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Idiopathic Gastroparesis: Lifestyle Modifications Versus Pharmacotherapy

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III. Abstract

Idiopathic gastroparesis is a chronic symptomatic motility disorder of the stomach of unknown cause characterized by delayed gastric emptying in the absence of mechanical obstruction, with the majority of gastroparesis cases being classified as idiopathic.[1-3] Idiopathic gastroparesis continues to be a challenging diagnosis to manage and difficulty remains in treating associated symptoms that result in decreased quality of life. Current non-invasive recommendations for the treatment of idiopathic gastroparesis are lifestyle modifications, including dietary adjustments to follow a gastroparesis diet, and pharmacotherapy prescribed for symptomatic relief. Metoclopramide is currently the only medication approved by the Food and Drug Administration (FDA) in the United States specifically for the indication of treating gastroparesis. Other medications are prescribed off-label for the indication of idiopathic gastroparesis or are prescribed to target specific symptoms. Response to treatment is both individualized and unpredictable, and medications' side-effects may necessitate discontinuance. In the treatment of adults with idiopathic gastroparesis, it has been concluded that lifestyle

modifications, pharmacotherapy, or both may improve, eliminate or fail to improve the symptoms of nausea, vomiting, early satiety, and poor appetite. Ultimately, risks and benefits of each option need to be discussed and shared decision-making needs to occur to establish a treatment regimen and management plan for patients with idiopathic gastroparesis.

IV. Introduction

Idiopathic gastroparesis continues to be a challenging diagnosis to manage and difficulty remains in treating associated symptoms, which result in morbidity, and complications, leading to both morbidity and mortality. Gastroparesis is a chronic symptomatic motility disorder of the stomach characterized by delayed gastric emptying in the absence of mechanical obstruction, with the majority of gastroparesis cases being classified as idiopathic.[1-3] Common causes of gastroparesis are diabetes, prior gastric surgery, and endocrine, neurologic, or hematologic disorders.[4] Medications, such as opioid analgesics and anticholinergic medications, can also cause gastroparesis by delaying gastric emptying.[4] When these common causes have been ruled-out and the cause remains unknown, the disorder is classified as idiopathic gastroparesis.[4]

In the United States, at least 4 million adults have the diagnosis of gastroparesis.[5] The incidence of gastroparesis is 6.3 per 100,000 persons per year.[5] Most patients with gastroparesis are females (often by a 3:1 margin) with age-adjusted prevalence of 37.8 per 100,000 persons for females and 9.6 per 100,000 persons for males.[4-6] Parkman et al. note that most gastroparesis studies enroll primarily white female patients,[4] and idiopathic gastroparesis is most commonly diagnosed in white patients.[4] Females also have slower gastric emptying than males, which is believed to be due to estrogen and progesterone (female sex hormones).[4,6] Compared to males, females reported more severe symptoms of stomach fullness, early satiety, postprandial fullness, bloating, and upper abdominal pain.[4] Females also had a stomach that was visibly larger.[4] Over

time, females reported better improvement in their symptoms than males.[4] On the other hand, more males than females were hospitalized during the year prior to the study.[4]

The constellation of symptoms most commonly associated with idiopathic gastroparesis are nausea (>90% of patients), vomiting (84% of patients), early satiety (feeling full after consuming only a small amount of food) (60% of patients), abdominal distension, bloating, abdominal pain, and postprandial fullness (feeling excessively full after meals).[2-7] Gastroparesis reported symptoms are listed in Table 1.[5] Nausea, vomiting, early satiety, and postprandial fullness are best correlated with a delay in gastric emptying, whereas bloating and abdominal pain may be related to sensory alterations that might be present.[6] Some patients experience constant persistent symptoms, while others may experience completely symptom-free periods of time alternating with intermittent symptomatic flares.[6] The symptoms and complications associated with idiopathic gastroparesis can result in permanent disability, vulnerability to thrombosis, and greater mortality.[2]

Idiopathic gastroparesis not only results in both morbidity and mortality, but also causes an accumulation of healthcare costs, impacts patients' quality of life, and has limited FDA (Food and Drug Administration) approved medication treatment options in the United States to manage the complex motility disorder. The side-effects associated with various medications also limit their use for long-term treatment. The varying symptoms and degree of symptom severity make formulating a treatment plan difficult, including determining whether lifestyle and dietary changes, medication, or both are necessary for management. In utilizing the least invasive treatment options first, the research question is: in adults with idiopathic gastroparesis, how does lifestyle modifications, including changing diet and eating habits, compared to pharmacotherapy (medications) affect the symptoms of nausea, vomiting, early satiety, and poor appetite? Due to

the variation in both symptoms and severity, more than likely the treatment regimen (lifestyle modifications and/or pharmacotherapy) will need to be adjusted on a case-by-case basis and will not be uniform across cases of patients with a diagnosis of idiopathic gastroparesis. This paper will outline how to establish the diagnosis of idiopathic gastroparesis, recommended eating habits and dietary modifications, and pharmacotherapy utilized to treat idiopathic gastroparesis.

V. Background: Literature Review

Establishing the Diagnosis of Idiopathic Gastroparesis

The gold standard for evaluating gastric emptying to establish the diagnosis of gastroparesis is scintigraphic gastric emptying of a solid meal, most reliably during a 4-hour study, during which the patient consumes a low-fat, egg white meal (scrambled eggs) labeled with a radionuclide (e.g., 99m technetium) that binds to protein in the eggs.[7-9] Patients must stop any medications that could potentially affect gastrointestinal motility 72 hours prior to the study, fast overnight (nothing to eat after midnight, which is an 8-hour fast), and report to the Nuclear Medicine Department where the test is scheduled and completed.[8-9] The Nuclear Medicine Department follows a multicenter protocol (endorsed by the Society of Nuclear Medicine and Molecular Imaging [SNMMI] and American Neurogastroenterology and Motility Society [ANMS]) to ensure standardized information about delayed gastric emptying is utilized across testing sites.[7,9] Scintigraphic images are obtained over a period of 4 hours (at 0, 1, 2, and 4 hours after meal ingestion), and the rate of gastric emptying is determined by the amount of food remaining in the stomach in each image.[7-9] Results demonstrating delayed gastric emptying of solids (solid food retention in the stomach) are scintigraphy of greater than 60% of food retained at 2 hours and/or greater than 10% at 4 hours.[7,9] Greater than 10% gastric retention after 4 hours is considered the gold standard for diagnosing gastroparesis.[5] Though there are no clearly agreed

upon standards for classifying the severity of delay in gastric emptying,[5] a couple studies noted that the delayed gastric emptying can then be graded according to the amount of gastric retention at 4 hours: mild (≤20% retention), moderate (>20 to 35%) and severe (>35%).[7,9] The Gastroparesis Cardinal Symptom Index (GCSI) is a questionnaire utilized to assess symptoms and severity, which scores symptoms of nausea and vomiting, postprandial fullness and early satiety, and bloating over the preceding two weeks.[6] Esophagogastroduodenoscopy (also known as an upper endoscopy or EGD) is utilized to view the esophagus, stomach and duodenum to rule-out obstruction as a cause of symptoms.

