

# A dangerous GI complication

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## How would you handle this case?

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Ms. X, age 61, undergoes emergent surgery for intestinal obstruction. Her paranoid schizophrenia has been well controlled on clozapine, but the drug might be causing her GI distress. What would you do?

### CASE GI surgery

Ms. X, age 61, presents to the emergency department (ED) complaining of nausea, vomiting, and abdominal pain and distension. CT scan of her abdomen reveals segmental ischemia in her colon with abscess formation, which leads to immediate surgery, including ileocecostomy with primary anastomosis. After surgery, Ms. X suffers from gastrointestinal (GI) dysmotility. The gastroenterology team recommends daily enemas along with a soft diet after she is discharged.

Ms. X has chronic paranoid schizophrenia, which has been treated successfully for 18 years with clozapine, 500 mg/d. During acute psychotic episodes, she experienced paranoid delusions and command auditory hallucinations telling her to kill herself. She had previous trials of several antipsychotics, including quetiapine, thiothixene, thioridazine, trifluoperazine, chlorpromazine, and haloperidol, all of which were ineffective and poorly tolerated because of serious side effects.

Within 1 month of discharge, Ms. X returns to the ED with nausea, vomiting, and abdominal distension. Abdominal CT scan suggests partial small bowel obstruction and significantly dilated loops of small bowel with decompressed rectum and sigmoid colon. Considering her recent GI surgery and absence of abdominal pain, she is managed with conservative measures, including naso-

gastric tube decompression and total parenteral nutrition. CT enterography demonstrates no areas of stricture formation with interval decompression.

The psychiatric service is consulted to evaluate the possibility of clozapine-induced paralytic ileus. During initial assessment, Ms. X denies any psychotic symptoms, including paranoid ideations, delusions, and auditory or visual hallucinations, and firmly believes that clozapine helps keep her stable. She also denies mood symptoms that could indicate mania or depression. She shows no signs or symptoms that suggest anticholinergic delirium.

### The authors' observations

Clozapine has proven efficacy in managing treatment-resistant schizophrenia,<sup>1-3</sup> but the drug has been associated with life-threatening side effects, including agranulocytosis/neutropenia, myocarditis/cardiomyopathy, arrhythmia, seizures, diabetic ketoacidosis, fulminant hepatic failure, pulmonary embolism, and GI complications.<sup>4</sup>

Clozapine-induced GI side effects include anorexia, nausea, vomiting, heartburn, abdominal discomfort, diarrhea, and

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Table 1

## Psychotropics associated with constipation

Class	Medications
Atypical antipsychotics	Clozapine, risperidone
Typical antipsychotics	Chlorpromazine, haloperidol, pimozide, thioridazine, thiothixene, trifluoperazine
Anticholinergics	Benztropine, trihexyphenidyl
Antidepressants	Amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, trimipramine

constipation. Clozapine-induced gastrointestinal hypomotility (CIGH) can lead to fecalith formation, which may result in intestinal obstruction/pseudo-obstruction, intestinal distension, necrosis, perforation, sepsis, aspiration from inhalation of feculent vomitus, or dysphagia.<sup>5</sup> Constipation has been reported in 14% to 60% of patients who take clozapine,<sup>6</sup> although other psychiatric medications also can cause constipation (*Table 1*). Severe constipation can lead to potentially fatal GI complications such as intestinal obstruction, necrosis, perforation, and sepsis, which is associated with significant morbidity due to bowel resection and a 27.5% mortality rate.<sup>5</sup>

The underlying mechanism of clozapine-induced constipation has been well established. The gut is innervated mainly by cholinergic and serotonergic receptors (5-HT<sub>3</sub>) and these receptors are responsible for peristalsis. Clozapine has a potent anticholinergic effect and acts as a strong antagonist of serotonin receptors (5-HT<sub>2</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub>), which can lead to gut hypomotility.<sup>7</sup> Risk factors associated with CIGH include:

- high dose of clozapine (mean dosage >428 mg/d)
- high serum clozapine levels (>500 ng/mL)
- coadministration of anticholinergic medications
- concomitant use of cytochrome P450 (CYP) enzyme inhibitors (medications inhibiting CYP1A2 enzyme)

