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CLINICAL UPDATE

Brand Name	Clozaril
Generic Name	clozapine

Clinical Update

FDA strengthens warning that untreated constipation caused by schizophrenia medicine clozapine (Clozaril) can lead to serious bowel problems.

FDA Approval Date: January 28, 2020

Overview

Clozapine is a medicine that has been used for more than 40 years to treat schizophrenia in patients whose symptoms are not controlled with standard treatment. Symptoms of schizophrenia include hearing voices, seeing things that are not there, and being suspicious or withdrawn. Clozapine is also effective in reducing the risk of suicidal thinking and self-harm in patients with schizophrenia or schizoaffective disorder. Clozapine has strong effects that can impair movement through the bowels, causing a blockage. Common side effects in addition to constipation include dry mouth, drooling, drowsiness, light-headedness, shaking or tremor, and blurred vision. In 2018, an estimated 782,000 clozapine prescriptions were dispensed from U.S. outpatient retail pharmacies, which was a 2.3% decline from 2016 (800,000 clozapine prescriptions).

On January 2020, The Food and Drug Administration (FDA) announced that it is strengthening an existing warning that constipation caused by the schizophrenia medicine clozapine (Clozaril, Fazaclo ODT, Versacloz, generics) can, uncommonly, progress to serious bowel complications, which can lead to hospitalization or even death if not diagnosed and treated timely. This side effect is experienced by the majority of patients. It produces effects ranging from constipation (trouble having a bowel movement), which is a common occurrence, to serious but uncommon bowel problems, including complete blockage of the bowel. On research FDA found that the risk with clozapine was greater than any other medicine for treating schizophrenia due to the way it works. The risk is further increased at higher doses of clozapine and when it is co-prescribed with a type of medicine called anticholinergics, which can slow the movement in the intestines, and other medicines that cause constipation, including opioids. FDA identified 10 cases of constipation that progressed to serious complications with clozapine use reported in the FDA Adverse Event Reporting System (FAERS) database from July 21, 2006, through July 20, 2016, and in the medical literature from July 21, 2006, through August 2, 2016. These cases resulted in hospitalization, surgery, and five deaths. Adverse events included necrotizing colitis2-5 (n=4), intestinal ischemia or necrosis6-8 (n=5), and volvulus (n=1). The total daily dose of clozapine administered ranged from 200 mg to 600 mg, with a median daily dose of 400 mg. The time to onset of serious bowel events ranged from 3 days to 6 months, with a median of 46 days. A preliminary review of additional FAERS data reported from July 21, 2016, through the end of 2019 found similar findings. Clozapine can do this alone; in contrast, serious complications of constipation have been identified with other antipsychotics (e.g., olanzapine) only when they were used with other anticholinergic medicines.

A New Zealand study of 37 patients conducted by Every-Palmer et al.2 objectively assessed and confirmed clozapine-induced gastrointestinal hypomotility by measuring colonic transit time (CTT) using radiopaque markers. The study reviewed the effects of clozapine (monotherapy and combination antipsychotic therapy, 20 patients) and non-clozapine antipsychotics (monotherapy and combination antipsychotic therapy, 17 patients) and concluded that nearly all patients receiving clozapine had increased CTTs, but most non-clozapine treated patients did not. An exposure-related increase in CTT was seen (that is, higher CTT with higher clozapine levels); however, patients did not report the hypomotility as subjective symptoms of constipation. The median CTT in patients

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treated with clozapine was more than four times longer than in patients not prescribed clozapine (105 hours vs. 23 hours, respectively).

FDA has started working on adding new warning and updates about the risk of clozapine to prescribing information of all clozapine products. FDA has advised patients who might not feel or be aware of constipation symptoms that they should contact their health care professionals if their bowel movements are less frequent than normal for them, especially if they do not have a bowel movement at least three times a week, they have hard or dry stools, or facing difficulty passing gas. Patient should contact their health care professionals right away if symptoms gets worse such as nausea and vomiting, bloating or belly swelling, or belly pain. In order to prevent constipation patients should eat more fruits, vegetables, and grains that are high in fiber; drink plenty of water and other liquids; and get enough exercise. Patient can take laxative after consulting it with their respective health care professionals, and patient must not stop taking their clozapine without consulting their health care professionals as topping treatment can cause schizophrenia symptoms to return or worsen.

Health Care Professionals should encourage patients to read the patient information leaflet they receive with their clozapine prescription, so they are aware of this additional information about the medicine. They should educate patients and caregivers on the risks, prevention, and treatment of clozapine induced constipation, including medicines to avoid such as other anticholinergic medicines. They should not prescribe clozapine with other anticholinergic medicines that can cause gastrointestinal hypomotility.