



# Mortality and Morbidity due to Constipation Associated with the Use of Clozapine

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## Abstract

**Background:** There are several serious side effects associated with the use of clozapine, an atypical antipsychotic medication. Constipation, however, is an increasingly overlooked side effect that has resulted in fatal complications. We present the case of a patient with severe constipation due to long-term use of clozapine.

**Case presentation:** A 51-year-old male with a history of schizoaffective disorder on clozapine for over 7 years was brought to the emergency department with severe abdominal distention and lower extremity edema. CT abdomen showed severe fecal retention throughout the colon with stercoral colitis and right ureteral hydronephrosis. Fecal retention was relieved by digital disimpaction and enemas. The patient was ultimately diagnosed with clozapine-associated constipation, as criteria for constipation due to IBS, colonic strictures, and psychogenic constipation were excluded.

**Conclusion:** Clozapine inhibits the normal innervation of gut peristalsis, leading to gastrointestinal hypomotility. It is imperative that we understand the anticholinergic properties of clozapine and its associated complications to improve treatment options. This case report outlines potential screening and preventive measures that can assist in the management of clozapine-associated constipation.

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**Keywords:** Clozapine; Constipation; Complications; Adverse effects; Prevention.

## Introduction

Clozapine is the only FDA-approved antipsychotic on the market for treatment-resistant schizophrenia [1-3]. Common side effects of clozapine include hypersalivation, sedation, seizures, and metabolic syndrome [4]. While agranulocytosis and myocarditis are among the better-known serious side effects, constipation associated with clozapine use is potentially underreported and may also be life-threatening [5].

Clozapine's peripheral muscarinic anticholinergic properties affect M3 receptors in the gastrointestinal tract, resulting in a hypomotile gut [6-9]. Thus, clozapine is associated with gastrointestinal obstruction, fecal impaction, paralytic ileus, and constipation. A study by Liebermann et al suggests constipation occurs in 33% of patients with acute treatment and in 23% of patients undergoing maintenance treatment with clozapine [10]. Another study found that clozapine-associated constipation has a 60% prevalence rate [11].

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Long-term constipation can lead to severe fecal impaction, ileus, bowel obstruction or perforation, ischemic colitis, gastro-intestinal necrosis, toxic megacolon, and even death [12-17]. To compound the risk of gastrointestinal hypomotility, symptoms of constipation are often unrecognized or unreported. It is therefore critical that physicians regularly screen for clozapine-associated constipation.

In this article, we present the case of a patient with schizoaffective disorder on clozapine with severe constipation requiring manual disimpaction.

### Case presentation

A 51-year-old Caucasian male presented to the emergency department for severe abdominal distention, abdominal mass, and lower extremity edema that started 10 days prior. His symptoms were not accompanied by abdominal pain, nausea, vomiting, fever, melena, or hematemesis. The patient's history included chronic schizoaffective disorder diagnosed in 2013, drug-induced dyskinesia, COPD, and hypertension. He was started on clozapine in 2014. On admission, he was being treated with clozapine 100 mg five tablets orally at night and clozapine 25 mg twice daily. He was also taking benzotropine, valproic acid, divalproex sodium, ferrous sulfate, sertraline, amlodipine, and metoprolol tartrate.

Abdominal ultrasound imaging and KUB were previously performed at a separate facility, and both were concerning for an abdominal mass. On examination, the patient was afebrile with stable vital signs and in no acute distress. Physical examination revealed a tense, distended, nontender, and firm abdomen with absent bowel sounds. There was also scrotal and penile swelling extending into the pubic region along with bilateral lower extremity edema (**Figure 1**). Inguinal lymph nodes were enlarged but no scrotal erythema or penile discharge was noted. The patient had paradoxical diarrhea secondary to chronic constipation. Radiographic imaging showed extensive fecal retention throughout the colon and rectum, stercoral colitis, and mild ascites (**Figure 2 & 3**). Severe right hydronephrosis likely due to distention of bowel was also observed.

Treatment was started with polyethylene glycol 1L daily and tap water enema every 6 hours until bowel movements occurred. Manual disimpaction was attempted on the first day of treatment without success. The patient refused enemas and was treated with golytely for 3 days without any significant changes. A psychiatrist was consulted, and it was recommended to discontinue clozapine, suspecting it may have been the constipation-causing agent. However, an alternate drug was not available to manage the patient's schizoaffective disorder and the patient was continued on clozapine.

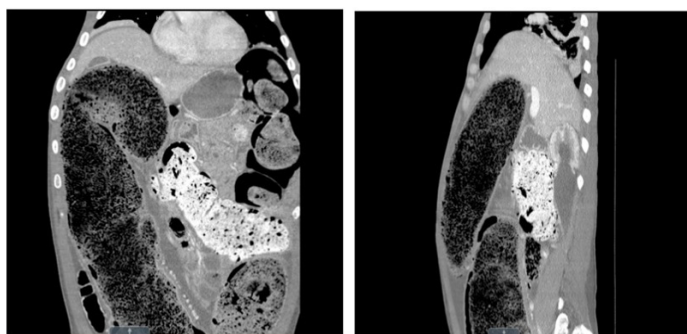
On the tenth day, the medical team was able to convince the patient of the need for manual disimpaction and repeated multiple enema treatment, at which point he finally produced a large bowel movement. Abdominal distention, scrotal and penile swelling, and bilateral lower extremity pedal edema rapidly improved after defecation and his abdomen returned to a soft and nontender state (**Figure 4 & 5**). The patient was discharged on miralax, clozapine, and the remainder of his medication regimen.



