

## Rapid improvement in post-infectious gastroparesis symptoms with mirtazapine

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### Abstract

We report the case of a 34-year-old woman with severe post-infectious gastroparesis who was transferred from an outside medical facility for a second opinion regarding management. This patient had no prior history of gastrointestinal symptoms. However, in the aftermath of a viral illness, she developed two months of intractable nausea, vomiting, and oral intake intolerance that resulted in numerous hospitalizations for dehydration and electrolyte disturbances. A solid-phase gastric emptying scan had confirmed delayed emptying, confirming gastroparesis. Unfortunately, conventional pro-kinetic agents and numerous anti-emetic drugs provided little or no relief of the patient's symptoms. At our institution, the patient experienced a cessation of vomiting, reported a significant reduction in nausea, and toler-

ated oral intake shortly after taking mirtazapine. Based on mirtazapine's primary action as a serotonin (5-HT) 1a receptor agonist, we infer that this receptor system mediated the clinical improvement through a combination of peripheral and central neural mechanisms. This report highlights the potential utility of 5-HT<sub>1a</sub> agonists in the management of nausea and vomiting. We conclude that mirtazapine may be effective in treating symptoms associated with non-diabetic gastroparesis that are refractory to conventional therapies.

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**Key words:** Nausea; Vomiting; Gastroparesis; Symptoms; Mirtazapine; Anti-emetics

**Core tip:** The management of symptoms associated with severe gastroparesis remains challenging because current therapeutic options are fairly limited. This case report documents the rapid improvement of nausea and vomiting in a patient with severe post-infectious gastroparesis with mirtazapine. Because mirtazapine acts primarily as a serotonin 1a receptor agonist, this receptor system may be an important adjunctive target for nausea and vomiting refractory to standard therapies. Thus, mirtazapine should be considered as a treatment option for gastroparesis.

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### INTRODUCTION

Gastroparesis is a disorder defined by delayed gastric emptying in the absence of mechanical gastric outlet

obstruction<sup>[1]</sup>. Patients with gastroparesis typically experience symptoms including anorexia, nausea and vomiting, abdominal pain, and other dyspeptic symptoms (*e.g.*, early satiety, post-prandial bloating)<sup>[1-3]</sup>. Patients can have a wide range of symptom severity, and those with more severe cases may require multiple hospitalizations<sup>[4]</sup>. Patients tend to have a clinical course that lasts several months to years<sup>[5,6]</sup>. The prevalence of gastroparesis has been extrapolated to include up to approximately 2% of the general population, but even this estimate has been thought to represent the “tip of the iceberg”<sup>[7,8]</sup>.

While the etiology of gastroparesis was once thought to be primarily caused by uncontrolled diabetes mellitus (*i.e.* visceral neuropathy) or prior gastric surgery resulting in vagal nerve injury, it is now appreciated that the majority of cases of gastroparesis are idiopathic<sup>[3,6]</sup>. However, a significant subset of patients with idiopathic gastroparesis can associate the onset of symptoms following a viral-like illness, and this subset of patients tends to present with more acute and severe symptoms. Fortunately, most cases of post-viral gastroparesis ultimately resolve, but patients typically have fairly durable symptoms during the course of the illness<sup>[6]</sup>.

The management of symptoms associated with severe gastroparesis is challenging because current therapeutic options are fairly limited. The current mainstay of treatment focuses on symptom control using a variety of pharmacologic approaches including prokinetic agents such as metoclopramide, domperidone, and erythromycin, and anti-emetic agents such as phenothiazines and 5-HT<sub>3</sub> antagonists (*e.g.* ondansetron)<sup>[1-3,7]</sup>. We report a case of a patient whose symptoms attributable to gastroparesis were refractory to such conventional treatments. This patient experienced significant improvement of her symptoms following initiation of treatment with mirtazapine.

## CASE REPORT

A 34-year-old woman was referred to the inpatient gastroenterology and consult-liaison psychiatry services for evaluation of intractable nausea, vomiting, and intolerance of oral intake. She had no significant past medical history other than occasional migraine headaches responsive to sumatriptan. Two months prior to presentation at our institution, she developed a presumptive upper gastrointestinal viral illness manifesting as nausea with vomiting, as the patient's two younger children had similar symptoms. However, despite the rapid resolution of symptoms in her children, the patient subsequently developed constant nausea and intractable vomiting requiring intermittent emergency room visits and eventual hospitalization. Initial workup at an outside hospital was consistent with mild dehydration, but multiple diagnostic studies were fairly unremarkable except for the finding of a decreased gallbladder ejection fraction. Based on this result, coupled with the continued symptoms of nausea and vomiting, she proceeded with a laparoscopic cholecystectomy. Subsequent to the surgery, she devel-

oped *C. difficile* colitis, which was effectively treated. Unfortunately, the patient's nausea and vomiting persisted for several weeks after the other issues had resolved. A 2 h, solid phase gastric emptying study using a standardized test meal was performed at an outside facility. This study demonstrated gastric emptying of < 23% at 2 h, and the patient was diagnosed with gastroparesis. This result was obtained without the patient having taken narcotics or anti-cholinergic agents. Ultimately, the patient had lost 16 lbs over the two months of illness prior to presenting to our institution for a second opinion regarding management.