- comorbid medical illnesses
- fever
- history of surgical bowel resection, GI pathology, and constipation.<sup>5</sup>

### HISTORY Medical comorbidities

Ms. X's medical history is significant for chronic constipation, hypertension, obstructive pulmonary disease, and hyperthyroidism. Her medications include trazodone, 25 mg/d; fluoxetine, 40 mg/d, for negative symptoms and insomnia; docusate sodium, 200 mg/d; polyethylene glycol, 17 g/d; and bisacodyl suppository, 10 mg as needed for constipation. On admission, her laboratory test results—including complete blood count, liver function tests, kidney function tests, thyroid function profile, and serum calcium levels—all were within normal range.

### How would you address Ms. X's GI symptoms?

- discontinue clozapine
- reduce clozapine dosage
- continue clozapine at the same dosage and add supportive GI measures
- switch her to a first-generation antipsychotic

### The authors' observations

Because the prevalence and severity of clozapine-induced constipation seem to be dose-dependent,<sup>8</sup> minimizing the dosage is a logical management strategy.<sup>9</sup> The life-threatening nature of clozapine-induced

### Clinical Point

Constipation has been reported in 14% to 60% of patients who take clozapine; other psychotropics also can cause GI complications

GI complications may require rapid dose reduction, which could compromise a patient's stability. There is a little evidence regarding systematic management of clozapine-induced GI complications (*Table 2*).

#### **TREATMENT** Clozapine reduction

We obtain a serum clozapine level, which is elevated at 553 ng/mL. We recommend gradual reducing Ms. X's clozapine dosage by 50 mg every 3 to 4 days to reach a target dose of 300 to 350 mg/d, to attain serum clozapine levels 350 to 400 ng/mL. Because of trazodone's potential anticholinergic action, which could be worsening Ms. X's constipation, we stop the drug and begin zolpidem, 5 to 10 mg/d, to manage her insomnia. During these medication changes, we closely monitor Ms. X for re-emerging psychotic symptoms.

### Clinical Point

Minimizing the clozapine dosage is a logical management strategy, but could compromise a patient's stability

#### Which can increase the risk of paralytic ileus in patients taking clozapine?

- concomitant antidepressant use
- clozapine serum levels >500 ng/mL
- recent GI surgery
- all of the above

#### The authors' observations

In addition to risk factors such as chronic constipation and recent GI surgery, Ms. X's supra-therapeutic serum clozapine level (553 ng/mL) significantly increased her risk of clozapine-induced paralytic ileus. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are known to increase tissue concentrations of clozapine and its major metabolite, norclozapine, by primarily inhibiting CYP1A2 and perhaps CYP2D6.<sup>10</sup> As a potent inhibitor of CYP1A2, fluvoxamine can inhibit clozapine metabo-

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lism, resulting in higher plasma concentrations.<sup>11</sup> In Ms. X's case, fluoxetine could have increased serum clozapine levels because of its ability to inhibit clozapine metabolism via CYP2D6-mediated mechanisms.<sup>12</sup>

Although clozapine serum levels are not routinely measured, such testing may be indicated in patients who do not respond to or are unable to tolerate clozapine. Clozapine levels should be obtained 12 hours after the bedtime dose (trough levels), several days after clozapine initiation. Serum clozapine levels <350 ng/mL are associated with lack of clinical response.<sup>13</sup> Higher serum levels (500 to 700 ng/mL) have been associated with greater incidences of serious GI complications. Serum clozapine levels also help guide clozapine dosage reduction because of its linear kinetics—halving the dose will halve the serum clozapine level.<sup>14</sup>

### OUTCOME GI symptoms improve

Ms. X shows improved GI motility within few days of the first decrease in her clozapine dosage. Nausea, vomiting, and abdominal distension gradually resolve over 2 weeks with concomitant reduction in clozapine dosage to 300 mg/d (50 mg in the morning and 250 mg at bedtime) without reemergence of psychotic symptoms. She is able to tolerate a soft diet, and conservative GI measures are no longer required. She is discharged home with outpatient surgical and psychiatric follow-up.