General Measures of Management

The management and treatment of idiopathic gastroparesis can be complicated and frustrating to both patients and healthcare providers due to the complexity of symptoms, unpredictable response to treatment, limited availability of medications, and side-effects associated with medications utilized for treatment. Symptoms of idiopathic gastroparesis can lead to food aversion and inadequate oral intake with subsequent dehydration, malnutrition, vitamin and mineral deficiencies, and weight loss, which can compromise the patient's quality of life and their ability to sustain their health and engage in social interactions.[2,4,7] Long-term gastroparesis has also been associated with esophagitis (inflammation of the esophagus), Mallory-Weiss tears (tears in the tissue of the lower esophagus), and severe peptic ulcer disease (stomach and/or duodenal ulcers).[3] Idiopathic gastroparesis cannot be cured; rather, the goal of treatment is to control associated symptoms.[10] Risks and benefits associated with specific treatment options and deciding whether to continue treatment need to be consistently analyzed and actively discussed. Patients diagnosed with gastroparesis are willing to take exceedingly high risks with medications in order to improve their symptoms, often trading longevity for

symptom relief, choosing quality of life over quantity of years.[5] Establishing rapport and participating in shared decision-making with patients with idiopathic gastroparesis during consistent follow-up office visits create a crucial foundation in evaluating the patient's symptoms and quality of life, discussing treatment goals, and ultimately formulating a treatment regimen.

The management of idiopathic gastroparesis depends on the severity of the gastric emptying and symptoms associated with the disorder. Most patients present with dehydration and electrolyte disturbances, complications of their symptoms.[3] Therefore, the goals of initial treatment include fluid resuscitation and maintaining adequate hydration; correcting the electrolyte abnormalities and nutritional deficiencies; management of any underlying comorbidities; and improving, suppressing, or eliminating symptoms.[3,6] Furthermore, a thorough history and physical examination should be performed to identify and treat comorbid conditions and to identify and discontinue any medications that may be delaying gastric emptying or causing the patient's symptoms.[3] Medications known to impair gastric motility include certain anticholinergic agents, Glucagon-like peptide 1 (GLP-1) analogs, and opiate narcotics.[11]

Lifestyle modifications, including dietary adjustments, and pharmacotherapy (to control symptoms) are recommended initially for the treatment of patients with mild idiopathic gastroparesis.[3] The most commonly prescribed medications are metoclopramide, domperidone and erythromycin.[5] Whereas more severe symptoms, including marked dehydration, intractable nausea with vomiting, and malnutrition, may require hospitalization, medications, and potentially more invasive interventions for treatment and subsequent management of the patient's idiopathic gastroparesis.[3] Figure 1 presents a stepwise approach to gastroparesis.[8] Figure 2 offers suggested therapeutic options for gastroparesis.[11]

Severely delayed gastric emptying has been associated with an increased risk of hospitalization and an increase in visits to the emergency department (ED).[5] Since 2005, hospitalizations and the associated costs have increased significantly for patients with gastroparesis.[5] Furthermore, these patients experience the longest length of hospitalization and the second highest total healthcare cost among upper gastrointestinal conditions,[5] demonstrating the need for active management of symptoms in the outpatient setting to potentially decrease or prevent ED visits and subsequent admissions. Lastly, the use of opioids in patients with idiopathic gastroparesis further complicates management and treatment, which will be discussed in the pharmacotherapy section. To reduce ED visits, hospitalizations, and associated healthcare costs, patients with severely delayed gastric emptying and severe symptoms associated with idiopathic gastroparesis need to be quickly identified and a treatment plan established and actively adjusted to manage the chronic motility disorder at the patient's home or in an outpatient setting.[5]

Lifestyle Modifications

Lifestyle modifications, specifically dietary adjustments, are generally the initial treatment when managing patients with idiopathic gastroparesis. Dietary goals include improving oral intake, maintaining hydration and nutrition, improving or eliminating symptoms, and managing any complications that arise. Patients with more severe delays in gastric emptying are less likely to meet their daily total energy requirement (TER) through oral intake.[7] Adjustments are recommended for both meal content and the frequency of meal consumption for patients with idiopathic gastroparesis.[3] Since larger volumes slow gastric emptying and worsen early satiety, small frequent meals (4 to 6 per day) are suggested to maintain caloric intake, prevent nutritional deficiencies, and minimize symptoms of postprandial fullness, nausea, and vomiting.[7-8,10]

If energy and nutrition supplementation is needed, high protein caloric liquids are recommended, since liquids more readily empty the stomach and are better tolerated than solids in patients with idiopathic gastroparesis.[7-8] Twenty percent of patients with gastroparesis report utilizing supplemental nutrition to meet their daily TER.[12] Since patients with idiopathic gastroparesis generally have preserved gastric emptying of liquids, liquid-based meals are recommended for patients who cannot tolerate solid food.[3] Patients should be encouraged to drink at least one to one-and-a-half liters of fluid per day to maintain hydration.[8] Fluids should also be drunk throughout the course of a meal, and patients should sit or walk for one to two hours after meals.[10] Carbonated beverages should be avoided as they exacerbate symptoms such as bloating, gastric distension, and gastroesophageal reflux.[8] Poor tolerance to a liquid diet is usually indicative of a future poor outcome.[10]

