Clozapine and COVID-19

Updated 5/22/2020

Due to the continuing COVID-19 pandemic, behavioral health organizations and clinicians have been making difficult decisions to balance the need for ongoing patient access to medically necessary services with infection control measures that protect patients and staff. Clozapine remains a critical element of treatment for many patients. However, administering clozapine during COVID-19 continues to pose challenges due to medical monitoring requirements and continued patient mobility and access limitations.

Therefore, CareOregon agrees with the National Council for Behavioral Health's Medical Director Institute (MDI) recommendation of May 21, 2020 for a modified blood test monitoring protocol that addresses patient safety while being responsive to infection control practices. These recommendations align with a consensus statement regarding the use of clozapine released by an international group of psychiatric researchers and clinicians on April 3, 2020.[1] The New York State Office of Mental Health endorsed the same recommendations on April 16, 2020.[2]

Therefore, CareOregon recommends for provider consideration that:

1. The frequency of absolute neutrophil count (ANC) reporting may be reduced to every three months, with dispensation of up to a 90-day supply — if it can be safely stored — for patients who fulfill all the following criteria:
    - **a.** Continuous clozapine treatment for greater than one year.
    - **b.** Never had an ANC less than 2000/µL (or less than 1500/µL if there is a history of benign ethnic neutropenia).
    - **c.** No safe or practical access to ANC testing.

2. For patients taking clozapine with any symptoms of infection (including those reported for severe acute respiratory syndrome coronavirus 2 [SARSCoV-2] such as cough, fever and chills, sore throat or other flu-like symptoms), the provider will conduct or refer patients to an urgent physician assessment including a complete blood count (with ANC).

3. If patients on clozapine become symptomatic with fever and flu-like symptoms, 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 three days after the fever has subsided, then increase clozapine incrementally to the pre-fever dose.

Following review and discussion, CareOregon agrees with the MDI that these recommendations better balance the risk of clozapine-induced agranulocytosis with the risk of COVID-19 infection, morbidity and mortality. These recommendations are the community standard of care for the duration of the COVID-19 emergency.

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[1] Siskind et al. (2020). Consensus statement on the use of clozapine during the COVID-19 pandemic. *Journal of Psychiatry Neuroscience*, 45(4):200061. doi: 10.1503/jpn.200061.
[2] New York State Office of Mental Health (2020). *Update: clozapine blood test monitoring recommendations.* Accessed May 7, 2020: omh.ny.gov/omhweb/guidance/omh-covid-19-guidance-clozapine-blood-test-monitoring.pdf.

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3/23/2020 update: The Food and Drug Administration (FDA) requires Risk Evaluation and Mitigation Strategy (REMS) monitoring of clozapine. People on established clozapine pharmacotherapy with required blood draw for ANC monitoring and reporting may be unable, unwilling or recommended not to have blood drawn during the current COVID-19 pandemic. This is a challenge for dispensing clinical pharmacists and prescribing providers.

On March 22, 2020, the FDA provided the following advisory: fda.gov/media/136317/download

The pertinent recommendation is found on the final page:

"FDA recognizes that during the COVID-19 PHE [Public Health Emergency], completion of REMS-required laboratory testing or imaging studies may be difficult because patients may need to avoid public places and patients suspected of having COVID-19, may be self-isolating and/or subject to quarantine. Under these circumstances, undergoing laboratory testing or imaging studies in order to obtain a drug subject to a REMS can put patients and others at risk for transmission of the coronavirus.

"For drugs subject to these REMS with laboratory testing or imaging requirements, health care providers prescribing and/or dispensing these drugs should consider whether there are compelling reasons not to complete these tests or studies during the PHE, and use their best medical judgment in weighing the benefits and risks of continuing treatment in the absence of laboratory testing and imaging studies. Health care providers should also communicate with their patients regarding these judgments, including the risks associated with it.

"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 imposed under sections 505-1(f)(3)(d) or (e) of the FD&C Act (21 U.S.C. 355-1 (f)(3)(d) or (e)) during the PHE declared by the Secretary of HHS on January 31, 2020, provided that such accommodations were made based on the judgment of a health care professional. 13 Manufacturers should document and summarize in their next REMS Assessment Report steps that were taken to accommodate patient access to these REMS drugs during this COVID-19 PHE."

Summary recommendations:

- Prescribing and dispensing providers are to use their best medical judgment in deciding whether to continue clozapine when there are compelling reasons to avoid monitoring or other testing.
- The FDA does not intend to take enforcement action regarding these medically determined accommodations during the public health emergency declared by HHS on January 31, 2020.
- Prescribing and dispensing providers should carefully and thoroughly document their decision-making regarding these medically determined accommodations.

For questions regarding the FDA document, contact Claudia Manzo, Center for Drug Evaluation and Research, Food and Drug Administration, at 800-835-4709.

Submit electronic comments at regulations.gov. All comments should be identified with the docket number FDA-2020-D-1106 and the complete title of the FDA guidance.