### The authors' observations

Successful reversal of severe clozapine-induced constipation—occurring at serum clozapine level of 490 ng/mL—has been reported in a 45-year-old man with treatment-resistant schizophrenia. This was accomplished by cautious reduction of clozapine dosage (400 mg/d to 250 mg/d) over 1 week.<sup>15</sup> Slower clozapine titration—reducing the dose by no more than 25 mg/d to a maximum of 100 mg/week—has been recommended.<sup>16</sup> It also has been suggested to replace part of the clozapine dose with a

Table 2

## Clinical pearls for treating clozapine-induced constipation

Serum clozapine levels >500 to 700 ng/mL have been associated with increased incidence of severe GI complications

Serum clozapine levels can guide reduction of clozapine dosage because of its linear kinetics (ie, halving the clozapine dose will halve the serum clozapine level)

Clozapine dosages should be reduced by no more than 25 mg/d to a maximum of 100 mg/week

less antimuscarinic antipsychotic, such as quetiapine or haloperidol, thereby using the second antipsychotic as a clozapine-sparing agent.<sup>9</sup> For example, the clozapine dose could be reduced by 25% by substituting 2 mg of quetiapine for every 1 mg of clozapine.

## Prevention

Psychiatrists who prescribe clozapine should take a careful history of risk factors that might predispose patients to clozapine-induced GI side effects. Caution patients to whom you prescribe clozapine about possible development of constipation and the risk of serious GI complications. Enlist family members and caseworkers to keep a close eye on GI side effects in patients receiving clozapine. Advise patients to prevent constipation by eating a high fiber diet, drinking adequate fluids, and getting regular exercise. Patients should be treated aggressively with laxatives to relieve constipation and educated about the warning signs of intestinal obstruction, such as worsening constipation, abdominal pain, vomiting, and inability to pass flatus.<sup>17</sup>

Rapidly fatal bowel ischemia caused by clozapine has been reported.<sup>18</sup> Therefore, urgently refer patients for medical evaluation if you have any concerns about worsening constipation or observe signs of intestinal obstruction. Vigilant consideration of clozapine as a likely culprit in se-

## Clinical Point

Advise patients taking clozapine to eat a high fiber diet, drink adequate liquids, and get regular exercise to prevent constipation

## Clinical Point

Refer patients for medical evaluation if you have concerns about worsening constipation or intestinal obstruction

## Related Resources

- Drew L, Herdson P. Clozapine and constipation: a serious issue. *Aust N Z J Psychiatry*. 1997;31(1):149-150.
- Winstead NS, Winstead DK. 5-step plan to treat constipation in psychiatric patients. *Current Psychiatry*. 2008;7(5):29-39.

### Drug Brand Names

Amitriptyline • Elavil	Nortriptyline • Aventyl, Pamelor
Benzotropine • Cogentin	Pimozide • Orap
Bisacodyl suppository • Dulcolax, others	Polyethylene glycol • MiraLax
Chlorpromazine • Thorazine	Quetiapine • Seroquel
Clomipramine • Anafranil	Risperidone • Risperdal
Clozapine • Clozaril	Thioridazine • Mellaril
Docusate sodium • Colace, others	Thiothixene • Navane
Doxepin • Adapin, Sinequan	Trazodone • Desyrel, Olepro
Fluoxetine • Prozac	Trifluoperazine • Stelazine
Fluvoxamine • Luvox	Trihexyphenidyl • Artane, Trihexane
Haloperidol • Haldol	Trimipramine • Surmontil
Imipramine • Tofranil	Zolpidem • Ambien

### Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

vere GI complications in inpatient settings can prevent morbidity and mortality.

In our case, cautious reduction of clozapine dosage, guided by serum clozapine levels, had obviated the need for surgery and prevented reemergence of psychotic symptoms.

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## Bottom Line

Clozapine use can lead to constipation, intestinal obstruction, or other potentially fatal gastrointestinal complications. Cautious reduction of clozapine dosage guided by serum clozapine levels can reverse these complications without surgical morbidity or reemergence of psychotic symptoms.