The consumption of fats or lipids is known to slow or delay gastric emptying, while fiber can increase bloating and may cause early satiety.[7] Fats and non-digestible fibers should be avoided, whereas foods low in fat and fiber are recommended to compensate for the impairment of gastric emptying.[3,7,11] A low fiber diet also decreases the risk of bezoar formation, a solid mass of indigestible material, usually retained food debris, that can form in the stomach and potentially cause obstruction.[8] A bezoars needs to be mechanically disrupted endoscopically or potentially enzymatically digested with an agent such as papain, cellulose, and N-acetylcysteine.[8] Foods worsening symptoms in patients with idiopathic gastroparesis are generally fatty, acidic, spicy, or roughage-based, including orange juice, fried chicken, cabbage, oranges, sausage, pizza, peppers, onions, tomato juice, lettuce, coffee, salsa, broccoli, bacon and roast beef.[13] Saltine crackers, jello, and graham crackers were shown to moderately improve symptoms.[13] Additional foods tolerated by patients (foods that did not provoke symptoms) are generally

bland, sweet, salty or starchy, including ginger ale, gluten-free foods, tea, sweet potatoes, pretzels, white fish, clear soup, salmon, potatoes, white rice, popsicles, and applesauce.[13] Table 2 details a nutritional analysis of aggravating and tolerated foods.[13] Table 3 specifies food qualities of aggravating and tolerated foods.[13]

Nutritional deficiencies, including calories, carbohydrates, protein, vitamins, and minerals, are common in patients with idiopathic gastroparesis.[2,6-7] Because symptoms can lead to food aversion and poor oral intake, malnutrition is a complication associated with idiopathic gastroparesis.[2,6-7] Patients with idiopathic gastroparesis are more likely to consume diets deficient in vitamins A, B6, C, K; iron; potassium; and zinc, but only about one-third of patients report taking a daily multivitamin supplement.[6-7] Screening blood tests that can be ordered to evaluate for malnutrition are a complete blood count (CBC) with differential, coagulation factors (international normalized ratio [INR]), and a complete metabolic panel (which includes both renal and liver profiles).[8] Kedar et al. further explored Vitamin D deficiencies in patients with gastroparesis.[2] Associations were identified between micronutrient deficiencies and impaired gastric motility, specifically indicating an association between low 25-Hydroxy (25-OH) Vitamin D levels and impaired motility in patients with gastroparesis.[2] Based on this association, baseline serum 25-OH Vitamin D levels are recommended to be drawn at the initial clinic visit for patients with gastroparesis and if low, supplementation prescribed to maintain healthy levels of serum 25-OH Vitamin D.[2] Further mineral and vitamin screening may also be ordered if warranted, including vitamin B_{12}, folic acid, serum iron, total iron binding capacity (TIBC), percentage of iron saturation, and zinc levels.[8]

Patients with deficient diets generally report more severe symptoms associated with idiopathic gastroparesis. Patients who reported energy-deficient diets experienced more severe

symptoms, specifically bloating and constipation.[6-7] Patients consuming caloric deficient diets (defined as less than 60% of estimated daily TER) reported significantly higher symptom scores for stomach fullness, excessive fullness after a meal, bloating and constipation.[7,14] In a study of gastroparesis patients (both idiopathic and diabetic etiologies were included), 64% of patients reported caloric-deficient diets, only 2% of patients followed a diet recommended for patients with gastroparesis, and only 32% had a nutritional consultation after the onset of gastroparesis.[7] Overall, due to the occurrence of nutritional deficiencies, patients with idiopathic gastroparesis may require additional vitamin and mineral supplementation.

As noted, a gastroparesis diet is rarely followed, and a nutritional consultation is often not completed. Proposed reasons for lack of adherence to following a gastroparesis diet are the lack of consensus regarding an optimal gastroparesis diet, inability to achieve the requirements of the gastroparesis diet as recommended (diet composition and/or frequency), unawareness of the existence of a gastroparesis diet, lack of education regarding dietary recommendations for gastroparesis, or patients choose not to follow the recommended diet.[7] Other obstacles may include the inability to prepare meals, lack of access to food, the patient's workplace prohibiting frequent breaks to adhere to consuming small frequent meals advised for patients with idiopathic gastroparesis, or workplaces prohibiting patients from keeping food near their work area. Nutritional consultations are helpful for not only education regarding a gastroparesis diet and meal preparation but also assistance in creating individualized, achievable diet plans for patients with idiopathic gastroparesis. Patients with longer duration of symptoms, those who were more ill (exhibiting increased severity of symptoms), and those who had more hospitalizations were more likely to have participated in nutritional consultations.[6-7] Not noted was who performed the nutritional consultations (a healthcare provider versus a registered dietitian). Also not noted was

whether the nutritional consultations occurred while admitted as an inpatient in a hospital setting or in an outpatient clinic setting. Nutritional consultation increased the chance that patients' oral intake met daily TER.[6]

Challenges exist preventing scheduling and completion of nutritional consultations. Patients may have difficulty taking time off work to attend appointments with a registered dietitian. An outpatient dietitian consultation appointment is not always covered by the patient's medical insurance, which results in the entire bill needing to be paid directly by the patient. Unfortunately, the cost of an appointment with a registered dietitian can deter patients from completing these nutrition consultations in an outpatient setting. Though a nutrition consult may be helpful for education regarding a gastroparesis diet, meal planning, and addressing nutritional deficiencies, it may not be financially feasible for all patients.

Pharmacotherapy

The goal of pharmacotherapy (treatment utilizing medication) is to alleviate symptoms and promote gastric emptying. However, no single medication is effective in managing the delay in gastric emptying and associated symptoms of gastroparesis, making treatment complicated and challenging for healthcare providers.[3] Table 4 displays pharmacotherapy treatments tried for gastroparesis symptoms in a study by Navas et al.[5] A combination of multiple medications, including prokinetics, antiemetics, and neuromodulators, may be required to relieve symptoms in severe cases.[14] The use of multiple medications metabolized by cytochrome P-450 enzymes in the liver may lead to drug-drug interactions, further complicating the combined use of these pharmacological classes.[14] Table 5 lists novel drugs and whether the medication exhibits antiemetic effects and/or prokinetic effects.[19] Table 6 provides the mechanisms of action of novel drugs utilized in the treatment of idiopathic gastroparesis.[19] One retrospective study notes that

neither the type of gastroparesis (determined by underlying cause) nor extent of delay in gastric emptying correlates with the patient's response to treatment, including antiemetics, prokinetics, tricyclic antidepressants, analgesic and invasive interventions.[15] The same study notes a correlation between the response to treatment and symptoms of stomach distention, bloating, and the Gastroparesis Cardinal Symptom Index.[15]