Review of the patient's prior therapy showed that she had trialed numerous oral and intravenous forms of anti-emetics including ondansetron, prochlorperazine, promethazine, scopolamine (*via* transdermal patch), dronabinol, and aprepitant. The prokinetic agents erythromycin and metoclopramide had both been tried without significant clinical benefit, and she experienced central side effects with metoclopramide. At our institution, she continued to have significant nausea and was unable to tolerate oral intake without vomiting. A head computed tomography was negative for any intracranial pathology to explain symptoms. On psychiatric evaluation, she did not meet DSM-IV criteria for any psychiatric illness such as depression, anxiety, somatoform disorder, or factitious disorder that could contribute to symptoms. Because of the poor oral intake and subsequent weight loss, she had a post-pyloric nasojejunal tube placed for enteral feeding, along with continuous IV fluids. She was also trialed on proton pump inhibitors and benzodiazepines, in addition to scheduled dosing of several other antiemetics. Several days after initiation of enteral feeding, she continued to have ongoing severe symptoms attributed to gastroparesis. Using an 11-point verbal rating scale, she reported that her nausea was 8/10 in severity with only brief and mild relief from combination therapy using clonazepam, promethazine, ondansetron, and a transdermal scopolamine patch. She continued to have increased nausea with vomiting after attempts at solid food ingestion and had generally poor tolerance of even minimal volumes of ingested liquids.

Given the lack of efficacy of conventional approaches, she was started on mirtazapine 15 mg PO qhs, in addition to the other agents as above. Within a couple of days after starting mirtazapine, she had a complete cessation of her vomiting and reported an improvement in nausea to 5/10 in severity. However, because nausea still remained and the patient still did not tolerate significant oral intake, a standardized, 4 h solid-phase gastric emptying study was repeated to clarify the diagnosis of gastroparesis. This study was performed while she was using the transdermal scopolamine patch. Interestingly, the study demonstrated some improvement in gastric emptying as compared to the previous study obtained at the outside hospital, with a normalization of early phases of gastric emptying - at 2 h, there was 55% emptying (normal > 40%). However, the same study still demonstrated per-

sistent delay in the later stages of gastric emptying, with a 3 h emptying of 65% (normal > 70%) and 4 h emptying of 70% (normal > 90%). Given that there was some clinical improvement in symptoms with the lower dose of mirtazapine, the medication was increased to a dose of 30 mg PO qhs. There were no discernible side effects reported with the increased dose. Within a couple of days, the patient subsequently reported further improvement in nausea to 4/10 in severity, a level which was deemed tolerable to her. She also experienced improved appetite and was able to drink larger volumes of liquids and to tolerate small volumes of soft foods. Intravenous hydration was stopped and she remained in stable condition. She was subsequently discharged home without readmission for the first time in 3 mo on a regimen only including mirtazapine 30 mg PO qhs, clonazepam 1 mg PO BID, and ondansetron PRN. While nocturnal nasojejunal feeding was continued over the ensuing 6 wk, this therapy was ultimately discontinued because the patient had continued to improve with no episodes of vomiting, generally improved nausea, further improvements in oral intake (including some tolerance of solid foods), and weight gain near to her prior baseline.

## DISCUSSION

To our knowledge, this is the first report of mirtazapine successfully used to treat symptoms of post-infectious gastroparesis. A previous report documented the successful use of mirtazapine in a patient with treatment-refractory diabetic gastroparesis<sup>[9]</sup>. Mirtazapine has well documented efficacy in managing symptoms of nausea and vomiting in other clinical contexts, such as in cancer chemotherapy<sup>[10]</sup> and in perioperative settings<sup>[11,12]</sup>. Therefore, we felt mirtazapine could be an effective medication for the treatment of similar symptoms related to gastroparesis.

Mirtazapine is a unique antidepressant that is currently approved for use in the treatment of major depression. It specifically blocks histamine H1<sup>[13]</sup> and serotonin 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, and 5-HT<sub>3</sub> receptors, and stimulates 5-HT<sub>1A</sub> receptors<sup>[14]</sup> both peripherally and in the central nervous system. Stimulation of 5-HT<sub>1A</sub> receptors is believed to be responsible for its antidepressant and anxiolytic effects, whereas blockade of H1, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors may also relate to some of its anxiolytic and sedating effects<sup>[13,14]</sup>. Mirtazapine's impact on central neural systems involved in mood regulation could have contributed to symptom improvement in this case. While our patient did not have any overt depression or anxiety disorder, some degree of dysregulated mood in the context of prolonged and repeated hospitalizations could have influenced the perceived severity of symptoms.

