

Severe GI distress: Is clozapine to blame?

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Mr. F, age 29, is being treated with clozapine for schizophrenia. He reports severe GI symptoms, especially after eating. Is clozapine the culprit?



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CASE GI distress while taking clozapine

Mr. F, age 29, has a history of psychiatric hospitalizations for psychotic episodes. It took a herculean effort to get him to agree to try clozapine, to which he has experienced a modest to good response. Unfortunately, recently he has been experiencing significant upper gastrointestinal (GI) distress. He attributes this to clozapine, and asks if he can discontinue this medication.

HISTORY Nausea becomes severe

Mr. F, age 29, resides in a long-term residential setting for patients with serious mental illness who need additional support following acute hospitalization. He has treatment-refractory schizophrenia. He first developed symptoms at age 18, and experienced multiple psychotic episodes requiring psychiatric hospitalizations that lasted for months. He has had numerous antipsychotic trials and a course of electroconvulsive therapy, with limited benefit.

More recently, Mr. F's symptoms began to stabilize on a medication regimen that includes clozapine, 350 mg/d at bedtime, and haloperidol, 2 mg/d. He has not required psychiatric hospitalization for the past year.

Within months of initiating clozapine, Mr. F starts to complain daily about symptoms

of worsening abdominal pain, abdominal bloating, nausea, intermittent episodes of emesis, and heartburn. The symptoms begin when he wakes up, are worse in the morning, and persist throughout the morning. He has experienced occasional mild constipation, but no diarrhea or weight loss. There have been no major changes in his diet, addition of new medications, or significant use of nonsteroidal anti-inflammatory drugs.

Mr. F's nausea worsens over the next several weeks, to the point he begins to significantly limit how much he eats to cope with it. His GI symptoms are also impacting his mood and daily functioning.

continued

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Disclosures

The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

doi: 10.12788/cp.0204

Clinical Point

Gastroparesis is diagnosed by a nuclear medicine solid gastric emptying scintigraphy study

This is not Mr. F's first experience with significant GI distress. A few months before his first psychotic episode, Mr. F began developing vision problems, joint and abdominal pain, and a general decline in social and academic functioning. At that time, he underwent a significant workup by both GI and integrative medicine, including stool testing, upper endoscopy, and a Cyrex panel (a complementary medicine approach to exploring for specific autoimmune conditions). Results were largely within expected parameters, though a hydrogen breath test was suggestive of possible small intestine bowel overgrowth. More recently, he has been adhering to a gluten-free diet, which his family felt may help prevent some of his physical symptoms as well as mitigate some of his psychotic symptoms. He now asks if he can stop taking clozapine.

What would be the most appropriate next step for Mr. F?

- a) immediately taper the clozapine
- b) prescribe ondansetron for nausea
- c) introduce diet and lifestyle interventions and try a proton pump inhibitor (PPI)
- d) consult GI

EVALUATION Establishing the correct diagnosis

Initially, Mr. F is diagnosed with gastroesophageal reflux disease (GERD) and attempts to manage his symptoms with pharmacologic and diet-based interventions. He significantly cuts down on soda consumption, and undergoes trials of calcium carbonate, antiemetics, and a PPI. Unfortunately, no material improvements are noted, and he continued to experience significant upper GI distress, especially after meals.

The psychiatric treatment team, Mr. F, and his family seek consultation with a GI specialist, who recommends that Mr. F undergo a nuclear medicine solid gastric emptying scintigraphy study to evaluate for gastroparesis (delayed gastric emptying).¹ Results

demonstrate grade 3 gastroparesis, with 56% radiotracer retainment at 4 hours. Mr. F is relieved to finally have an explanation for his persistent GI symptoms, and discusses his treatment options with the GI consultant and psychiatry team.

The authors' observations

Mr. F and his family are opposed to starting a dopamine antagonist such as metoclopramide or domperidone (the latter is not FDA-approved but is available by special application to the FDA). These are first-line treatments for gastroparesis, but Mr. F and his family do not want them because of the risk of tardive dyskinesia. This is consistent with their previously expressed concerns regarding first-generation antipsychotics, and is why Mr. F has only been treated with a very low dose of haloperidol while the clozapine was titrated. Instead, Mr. F, his family, the psychiatry treatment team, and the GI specialist agree to pursue a combination of a GI hypomotility diet—which includes frequent small meals (4 to 6 per day), ideally with low fiber, low fat, and increased fluid intake—and a trial of the second line agent for gastroparesis, erythromycin, a medication with known hepatic cytochrome P450 (CYP) drug-drug interactions that impacts the clearance of clozapine.