Nausea severity decreases the quality of life for patients with idiopathic gastroparesis, so the disabling symptoms of nausea and vomiting need to be specifically evaluated and treated.[9-10] A significant association was found between increased antiemetic use and increased ED visits and hospitalizations.[5] Navas et al. report that more than half of the patients in their study had been prescribed an antiemetic medication for symptomatic treatment,[5] and most patients had tried more than one antiemtetic.[5] Antiemetics, including phenothiazines, antihistamines, and 5-hydroxytryptamine 3 (5-HT$_3$) receptor antagonists, are prescribed to improve or suppress symptoms of nausea and vomiting in patients with idiopathic gastroparesis.[6,11] There is not a single antiemetic drug or class of drugs that has emerged as the best option for treating nausea and vomiting in patients with idiopathic gastroparesis.[8,11] Phenothiazines, which includes prochlorperazine, are dopamine and cholinergic receptor antagonists.[10] This class of medication acts on the chemoreceptor trigger zone in the brainstem.[10] Side effects of phenothiazines include sedation, extrapyramidal effects (movement disorders), tardive dyskinesia (involuntary movements of the face and jaw), drowsiness, dry mouth, constipation, and skin rashes.[10] 5-HT$_3$ antagonists, such as granisetron and ondansetron, can be prescribed for patients with idiopathic gastroparesis when nausea and vomiting are the dominating symptoms and cardiac risks are increased by prokinetics.[14] Aprepitant is another antiemetic, a neurokinin-1 receptor antagonist, that increases gastric accommodation, improves some digestive symptoms, and has been shown

to be effective in case reports of severe gastroparesis.[11] However, aprepitant does not affect gastric emptying.[14] Tradipitant is a new neurokinin antagonist that has shown improvement in nausea in patients with idiopathic gastroparesis with moderate-to-severe nausea.[14] Ultimately, the choice of antiemetic used to treat the patient with idiopathic gastroparesis should be based on the patient's response to and tolerance of the medication, cost of the medication, and necessary route of administration, as some antiemetics are available transdermally, such as transdermal granisetron, or rectally, reducing the variability in drug absorption in patients with frequent vomiting.[8,11,14] Transdermal granisetron delivers a sustained controlled dose over the course of 24 hours, reduces nausea and vomiting in patients with gastroparesis, and has a decreased risk of electric dysrhythmias when compared to oral granisetron.[16,19]

Prokinetic medications stimulate gastric motor activity through an increase in antral contractility, correct gastric dysrhythmias, and improve coordination between the antrum and duodenum leading to enhanced propulsive motility, thereby promoting the movement of contents from the stomach, causing caudal displacement of luminal contents.[3,6,10] These agents may predominantly improve symptoms of nausea, vomiting and bloating as they do not seem to relieve abdominal pain nor early satiety associated with gastroparesis.[10] Though prokinetic agents may improve the rate of gastric emptying, the medication may not improve symptoms associated with idiopathic gastroparesis.[5] Prokinetic agents are noted to have modest efficacy and should be adjusted or discontinued based on symptom response and side-effects.[3] One study demonstrated that utilizing prokinetic medications to treat patients with gastroparesis did not decrease their length of hospitalization nor their rates of 30-day readmission.[17]

Dopamine receptor antagonists utilized in the treatment of idiopathic gastroparesis include metoclopramide and domperidone. Both metoclopramide and domperidone accelerate

gastric emptying and have independent anti-nausea effects.[3] These two medications will be further discussed. Levosulpiride, an antipsychotic agent, is a dopamine receptor D_2-antagonist that accelerates gastric emptying by exerting both antidopaminergic and 5-hydroxytyramine 4 (5-HT_4) agonistic properties and is expected to reverse dopaminergic inhibition on gastric contraction, but it is not yet approved by the FDA.[10,14] Levosulpiride improved symptoms in patients with idiopathic gastroparesis without correlation with the acceleration of gastric emptying.[14]

Metoclopramide is the only pharmacotherapy currently approved by the United States FDA for the treatment of gastroparesis.[1,3,5,8] It is a benzamide derivative that primarily acts as a peripheral dopamine D_2-receptor antagonist but stimulates 5-HT_4 receptors, which augments the release of acetylcholine in the myenteric plexus within the gut wall, causing increased lower esophageal sphincter tone, antral contractility, fundic tone, pyloric function, antroduodenal tone and coordination, and jejunal peristalsis.[3,8] Therefore, this medication accelerates gastric emptying. Metoclopramide directly acts on both the chemoreceptor trigger zone and intracerebral vomiting center, which causes central antiemetic effects and symptom improvement.[8] Navas et al. report that just under half of patients in their study had been prescribed metoclopramide.[5] Of these patients, 43% reported experiencing symptomatic improvement while taking metoclopramide.[5] 35% of patients reported experiencing adverse effects directly related to taking this medication.[5] Yet, the FDA estimates that adverse effects occur in only about 10% of patients taking metoclopramide.[5] Metoclopramide crosses the blood-brain barrier and can result in neurological adverse-effects and extrapyramidal movement disorders, including Parkinsonism, tardive dyskinesia, akathisia, and acute dystonic reactions (facial spasm, oculogyric crisis, trismus and torticollis), resulting in the need to discontinue the medication and ultimately

limiting its use.[1,3,10] Due to the extrapyramidal side effects, the FDA placed a black-box warning on metoclopramide in 2009, which consequently caused the number of patients taking the medication to decline by more than 50%.[8,18] Other reported side-effects include somnolence, drowsiness, fatigue, lassitude, anxiety, restlessness, irritability, depression, reduced mental acuity, and hyperprolactinemia.[3,10] Metoclopramide is also available as a nasal spray, which is helpful for patients unable to tolerate oral medications.[19] Side-effects associated with intranasal metoclopramide are dysgeusia, headache and fatigue.[19] Despite the chronicity of idiopathic gastroparesis, the FDA recommends the use of metoclopramide for no longer than 12 weeks, unless patients experience a therapeutic benefit that outweighs the potential risks of the medication.[8,14]