**Figure 1:** Initial presentation: Abdominal distention, scrotal, and penile swelling extending into the pubic region with bilateral lower extremity edema.



**Figure 2:** KUB X-ray shows retention of stool throughout the large bowel with near-complete effacement of the remaining visualized bowel.



a) Triple phase CT abdomen with IV contrast

b) Triple phase CT abdomen with IV contrast



c) Triple phase CT abdomen with IV contrast

**Figure 3a-c:** There is fecal retention throughout the colon, particularly of the sigmoid colon and rectum with the expansion of the colon throughout the abdomen particularly of the elongated dilated sigmoid colon. Diffuse bowel wall thickening is noted in most of the distal aspects of the sigmoid colon. Fecal impaction and expansion of the rectum can also be seen. Due to distention of the bowel, there is likely compression of the distal right ureter with moderate to severe right hydronephrosis. Additionally, there appears to be intra-abdominal ascites with mild diffuse mesenteric edema as well as subcutaneous edema throughout the abdominal wall and about the pelvis which may reflect developing anasarca.

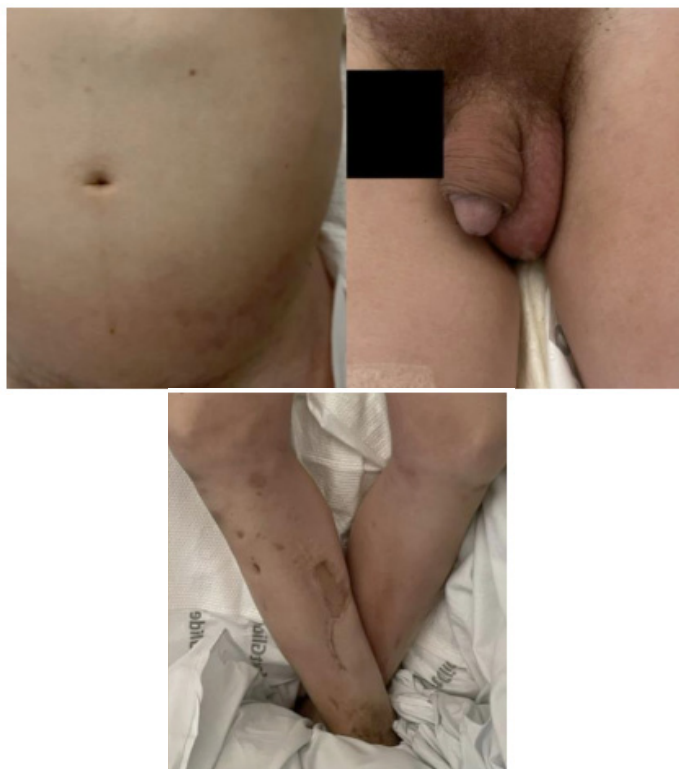


**Figure 5:** KUB X-ray shows severe constipation. However, no gaseous distention or abnormal calcifications of bowel can be seen.

**Discussion**

Agranulocytosis, a life-threatening side effect of clozapine, is regularly assessed in patients via routine blood draws throughout the duration of treatment. On the other hand, constipation is a common side effect of clozapine but is frequently overlooked. Cohen et al showed that the incidence of agranulocytosis is approximately 1-2 times more likely than GI hypomotility; however, the case-fatality rate of GI hypomotility is approximately 10 times higher than that of agranulocytosis. The reduced rate of fatality due to agranulocytosis reflects the efficacy of preemptive, regular monitoring [18]. In contrast, screening methods to regularly assess for constipation in clozapine patients have yet to be incorporated in standard treatment guidelines. Patients taking clozapine are routinely asked about constipation in the outpatient setting. However, there are various levels of functional and communication impairments in the clozapine-treated patient population that renders this type of questioning an ineffective screening measure. Moreover, the subjective quality of constipation as a symptom may further mask its prevalence and severity, explaining why a large number of cases go unidentified or unrecorded [13,19]. The requirement of lifelong treatment for schizophrenia and schizoaffective disorders with clozapine increases the risk of chronic constipation in an already-vulnerable population. Thus, this case report attempts to capture the implications of this risk in clozapine-treated patients by highlighting the acute onset of life-threatening symptoms due to undetected constipation.

Accordingly, a few strategies have been suggested to better manage and assess constipation as a side effect of clozapine. In addition to patient education, physicians prescribing clozapine should slowly titrate up the dose, by no more than 25 mg/day and to a maximum of 100 mg/week. Every time the dose of



**Figure 4:** Post-disimpaction: patient status is significantly improved.

clozapine is increased, the presence of constipation should be thoroughly assessed. Hayes and Gibler proposed the initiation of a clozapine constipation protocol that would include a thorough radiographic and physical assessment before starting clozapine [11]. Reinstein et al suggested replacing part of the dose of clozapine with quetiapine to mitigate constipation [20]. The GASS-C tool, which consists of 16 questions and was developed to assess side effects that cannot be easily measured, could also be implemented as a preventative measure. Hymes et al found the GASS-C to be a valid and reliable tool for detecting side effects of clozapine, including constipation. [21].

Clozapine-associated constipation can lead to fatal outcomes if not treated early. Thus, increasing our awareness regarding this possibility is key to minimizing complications. We emphasize the need to update clinical guidelines with systematic monitoring, screening, and prevention strategies that would improve the treatment of constipation associated with clozapine use.

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