Shared decision making is an evidence-based approach to engaging patients in medical decision making. It allows clinicians to provide education on potential treatment options and includes a discussion of risks and benefits. It also includes an assessment of the patient's understanding of their condition, explores attitudes towards treatment, and elicits patient values specific to the desired outcome. Even in very ill patients with schizophrenia, shared decision making has been demonstrated to increase patient perception of involvement in their own care and knowledge about their condition.² Using this



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framework, Mr. F and his family, as well as the GI and psychiatric teams, felt confident that the agreed-upon approach was the best one for Mr. F.

TREATMENT Erythromycin and continued clozapine

Mr. F. is started on erythromycin, 100 mg 3 times a day. Erythromycin is a prokinetic agent that acts as a motilin agonist and increases the rate of gastric emptying. The liquid formulation of the medication is a suspension typically taken in 3- to 4-week courses, with 1 week “off” to prevent tachyphylaxis.³ Compared to the tablet, the liquid suspension has higher bioavailability, allows for easier dose adjustment, and takes less time to reach peak serum concentrations, which make it the preferred formulation for gastroparesis treatment.

Per the GI consultant’s recommendation, Mr. F receives a total of 3 courses of erythromycin, with some improvement in the frequency of his nausea noted only during the third erythromycin course. His clozapine levels are closely monitored during this time, as well as symptoms of clozapine toxicity (ie, sedation, confusion, hypersalivation, seizures, myoclonic jerks), because erythromycin can directly affect clozapine levels.^{4,5} Case reports suggest that when these 2 medications are taken concomitantly, erythromycin inhibits the metabolism of hepatic enzyme CYP3A4, causing increased plasma concentrations of clozapine. Before starting erythromycin, Mr. F’s clozapine levels were 809 ng/mL at 350 mg/d. During the erythromycin courses, his levels are 1,043 to 1,074 ng/mL, despite reducing clozapine to 300 mg/d. However, he does not experience any adverse effects of clozapine (including seizures), which were being monitored closely.

The authors’ observations

Clozapine is the most effective medication for treatment-refractory schizophrenia.⁶

Compared to the other second-generation antipsychotics, it is associated with a lower risk of rehospitalization and treatment discontinuation, a significant decrease of positive symptom burden, and a reduction in suicidality.^{7,8} Unfortunately, clozapine use is not without significant risk. FDA black box warnings highlight severe neutropenia, myocarditis, seizures, and hypotension as potentially life-threatening adverse effects that require close monitoring.⁹

Recently, clinicians have increasingly focused on the underrecognized but well-established finding that clozapine can cause significant GI adverse effects. While constipation is a known adverse effect of other antipsychotics, a 2016 meta-analysis of 32 studies estimated that the pooled prevalence of clozapine-associated constipation was 31.2%, and showed that patients receiving clozapine were 3 times more likely to be constipated than patients receiving other antipsychotics (odds ratio 3.02, CI 1.91-4.77, $P < .001$, $n = 11$ studies).¹⁰ A 2012 review of 16 studies involving potentially lethal adverse effects of clozapine demonstrated that rates of agranulocytosis and GI hypomotility were nearly identical, but that mortality from constipation was 3.6 to 12.5 times higher than mortality from agranulocytosis.¹¹

In 2020, the FDA issued an increased warning regarding severe bowel-related complications in patients receiving clozapine, ranging in severity from mild discomfort to ileus, bowel obstruction, toxic megacolon, and death.⁹

As exemplified by Mr. F’s case, upper GI symptoms associated with clozapine also are distressing and can have a significant impact on quality of life. Dyspepsia is a common complaint in patients with chronic psychiatric illness. A study of 79 psychiatric inpatients hospitalized long-term found that 80% reported at least 1 symptom of dyspepsia.¹² There are few older studies describing the effect of clozapine on the upper GI system. We and

Clinical Point

Treatments for gastroparesis include metoclopramine, domperidone, and erythromycin

Clinical Point

A review of 16 clozapine studies found that mortality from constipation was higher than mortality from agranulocytosis