Domperidone is a dopamine receptor antagonist that chiefly acts on the peripheral dopamine D_2-receptors, exhibiting both prokinetic and antiemetic effects.[3,8,14] Its mechanism of action is similar to metoclopramide, as it accelerates gastric emptying by inhibiting fundic relaxation and promotes antroduodenal coordination.[3] However, domperidone does not cross the blood-brain barrier and therefore causes fewer central nervous system side effects than metoclopramide.[8] One study notes that gastroparesis patients reported better tolerance and greater symptom improvement while taking domperidone than metoclopramide.[5] Although, domperidone is more challenging to prescribe due to its lack of FDA approval in the United States.[5] Navas et al. report that domperidone was prescribed to over 25% of patients in their study.[5] Of these patients, 46% reported symptom improvement while taking domperidone, and 9% reported adverse effects associated with the medication.[5] Patients with gastroparesis taking domperidone experience improvement in postprandial fullness, nausea, vomiting and stomach fullness.[20] Furthermore, domperidone improved the observed diminished quality of life in

patients with gastroparesis in three separate studies.[11] Side-effects of domperidone include dry mouth, headaches, hyperprolactinemia symptoms, may prolong QTc interval, and though rare, can cause cardiac arrhythmias and increase the risk of sudden cardiac death.[8,11] Due to potential cardiac adverse effects, a baseline electrocardiogram (ECG) is recommended prior to initiation of therapy, and follow-up ECGs while on therapy should also be considered.[8] Though domperidone is widely used in many countries and available over the counter in some countries, it is not currently approved by the FDA in the United States for use in patients with idiopathic gastroparesis and is only approved as a special FDA investigational drug program in the United States for patients who have failed standard therapy.[1,3,8,14,19] According to one study, healthcare providers may write or print a prescription for domperidone and provide it to the patient for the patient to legally purchase domperidone through an international pharmacy.[11] Stein et al. caution this, however, due to the potential cardiac adverse events associated with domperidone and further state that there has also been an increase in requests for the medication to be withdrawn from the market completely.[11] Risks and benefits need to be discussed with patients contemplating the initiation of domperidone for treatment of their symptoms associated with idiopathic gastroparesis.

Bethanechol is a smooth muscle muscarinic agonist that is prescribed in addition to other prokinetic medications in patients whose symptoms have not improved with commonly prescribed prokinetic and antiemetic drugs.[10] Adverse effects of bethanechol include abdominal cramps, skin flushing, diaphoresis, lacrimation, salivation, nausea, vomiting, bronchial-constriction, urinary urgency, and miosis.[10] Efficacy of bethanechol in patients with idiopathic gastroparesis was not noted.

Motilin receptor agonists include erythromycin, mitemcinal, antimotin, and ghrelin.[3] Motilin is an endogenous hormone that stimulates gastric emptying through cholinergic activity in the antrum.[8,19] Previous studies with motilin receptor agonists demonstrated that they were ineffective in treating symptoms of gastroparesis, and tachyphylaxis (development of tolerance to the medication) was a common side effect.[19]

Erythromycin is a macrolide antibiotic that acts as a motilin receptor agonist and is a potent prokinetic agent, improving gastric emptying.[1,3,8,11] Erythromycin does cause side-effects of an antibiotic agent, including skin rashes, nausea, cramping and abdominal pain.[3,10] When used in the treatment of idiopathic gastroparesis, a lower dosage is prescribed since erythromycin exhibits its gastric emptying effects even in lower doses.[3] Similar to other agents, erythromycin may be associated with prolongation of the QTc interval and increased risk of sudden cardiac arrest, thus careful ECG monitoring is necessary.[8,10,11] Tachyphylaxis continues to be a major problem in the utilization of erythromycin, limiting its use long-term for the treatment of idiopathic gastroparesis.[1,3,8]

Azithromycin, a macrolide antibiotic similar to erythromycin, is also a motilin receptor agonist that improves antroduodenal contraction after intravenous (IV) administration.[10] Azithromycin has a lower potential to cause cardiac arrhythmias than erythromycin and fewer adverse effects since it is not metabolized by the cytochrome P-450 metabolic pathway in the liver.[10] However, IV administration of azithromycin did not show improvement in gastric emptying or patient symptoms.[10]

Mitemcinal may have a role in the treatment of symptoms experienced by patients with idiopathic gastroparesis. Mitemcinal (GM-611) is a macrolide-derived motilin receptor agonist with prokinetic properties.[3,10,19] Mitemcinal improved upper gastrointestinal symptoms when

prescribed to patients with type 1 and 2 diabetes at 10 milligrams twice daily,[3] but no study results were provided regarding its effects on symptoms in patients with idiopathic gastroparesis.[3] Another study with mitemcinal failed to demonstrate an increase in gastric emptying when compared to placebo.[19]

Antimotin is a motilin receptor agonist.[3] IV administration of Antimotin in healthy individuals accelerated gastric emptying of liquids and solids without significant effects on colon transit.[3] However, no studies have demonstrated this effect in patients with idiopathic gastroparesis.[3]

Ghrelin is an endogenous peptide (hormone) derived from the gastric mucosa.[3,19] It is similar in structure to motilin, exhibiting prokinetic effects mediated by vagal signaling, which seems to play an important role in the regulation of both appetite and body weight.[3,19] In animals, ghrelin has shown prokinetic (motility-stimulating) properties.[3] Ghrelin accelerated gastric emptying after a test meal in diabetic patients with slow gastric emptying in one study and improved gastric emptying in patients with idiopathic gastroparesis in another study.[3] TZP-101 is a cyclic ghrelin analog that, when administered intravenously, accelerated gastric emptying and improved symptom severity when compared with placebo.[11] Its oral counterpart TZP-102 failed to demonstrate a benefit during the follow-up 12-week phase IIb trial.[11]

Two medications studied in clinical trials for the treatment of gastroparesis are Relamorelin and Camicinal. Relamorelin is a medication that has shown potential in the treatment of gastroparesis symptoms. A clinical trial of subcutaneous injection of Relamorelin (RM-131), a small molecule synthetic pentapeptide ghrelin agonist, accelerated gastric emptying of solids via stimulation of gastric contractions in patients with diabetic gastroparesis and improved subjective vomiting severity and symptoms of nausea, fullness, bloating and

pain.[11,14,19] Two additional trials also demonstrated that Relamorelin accelerated gastric emptying with mixed results regarding symptomatic improvement in patients with gastroparesis.[14] The most common adverse effects reported for Relamorelin are dizziness, headache, and hyperglycemia.[19] In different clinical trial, Camicinal (GSK962040), a small molecule selective motilin receptor agonist, improved gastric emptying and symptoms in patients with diabetic gastroparesis and had a reduced incidence of tachyphylaxis.[11,19] The effects of Relamorelin and Camicinal in patients with idiopathic gastroparesis was not specifically noted.