Mirtazapine blocks 5-HT<sub>3</sub> receptors with similar efficacy to ondansetron<sup>[10]</sup>, and this mechanism may have contributed to the anti-emetic effects observed in the present case. However, 5HT-3 receptor blockade alone was unlikely the primary mechanism driving this patient's clinical

improvement, given that high doses of intravenous ondansetron had not been particularly effective. Furthermore, while we observed mildly improved gastric emptying following the administration of a lower dose of mirtazapine, symptoms of nausea and general intolerance to oral intake still persisted at that time. This observation fits with the generally poor correlation of gastroparesis symptom severity with the degree of delay in gastric emptying<sup>[15]</sup>. Therefore, it is unlikely that the beneficial effects of the medication were driven by improved gastric emptying *per se*.

Interestingly, receptive fundic relaxation, a process largely controlled by the activity of nitrenergic neurons, is influenced by the stimulation of 5-HT<sub>1A</sub> receptors<sup>[16]</sup>. Selective 5-HT<sub>1A</sub> receptor agonism using the agent buspirone has been shown to dose-dependently and acutely increase gastric accommodation in healthy subjects<sup>[16]</sup>. This mechanism also operates in those with functional dyspepsia, and buspirone can improve symptoms in this patient population<sup>[17]</sup>. Improved gastric accommodation would be predicted to allow for larger ingested volumes of liquids or solid food. Gastric wall tone influences intragastric pressures and may drive the perception of nausea *via* increased vagal afferent activity. While mirtazapine has not been studied in this specific context, its shared pharmacology with buspirone implicates improved gastric accommodation *via* stimulation of 5-HT<sub>1A</sub> receptors as a potential mechanism that could account for some of the clinical improvement seen in our patient. Finally, given the pleiotropic pharmacological effects of mirtazapine, it is possible that its therapeutic effect could also be mediated by an impact on multiple central neural systems important for the generation of the percept of nausea, autonomic sensorimotor integration important for stomach motility and sensation, and the central regulation of appetite. Thus, it is clear that mirtazapine could be beneficial through multiple potential mechanisms. However, regardless of mechanism, the dramatic improvement in this patient's symptoms after the initiation of mirtazapine suggests that this medication may be an effective treatment for severe gastroparesis-related symptoms.

While the current case is confounded by the concurrent use of other medications (benzodiazepine, 5-HT<sub>3</sub> antagonist, and anti-cholinergic agents), these other medications had been used for a week or more with only modest clinical benefits. The significant improvement in both the nature and severity of the symptoms after only two doses of mirtazapine would suggest that mirtazapine was primarily responsible for the clinical effect. Secondly, while post-viral gastroparesis symptoms can improve as a part of the natural history of the illness, symptoms tend to last at least several months. This patient's symptoms were durable for nearly 3 mo and refractory to standard therapies at the time mirtazapine was started. It appears quite unlikely that her illness spontaneously improved in the days during which mirtazapine was started. Also, the fact that symptoms were only partially improved on mirtazapine, would argue against a spontaneous remission of

the underlying gastroparesis.

Treatment for post-infectious gastroparesis can be challenging because symptoms are often severe and conventional therapies may not be effective. We report a case of patient with post-infectious gastroparesis who had an excellent clinical improvement after starting mirtazapine. The specific mechanism driving this response remains to be clarified, but mirtazapine could exert a therapeutic effect on nausea and vomiting *via* 5-HT<sub>1</sub> receptor agonism. Mirtazapine could represent an effective, alternative treatment for patients with gastroparesis who are refractory to conventional prokinetic and anti-emetic medications.

## COMMENTS

### Case characteristics

A 34-year-old woman with no major past medical history presented with two months of intractable nausea and vomiting.

### Differential diagnosis

Gastroparesis, functional dyspepsia, chronic idiopathic nausea

### Laboratory diagnosis

On initial presentation, the patient had a K 3.2 mmol/dL with a slight anion gap acidosis of 16 mEq/L and 2+ ketonuria; otherwise, CBC and liver function tests were within normal limits.

### Imaging diagnosis

A 4-h solid phase gastric emptying scan was obtained at the institution, using the ingestion of 1.06 mCi of Tc-99m sulfur colloid mixed with a solid meal. This demonstrated a delay in emptying at the 3- and 4-h time points.

### Treatment

Along with stable doses of clonazepam, ondansetron, and scopolamine, the patient was then treated with mirtazapine 15 mg PO qhs, with the dose increased to 30 mg PO qhs after several days.

### Related reports

There is one other case report documenting the use of mirtazapine for symptoms of diabetic gastroparesis.

### Term explanation

Post-infectious gastroparesis refers to a subset of patients who can clearly identify an acute infectious gastroenteritis, typically viral in nature, in the days to weeks prior to developing gastroparesis.

### Experiences and lessons

To our knowledge, this is the first report of mirtazapine successfully used to treat symptoms of post-infectious gastroparesis.

### Peer review

This report describes the use of mirtazapine to induce a rapid improvement in nausea and vomiting in a patient with post-viral gastroparesis.

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