Table

GERD and gastroparesis: A comparison

	GERD	Gastroparesis
Prevalence	Common (15% to 30%) in general community population, varies among countries	Low (<.1%) in general community population
Etiology	<ul style="list-style-type: none"> Anatomical (lower esophageal sphincter relaxation, hiatal hernia) Medication-induced Diet Obesity Pregnancy 	<ul style="list-style-type: none"> Idiopathic Diabetes Medication-induced Surgical
Symptoms	Heartburn, regurgitation, chest pain, stomach pain, chronic cough, laryngitis, asthma exacerbation	Abdominal pain and bloating, early satiety, nausea, vomiting, and heartburn. Symptoms mostly cluster together and are noted after eating
Diagnosis	<ul style="list-style-type: none"> Clinical interview and exam PPI trial <i>H. Pylori</i> breath test and treatment Upper GI endoscopy (if alarm symptoms) Ambulatory esophageal reflux monitoring 	<ul style="list-style-type: none"> Clinical interview and examination Imaging Upper GI endoscopy Gastric emptying test with scintigraphy Wireless motility capsule
Treatment	<p>Lifestyle modifications:</p> <ul style="list-style-type: none"> Stop eating >3 hours before bed Decrease intake of spicy foods, citrus, alcohol, caffeine Weight loss Smoking cessation Elevate the head of the bed while sleeping <p>Medications:</p> <ul style="list-style-type: none"> Test and treat for <i>H. Pylori</i> Acid suppression (PPIs, H2 receptor antagonists) <p>Surgical intervention:</p> <ul style="list-style-type: none"> Nissen fundoplication 	<p>Lifestyle modifications:</p> <ul style="list-style-type: none"> Eat 4 to 6 small meals each day Consume meals with low fat and low fiber Increase liquid intake <p>Medications:</p> <ul style="list-style-type: none"> As-needed antiemetics Prokinetics (metoclopramide, erythromycin) <p>Surgical intervention:</p> <ul style="list-style-type: none"> Gastric electric stimulation Pyloroplasty

Source: References 18,19

GERD: gastroesophageal reflux disease; GI: gastrointestinal; PPI: proton pump inhibitor

others previously reported on significantly increased use of—not only antacids—but also H2 blockers and prokinetic agents after initiating clozapine, but sample sizes are small.¹³⁻¹⁵ These older data and newer studies suggest that GERD is a common upper GI disorder diagnosis following clozapine initiation, perhaps reflecting a knowledge gap and infrequent use of the more complex testing required to confirm a diagnosis of GI motility disorders such as gastroparesis.

In a study of 17 patients receiving clozapine, wireless motility capsules were used to measure whole gut motility, including gastric emptying time, small bowel transit time, and colonic transit time. In 82% of patients, there was demonstrated GI hypomotility in at least 1 region, and 41% of participants exhibited delayed gastric emptying, with a cut-off time of >5 hours required for a gastroparesis diagnosis.¹⁶ This is significantly higher than the prevalence of gastroparesis observed in

studies of the general community.¹⁷ The *Table*^{18,19} (page 50) summarizes the differences between GERD and gastroparesis.

OUTCOME Some improvement

Mr. F experiences limited improvement of some of his nausea symptoms during the third erythromycin cycle and returns to the gastroenterologist for a follow-up appointment. The GI specialist decides to discontinue erythromycin in view of potential drug-drug interactions and Mr. F's elevated clozapine levels and the associated risks that might entail. Mr. F is again offered the D2 dopamine antagonist metoclopramide, but again refuses due to the risk for tardive dyskinesia. He is asked to continue the GI dysmotility diet. Mr. F finds some relief of nausea symptoms from an over-the-counter product for nausea (a nasal inhalant containing essential oils) and is advised to follow up with the GI specialist in 3 months. Shortly thereafter, he is discharged to live in a less restrictive supportive housing environment, and his follow-up psychiatric care is provided by an assertive community treatment team. Over the next several months, the dosage of clozapine is decreased to 250 mg/d. Mr. F initially experiences worsening psychiatric symptoms, but stabilizes thereafter. He then moves out of state to be closer to his family.

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Related Resources

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Drug Brand Names

Clozapine • Clozaril	Metoclopramide •
Haloperidol • Haldol	Reglan, Metozolv ODT
Erythromycin • Erythromycin	Ondansetron • Zofran
Ethylsuccinate oral suspension	

Clinical Point

GERD is a common upper GI diagnosis in patients receiving clozapine, but GI motility disorders may be underdiagnosed

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continued

Bottom Line

In patients receiving clozapine, frequent nausea along with clustering of heartburn, abdominal pain, bloating, early satiety, and vomiting (especially after meals) may signal gastroparesis rather than gastroesophageal reflux disease. Such patients may require consultation with a gastroenterologist, a scintigraphy-based gastric emptying test, and treatment if gastroparesis is confirmed.

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In a small study of patients receiving clozapine, 41% had delayed gastric emptying

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