5-HT$_4$ receptors are located throughout the gastrointestinal tract and when activated, release acetylcholine at the myenteric plexus.[19] This leads to increased muscular contractions and accelerated transit throughout the gastrointestinal tract.[19] Cisapride and tegaserod are both non-selective 5-HT$_4$ agonists.[3,8,19] Unfortunately, these two 5-HT$_4$ agonists are associated with cardiac dysrhythmias.[8] Cisapride was formerly the treatment of choice for gastroparesis and gastroparesis-related symptoms, as it demonstrated efficacy in improving gastric emptying.[3,11] Cisapride was withdrawn from the market due to significant cardiac side effects, including ventricular cardiac arrhythmias and sudden cardiac death.[3,11] It is now only available under compassionate care programs.[3] Tegaserod is another 5-HT$_4$ agonist that has shown conflicting results in its effects on gastric emptying in healthy individuals but was possibly associated with ischemic cardiovascular events.[3,19] Tegaserod was also removed from the market due to adverse cardiac effects.[19] Revexepride is a highly specific potent 5-HT$_4$ receptor agonist that failed to show differences in gastric emptying or symptomatic improvement in clinical trials.[19] Velusetrag is a selective 5-HT$_4$ receptor agonist that has a 500-fold selectivity and affinity to the 5-HT$_4$ receptor with no effect on the 5-HT cardiac receptors and was considered a promising prokinetic as it indeed provided symptom relief and accelerated gastric emptying.[8,14,19] RQ-00000010, a

well-tolerated highly selective 5-HT4 receptor agonist, is currently under investigation and demonstrated improved gastric emptying.[19] Prucalopride, a selective 5-HT4 receptor agonist without adverse cardiac effects, exerts an enterokinetic effect and is approved in the United States for the treatment of chronic constipation.[14] Prucalopride has been shown to exhibit a gastrokinetic effect and improved symptoms in patients with idiopathic gastroparesis, significantly improving symptoms of nausea/vomiting, fullness/satiety, and bloating/distention; improved quality of life; and enhanced solid gastric emptying compared to placebo.[14,21] Adverse effects of prucalopride are diarrhea, headache and nausea, though most events were transient.[21] Though 5-HT4 agonists were previously utilized to treat gastroparesis, currently no other 5-HT4 agonists have been FDA-approved.[3]

Buspirone and acotiamide are fundic relaxants being investigated for symptomatic treatment in patients with gastroparesis.[14] Buspirone is an anxiolytic 5-HT1A agonist that enhances gastric accommodation through fundic relaxation and improves postprandial symptoms in patients with gastroparesis independently from its anxiolytic effect.[14] Acotiamide, a cholinesterase inhibitor, exerts presynaptic muscarinic autoreceptor inhibitory activity, enhancing both contractile and accommodation activities of the stomach and improving dyspeptic symptoms but not epigastric pain or burning symptoms.[14]

Tricyclic antidepressants (TCAs), such as nortriptyline and amitriptyline, are psychotropic agents that have been utilized for patients with idiopathic gastroparesis to treat refractory symptoms of nausea, vomiting, and abdominal pain.[1,6,8] Some TCAs delay gastric emptying, but nortriptyline was indicated as the least likely TCA to affect gastric emptying since it exhibits less anticholinergic side effects than other TCAs.[1] A randomized, placebo-controlled study demonstrated that nortriptyline did not result in improvement in overall symptoms in

patients with idiopathic gastroparesis, which does not support the use of TCAs for the treatment of idiopathic gastroparesis.[1,6,11] Mirtazapine is an antidepressant with central adrenergic and serotonergic activity.[14] Mirtazapine may be helpful in patients with idiopathic gastroparesis experiencing loss of appetite and weight loss as it was shown to improve nausea, vomiting and loss of appetite in patients with gastroparesis.[14]

Patients with gastroparesis may experience pylorospasm due to excessive smooth muscle tone, resulting in failure of the pylorus to relax and causing functional resistance to gastric outflow.[10] Botulinum toxin (BTX) is a neurotoxin that inhibits acetylcholine release from synaptic vesicles at synaptic junctions, which decreases the release of excitatory transmitter substances in muscles, promoting relaxation.[3,8,10] BTX injected intrapylorically has been utilized in patients with idiopathic gastroparesis experiencing pylorospasm to decrease pyloric resistance and subsequently improve gastric emptying.[3,10] It is more invasive due to the injection needing to be administered endoscopically. BTX has shown mixed results in its effects on symptoms and gastric emptying in patients across various studies.[3,8,10,14] Its use remains controversial in the treatment of idiopathic gastroparesis due to its utilization being considered an off-label indication in treating patients with idiopathic gastroparesis and the lack of clinical evidence to support widespread use in patients with idiopathic gastroparesis.[3,8,10,14]

Pain is an important symptom in patients with idiopathic gastroparesis that typically does not improve with dietary adjustments or other medical interventions, which reduces patients' quality of life.[12,15,18] Abdominal pain in patients with idiopathic gastroparesis is poorly understood and frequently difficult to treat, often driving patients toward opioids.[5,14] However, opioid medications should be avoided in patients with idiopathic gastroparesis. Suggested medications to treat abdominal pain in patients with idiopathic gastroparesis are non-steroidal

anti-inflammatory drugs (NSAIDs) that may help by improving gastric dysrhythmias.[10] Other options are antidepressant medications like selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin/norepinephrine reuptake inhibitors (SNRIs), gabapentin, and pregabalin, which may help improve neuropathic pain associated with gastroparesis.[10,15] Haloperidol administered intravenously in the Emergency Department decreased abdominal pain and nausea in severely ill patients with gastroparesis.[14]

Opioid analgesics may acutely improve abdominal pain.[6] However, they delay gastric emptying, can cause symptoms of both nausea and vomiting, may actually upregulate abdominal pain, and lead to dependence due to chronic usage.[6] Therefore, treatment guidelines advise that opioid analgesics not be used to manage abdominal pain in patients with idiopathic gastroparesis.[5,10] Figure 3 features data regarding the degree of gastric emptying delay in patients prescribed opioids.[5] Navas et al. report that about 25% of patients in their study had an active opioid prescription at the time the patient's gastric emptying study was ordered.[5] Specifically, oxycodone was the most common opioid prescribed to the patients in their study.[5] Others have published that up to 42% of patients with gastroparesis have been prescribed opioids.[5] Opiate analgesic use correlates with increased severity of gastric emptying, worsens nausea and vomiting, lowers quality of life, causes greater resource utilization, and carries an addictive potential.[5,15,16,22] Potent opioids (morphine, hydrocodone, oxycodone, methadone, hydromorphone, buprenorphine, or fentanyl) are associated with larger effects than weaker agents (tapentadol, tramadol, codeine, or propoxyphene).[22] Furthermore, gastroparesis patients taking opioids report greater severity of symptoms and experience more than double the hospitalization rates when compared to those who do not take opioids.[5]

