

"Giving Voice to Those Seldom Heard"

Clozapine and Constipation Medical Alert

This Medical Alert is based on the work of the Office of Ombudsman for Mental Health and Developmental Disabilities Medical Review Subcommittee and should be posted prominently. The Office of Ombudsman for Mental Health and Developmental Disabilities works to improve the services provided to people with disabilities by communicating important information found in the Medical Review Subcommittee's reviews of deaths and serious injuries. Thank you for promptly reporting deaths and serious injuries. You are helping us to meet the agency's mission.

The Medical Review Subcommittee wants to ensure that you are aware of the following FDA Drug Safety Communication, issued on 1/28/2020, as follows:

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

Risk increased at higher doses or when taken with other constipating medicines

The Food and Drug Administration (FDA) 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. This can lead to hospitalization or even death if constipation is not diagnosed and treated quickly. Constipation is a frequent and known side effect of clozapine, but serious and fatal events continue to be reported.

Clozapine affects how the intestines (bowels) function in 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 bowels. We found that because of the way clozapine works this risk is greater with clozapine than with the other schizophrenia medicines in its drug class. 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. Many different kinds of medicines have these anticholinergic effects...

- FDA is strengthening an existing warning that constipation caused by the schizophrenia medicine clozapine (Clozaril, Fazaclo ODT, Versacloz) can progress to serious bowel complications. This can lead to hospitalization or even death if constipation is not diagnosed and treated quickly.
- Clozapine impairs bowel function in the majority of patients. It produces effects ranging from constipation (common) to complete bowel obstruction, paralytic ileus and intestinal ischemia or infarction (uncommon). Constipation is a

frequent and known side effect of clozapine, but serious and fatal events continue to be reported.

- The risk is greater with clozapine than the other schizophrenia medicines we reviewed in its drug class because of clozapine's potent anticholinergic activity.
- The risk is further increased at higher doses of clozapine or when it is co-prescribed with anticholinergic agents and other medicines that cause constipation, including opioids.
- As a result, we are requiring a new warning and updates about this risk to be added to the prescribing information of all clozapine products.
- Be aware that subjective symptoms of constipation reported by patients may not accurately reflect gastrointestinal hypomotility; therefore, it is essential to question patients regarding the frequency and character of bowel movements and any changes.
- Avoid co-prescribing clozapine with other anticholinergic medicines that can cause gastrointestinal hypomotility.
- Consider prophylactic use of laxatives when starting clozapine in high-risk patients.
- If constipation is identified, promptly treat it with laxatives and adjust as necessary. Consult a gastroenterologist in more serious cases.
- Encourage appropriate hydration, physical activity, and foods that are high in fiber.
- Educate patients and caregivers on the risks, prevention, and treatment of clozapine-induced constipation, including medicines to avoid such as other anticholinergic medicines.
- Emphasize that prompt attention and treatment for constipation and other gastrointestinal symptoms is critical to preventing serious complications.
- 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.
- To help FDA track safety issues with medicines, report adverse events involving clozapine or other medicines to the FDA MedWatch program....

The entire Drug Safety Communication can be accessed at the website below:

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-strengthens-warning-untreated-constipation-caused-schizophrenia-medicine-clozapine-clozaril-can>

Could this happen to your client?

The Medical Review Subcommittee recently reviewed the death of a client, as follows:

Unexpected death of a client receiving services for mental illness, who had been prescribed clozapine. This 65-year-old man, with schizoaffective disorder, dementia, tobacco use disorder, epilepsy, hyperlipidemia, hypertension, diabetes insipidus, subacute dyskinesia due to medications, constipation, obesity, and other medical problems, died while receiving palliative end of life care after a three and one-half week hospitalization for a twisted and necrotic small bowel. It was reported that the client had undergone surgery to remove fifteen feet of necrotic small intestine. His death was not reported to the medical examiner. No autopsy was performed. His manner of death was natural, and his immediate cause of death was attributed to septic shock due to small bowel volvulus. Acute respiratory failure with hypercapnia and acute kidney injury were noted on his death record as other significant conditions contributing to his death.

The client was under neither guardianship nor conservatorship. Prior to his terminal hospitalization, he had lived in a corporate adult foster care home. He had received CADI case management services, targeted case management services, and outpatient psychiatric services for medication management. It was reported that the client had been taken to the hospital three times in the month before his terminal hospitalization. He reportedly had complained of stomach pain, was losing weight, and had loss of appetite. Each time he had been taken to the hospital, no treatable issues had been diagnosed except for constipation, which was noted one time. The client had been prescribed the following medications: clozapine 200mg every morning, clozapine 400mg at bedtime, quetiapine 400mg at bedtime, valproic acid 500mg every morning, and valproic acid 500mg at bedtime, in addition to other medications.

Three and one-half weeks before his death, group home staff brought him to the hospital emergency room again for the evaluation of abdominal pain, distension, weakness, and shortness of breath. He was intubated and found to have septic shock related to acute abdomen. He was admitted and underwent bowel resection to remove about fifteen feet of necrotic small intestine. He was extubated following surgery and received dialysis during the entire hospitalization. Approximately two weeks later, while still in the hospital, he had an acute hypoxic episode and was reintubated. An MRI indicated that he had brain damage. He was placed on comfort cares and was extubated, dying shortly thereafter.

The MRS noted that the client had received other medications, in addition to Clozaril/clozapine, with additive anticholinergic side effects: Cogentin/ benztropine, Seroquel/quetiapine, and Zantac/ranitidine.

A report to the FDA's MedWatch program has been submitted for this case.

The MRS recommended that the FDA MedWatch warning about clozapine be publicized in a Medical Alert and to the corporate foster care home, to the client's mental health case manager, to the community hospital and its Emergency Department, to the client's treating psychiatrist, and to the Minnesota Psychiatric Society.