Clozapine REMS Program COVID-19 Updates

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Clozapine is FDA-approved for the treatment of resistant schizophrenia and suicidal behavior in schizophrenia or schizoaffective disorder. Along with this, it may be used off-label for the treatment of resistant bipolar disorder, psychosis or agitation associated with dementia or psychosis in Parkinson disease. Clozapine contains five black box warnings, one of which states that it may lead to severe neutropenia. Severe neutropenia is defined as an absolute neutrophil count (ANC) of less than 500/mm^3. When patients develop severe neutropenia, this may lead to serious infection or death.

Due to the potential for clozapine to cause severe neutropenia, patients are only able to receive clozapine therapy if they are enrolled in the Clozapine Risk Evaluation Mitigation Strategies (REMS) Program. This Clozapine REMS Program generally requires patients to have a baseline ANC of at least 1,500/mm^3 to initiate therapy. The only exception to this is that patients with known benign ethnic neutropenia may initiate the medication with an ANC of 1,000/mm^3. Throughout treatment with clozapine, patients are required to undergo regular ANC monitoring. Each patient's current ANC must be submitted to the REMS Program database before dispensing each fill of the medication.

Because of recent concerns during the current COVID-19 pandemic, many questions have arisen regarding laboratory monitoring requirements for REMS medications. The FDA released a statement on March 22, 2020 stating that they recognize the difficulty of completing REMS-required laboratory testing during this pandemic, especially for patients who are suspected of having COVID-19 and have been self-isolating or have been required to quarantine. The FDA states they realize that completing lab tests among these patients may put others at risk of contracting COVID-19. For this reason, they recommend that healthcare professionals weigh the benefits of completing the REMS-required lab testing versus the risks of continuing treatment without it. Although all REMS requirements remain in effect, the FDA has also stated that they will not penalize healthcare professionals who fail to adhere to REMS requirements for the duration of this pandemic.

Studies suggest it may be reasonable to dispense clozapine without ANC monitoring in those who have been stable on the medication. For example, one meta-analysis from Myles *et al*. published in 2018 states that the risk of neutropenia peaks within the first month of taking clozapine, and the risk is nearly insignificant by the time the patient has been on it for one year. Another study from Schulte in 2006 showed that the mortality associated with discontinuing ANC monitoring in patients taking clozapine for over 6 months was approximately the same as mortality due to other medications or life, in general. However, ANC monitoring is currently considered best practice for all patients who are still able to safely get their blood drawn.

If a pharmacist feels it is appropriate to dispense clozapine without ANC monitoring after consultation with the prescriber, the patient should continue to be monitored for signs and symptoms of severe neutropenia, such as fever, weakness, lethargy or sore throat. Likewise, it is recommended for any patient taking clozapine who is experiencing symptoms of sore throat and

fever to be assessed for neutropenia, as well as for COVID-19, as the symptoms of these two conditions may initially make them difficult to differentiate. Finally, healthcare providers should be sure to document the rationale behind their decision and ensure they communicate with their patients regarding the potential risks associated with dispensing clozapine without ANC monitoring.

References:

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