Overall, healthcare providers are advised to not prescribe opioids to patients with idiopathic gastroparesis.[5] Providers are also advised to wean patients with idiopathic gastroparesis off opioids and choose an alternative analgesic to treat the abdominal pain associated with the motility disorder, specifically choosing alternative medications that do not further delay gastric emptying nor directly cause nausea and vomiting.[5] Pain improvement should result in better symptom control, improved quality of life, restoration of productivity, and reduced ED visits, hospitalizations, and associated healthcare costs.[5,12]

VI. Methods

Idiopathic Gastroparesis General Information

To compile background information regarding idiopathic gastroparesis, a PubMed search was performed using the terms "Idiopathic AND gastroparesis" and search filter was applied for articles published in the last 10 years. Articles selected broadly discussed the definition, prevalence, and methods of diagnosing idiopathic gastroparesis. Other articles selected also included the treatment and management of the chronic motility disorder.

Lifestyle Modifications for the Treatment of Idiopathic Gastroparesis

To compile information regarding the treatment of idiopathic gastroparesis utilizing lifestyle modifications, including dietary adjustments and changes in eating habits, a PubMed search was performed using the following terms and search filter applied for articles published in the last 10 years: "Idiopathic AND gastroparesis AND treatment AND lifestyle;" "Idiopathic AND gastroparesis AND lifestyle;" "Idiopathic AND gastroparesis AND treatment AND diet;" "Idiopathic AND gastroparesis AND diet;" and "Idiopathic AND gastroparesis AND nutrition." Articles chosen discussed lifestyle modifications, dietary recommendations, nutritional deficiencies, and overall discussion of health and nutrition in patients with idiopathic

gastroparesis.

Pharmacotherapy for the Treatment of Idiopathic Gastroparesis

To compile further information regarding pharmacotherapy utilized for treating the symptoms and delayed gastric emptying associated with idiopathic gastroparesis, a PubMed search was performed using the following terms and search filter applied for articles published in the last 10 years: "Idiopathic AND gastroparesis AND treatment;" "Idiopathic AND gastroparesis AND management;" "Idiopathic AND gastroparesis AND pharmacotherapy;" and "Idiopathic AND gastroparesis AND medication." Articles that were chosen not only discussed FDA-approved medications but also medications being used off-label for the treatment of symptoms and delayed gastric emptying associated with idiopathic gastroparesis. Other articles chosen provided a review of medications being investigated through clinical trials for potential use in the treatment of idiopathic gastroparesis.

VII. Discussion

Idiopathic gastroparesis is a chronic gastric motility disorder that impacts patients' quality of life and has limited FDA-approved pharmacotherapy options for the treatment of symptoms and management of the complex disorder. It is concerning that patients are willing to take high risks with medications in order to achieve symptom relief, but this is also understandable once the extent of symptoms' impact on quality of life is observed. Patients with idiopathic gastroparesis require a treatment plan to include dietary adjustments and potentially pharmacotherapy to treat symptoms either at the patient's home or in an outpatient clinic setting to prevent ED visits, hospitalizations, and accumulation of healthcare costs. In utilizing the least invasive treatment options first, the research question investigated through this literature review was: in adults with idiopathic gastroparesis, how does lifestyle modifications, including changing

diet and eating habits, compared to pharmacotherapy affect the symptoms of nausea, vomiting, early satiety, and poor appetite?

The evaluation of patients with idiopathic gastroparesis and the treatment plan for their symptoms and delayed gastric emptying needs to be thorough. A 4-hour gastric emptying study is the gold standard to establish the diagnosis of gastroparesis. However, a protocol to further classify the delay as mild, moderate or severely delayed has not been agreed upon nor published. A thorough history and physical examination should be performed to identify and minimize or eliminate any factors that may be contributing to symptoms, including discontinuing medications that provoke symptoms or delay gastric emptying, addressing hydration and nutritional deficiencies, and treating any comorbidities. Laboratory studies are a vital component to evaluate for and identify electrolyte and nutritional abnormalities and any other underlying conditions that may be contributing to symptoms. If nutritional supplementation is required, high protein caloric liquids are recommended, as liquids are often better tolerated than solids.

Patient education is crucial in helping patients understand their diagnosis, the importance of following a gastroparesis diet, and understanding the purpose of prescribed pharmacotherapy. Education empowers patients to take charge of their health and helps them make appropriate lifestyle modifications to improve and potentially eliminate their symptoms. The provider should perform education regarding a gastroparesis diet, to include the frequency and composition of meals. Small frequent meals (4 to 6 meals daily) low in fiber and fats are recommended for patients with the diagnosis of idiopathic gastroparesis to maintain nutrition. Additionally, liquid-based meals to maintain nutrition and adequate fluid intake to maintain hydration are recommended during symptomatic flares. This may also help resolve associated complications and prevent future complications associated with persistent symptoms. Based on the data

available indicating that very few patients follow a gastroparesis diet, the challenges with adherence need to be quickly identified and addressed. If possible, a registered dietitian should be involved in the patient education regarding a gastroparesis diet, nutritional assessment, and meal planning. If not possible, it is the responsibility of the provider to educate and aid the patient in each of these areas and address any challenges as they arise.

If symptoms are still present after lifestyle and dietary modifications, pharmacotherapy can be instituted and individualized to target specific symptoms, such as antiemetics, prokinetic medications, analgesic medications, and antidepressants. However, opioid analgesics are not recommended and should be completely avoided to treat pain in patients with idiopathic gastroparesis because they delay gastric emptying and can directly cause the symptoms of nausea and vomiting. Unfortunately, metoclopramide is the only medication FDA-approved in the United States for the indication of treating gastroparesis. This highlights the need for more medications to be investigated for the treatment of idiopathic gastroparesis and the need for these medications to be approved specifically for the indication of idiopathic gastroparesis or symptoms induced by the disorder.

