapine due the decision to defer ANC testing. In our investigation, most pharmacies indicated that clozapine would be dispensed at the usual testing interval if the last reported ANC was within 56 days or the prescriber indicated that the benefits of continuation outweighed the risks of deferring ANC monitoring secondary to a COVID-19 circumstance. However, at the time of this writing, one pharmacy stated they would only allow up to 2 weeks of clozapine before requiring an ANC be reported to REMS (i.e. not allow dispensing if an ANC was late beyond 2 weeks), even if a patient was on every 4 week dispensing intervals. This highlights the fact that pharmacists may dispense medications based on their clinical judgment. Yet, it may be as more community experience, expert opinion, and research emerge, barriers to fill clozapine prescriptions with REMS deviation is minimized.

In a recent international consensus statement, recommendations were made to consider a reduced hematologic monitoring frequentcy of every 3 months with the dispensing of a 90 day clozapine supply (if safe). This applied to patients that have been taking clozapine for greater than a 1 year time period without neutropenia or for those without safe/practical means to obtain an ANC (Siskind et al., 2020). Despite this recommendation, in the United States, pharmacies still may only dispense of enough medication adequate for a patient's current testing interval. Additionally, insurance plans may limit the quantity dispensed. Other recommendations from the international group included urgent patient assessment and obtaining a CBC with differential if signs or symptoms of infection occur, as well as the consideration that acute infection can significantly increase clozapine levels. In the setting of an acute inflammatory or infectious process, up to a 50% clozapine dose reduction or temporary discontinuation may be needed depending on the degree of toxicity. (Siskind et al., 2020; de Leon et al., 2020). Infection can dramatically increase serum clozapine levels via the effects of cytokines on cytochrome P450 1A2, the major metabolic pathway for clozapine. The increase in serum level can be significant enough to produce symptoms that necessitate care within a critical care unit. (Leung et al., 2014) Yet, elevated levels or toxicity may not always occur with acute infectious processes, therefore dose reductions should be individualized and paired with retitration as necessary. Clinical decision making must guide management and dosing since clozapine levels, which may be a "send-out" test can take several days to become available for review.

To meet the needs of the patients, collaborative teamwork between prescribers and pharmacists is a must to discuss the risks and benefits of allowing variance from the REMS requirements. The FDA has released some guidance related to REMS programs for medications that require laboratory monitoring, "*Although all REMS requirements remain in effect, FDA does not intend to take 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.*" ("Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals | FDA,")

In order to consider any variance from REMS, it is important that prescribers and pharmacists understand the risk of neutropenia associated with clozapine. Neutropenia increases the risk of infection, particularly when the ANC is <500/microL. The baseline risk of severe neutropenia for clozapine is approximately 1.3% overall, with peak risk around 1 month after initiation with substantial reduction in risk at 18 weeks (Citrome et al., 2016; Myles et al., 2018). This is a consideration for why in the United Kingdom, Netherlands, Denmark, New Zealand, and Romania weekly monitoring occurs for the first 18 weeks (Nielsen et al., 2016). After 6 months, testing as infrequently as 4 times per year in certain cases has been described (Cohen and

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Monden, 2013). This is in contrast to the weekly monitoring required for 26 weeks in the United States. One study reported that after the first 6 months of therapy until the 12 month time period, the risk of neutropenia was estimated to be 0.70/1000 patient-years. After 12 months this reduced further to 0.39/1000 patient-years (Schulte, 2006). These risk estimates then become very similar to other first generation antipsychotics, which were reported to be 0.1–1.4/1000 patient years (Schulte, 2006). The lower risk after 1 year of clozapine has raised questions about the need for indefinite hematologic monitoring by experts, studies, and even meta-analyses (Atkin et al., 1996; Kang et al., 2006; Ingimarsson et al., 2016; Li et al., 2019; Myles et al., 2018; Ratanajamit et al., 2010). In fact, vigilant monitoring after 6 months has been described as not evidence based (Cohen and Monden, 2013). Following the COVID-19 pandemic, there is a unique opportunity for stakeholders in the field to continue to challenge the current laboratory requirements in the United States that mandate monthly ANC testing.

Given the risks of neutropenia within the first 18 weeks, attempts to obtain ANC values for REMS reporting should still be attempted during the COVID-19 pandemic. And although the REMS program in the United States requires weekly testing for the first 26 weeks, clinical decisions to safely defer a blood draw could be considered after 18 weeks if needed due to COVID-19 barriers. At the same time, very rare cases of neutropenia have been reported after many years of clozapine therapy, so deferral of ANC testing should not mean deferral of a “clinic visit”, substituting telehealth as able, to ensure ongoing timely patient assessment (Cohen and Monden, 2013). The COVID-19 pandemic also has allowed consideration for novel ANC testing via point-of-care devices. Continued development and improvement of these products will be important for improving access to clozapine. Despite availability of point-of-care devices, barriers such as their use being limited to clinic settings, reliance of result management via third-party laboratories, and lack of ability to integrate into an institution's electronic health record exist.

Finally, other considerations that should be addressed related to variance from REMS include informed consent with discussion of the signs and symptoms of infection such as fever, cough, sore throat, and headache (Marrs, 2006). A patient's access or ability to obtain a thermometer is important as well. If patients call with symptoms of infection, whether due to suspected neutropenia or COVID-19, they should contact a healthcare worker as soon as possible for further guidance. Other practical considerations include assessing changes to smoking, caffeine habits, activity, and diet during which may alter clozapine metabolism or affect gastrointestinal hypomotility (Hägg et al., 2000; Lowe and Ackman, 2010; Palmer et al., 2008).

Overall, as the duration and full impacts of the COVID-19 pandemic are unknown, prescribers and pharmacists must work jointly to determine a clozapine monitoring plan on a case-by-case basis rather than either defer on all ANC monitoring or rigidly hold to the REMS monitoring schedule. In post-COVID-19 times, research must emerge assessing the necessity of indefinite monthly monitoring given the many barriers that exist for successful clozapine use at baseline.

Contributors

Author JG Leung drafted the letter submitted. Author K Schak and T Wittenberger reviewed the letter and added crucial edits to the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

Authors involved with this work have no conflicts of interest to declare.

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