Other medications are prescribed to treat specific symptoms or prescribed off-label for treating idiopathic gastroparesis. Antiemetics, for example, are often prescribed and labeled for the indication of pregnancy-induced or chemotherapy-induced nausea and vomiting but are utilized off-label to treat nausea and vomiting associated with idiopathic gastroparesis. The largest challenge with prescribing medications for off-label use is the ability to obtain pharmaceutical insurance coverage for the cost of the medications. Thorough documentation (including medication name, dosage, dates and duration of trials, and reason for failure) of previous medication trials needs to occur with every patient encounter and the information

utilized when performing medication prior authorizations for pharmaceutical insurance coverage. If the insurance company will not pay for the medication, either the patient will need to pay out-of-pocket for the medication or the healthcare provider needs to choose a formulary alternative (a medication that the insurance will cover based on the patient's pharmaceutical plan). This process can unfortunately delay the start of pharmacotherapy needed to control the patient's symptoms, so shared decision-making is important when deciding which medications to prescribe to target specific symptoms. Once started, each medication dose will need to be adjusted or discontinued based on symptom response and associated side-effects. More severe symptoms may need to be initially treated with both lifestyle modifications and pharmacotherapy.

Based on the literature review, the treatment regimen for a patient with idiopathic gastroparesis, including lifestyle modifications, dietary adjustments and pharmacotherapy, will need to be formulated and adjusted on a case-by-case basis depending on presenting symptoms and the severity of symptoms. Lifestyle modifications, including changing diet and eating habits compared to pharmacotherapy affect the symptoms of nausea, vomiting, early satiety, and poor appetite unpredictably. This information is crucial to communicate to the patient during the patient education component of each visit, reminding patients that the goal of treatment is to control symptoms and improve their quality of life through lifestyle modifications, pharmacotherapy, or both. Since the response to dietary changes and pharmacotherapy is unpredictable, consistent follow-up is required to evaluate for symptom improvement, monitor for medication side-effects, and assess the effect of treatment on the patient's quality of life.

VIII. Conclusion

Idiopathic gastroparesis is a chronic gastric motility disorder of unknown cause that greatly impacts patients' quality of life and is often difficult to treat. The goal of treatment for patients with idiopathic gastroparesis is to control symptoms, not cure the disorder, which is an important education distinction to provide to the patient upon establishing the diagnosis of idiopathic gastroparesis. The delay in gastric emptying may predict negative health outcomes and exacerbate comorbid conditions in patients with symptomatic gastroparesis, increasing the possibility of a necessary hospitalization for a higher level of treatment and management.[5] The increase in hospitalizations of gastroparesis patients and increase in associated healthcare costs over the last 15 years emphasizes the importance and necessity of outpatient clinical treatment and management plans of this chronic motility disorder.[5]

Lifestyle modifications and dietary adjustments are the first step in treating patients with idiopathic gastroparesis with the potential for pharmacotherapy to also be instituted to reduce or potentially eliminate symptoms. Patients should eat four to six small meals daily that are both low in fat and fiber to maintain nutrition. During symptomatic flares, patients should consume liquid-based meals to maintain nutrition and drink fluids as tolerated to maintain hydration. Metoclopramide is the only FDA-approved mediation for the treatment of gastroparesis, which means pharmacotherapy options are limited at this time. There are many emerging medications currently in clinical trials for the treatment of idiopathic gastroparesis, associated symptoms, and/or delay in gastric emptying. Pharmacotherapy is available to treat individual symptoms, such as antiemetics for the treatment of nausea and vomiting; however, the majority of other medications (those indicated for the treatment of other chronic conditions) are prescribed as an

off-label use of the medication for the treatment of symptoms and delayed gastric emptying associated with idiopathic gastroparesis.

Utilizing pharmacotherapy to treat symptoms and delayed gastric emptying associated with idiopathic gastroparesis can be both complicated and frustrating for patients and healthcare providers. The challenge in using medications for off-label indications is that patients' pharmaceutical insurance plans may not cover the cost of the medications, since the diagnosis of idiopathic gastroparesis is not listed as an FDA-approved indication. When pharmaceutical insurance companies do not pay for the medication, either the patient has to pay out-of-pocket for the entire cost of the medication or an alternative medication will need to be prescribed. Further research needs to evaluate and approve medications for the indication of treating symptoms and/or delayed gastric emptying associated with idiopathic gastroparesis. Furthermore, side-effects associated with medications also limit the use of pharmacotherapy in the treatment of idiopathic gastroparesis. Mediation is utilized to treat specific symptoms or the specific cause of symptoms; however, patient tolerance, symptom response, and side-effects must be monitored closely and adjustments to doses or changes in medications made as needed.

Since associate providers, such as physician assistants, have been shown to reduce costs and readmission rates for other chronic disease models as well as improve outcomes in the primary care setting, certified physician assistants have the opportunity to contribute to reduced costs and improved outcomes for patients with idiopathic gastroparesis.[5] The recommendations regarding symptomatic treatment and management of patients with idiopathic gastroparesis will influence the medical practice of not only certified physician assistants (PAs) but also physicians and nurse practitioners (NPs) treating these patients. With data demonstrating that very few patients follow a gastroparesis diet, healthcare providers have a unique opportunity to educate

patients with idiopathic gastroparesis regarding lifestyle modifications and dietary recommendations. Physicians, PAs, and NPs have the opportunity to troubleshoot appointment scheduling and insurance coverage on a case-by-case basis in order to facilitate appointments not only with themselves but also with a registered dietitian, improve patients' quality of life, hopefully minimize or eliminate the need for ED visits and hospitalizations, and reduce healthcare costs not only for the patient but also for our healthcare systems as a whole. Since most patients are not following a gastroparesis diet, patient education by healthcare providers regarding diet is a necessary component of management and treatment of patients with idiopathic gastroparesis, especially if patients' insurance companies will not pay for a dedicated nutritional consultation with a registered dietitian. Another question that arose during this literature review was whether following a gastroparesis diet customized to the patient's nutritional requirements and individualized to their lifestyle may relieve symptoms more than pharmacotherapy in patients with idiopathic gastroparesis. Further research should specifically evaluate the effect of following a gastroparesis diet on patients' symptoms and quality of life. Based on the literature review performed for this paper, customization is key in the treatment and management of patients with idiopathic gastroparesis.

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X. Appendices

Table 1: Gastroparesis Reported Symptoms[5]

	% of patients
Most bothersome symptom reported	
Nausea	29.0
Upper abdominal pain	29.0
Vomiting	12.0
Early satiety	6.5
All symptoms reported (not the most bothersome)	–
Nausea	44.8
Early satiety	40.8
Constipation	38.9
Vomiting	37.9
Bloating	31.4
Upper abdominal pain	22.7
Heartburn	27.1
Abdominal fullness	23.8
Dysphagia	18.0
Regurgitation	15.2
Anorexia	12.6

Figure 1: Stepwise Approach to Gastroparesis[8]

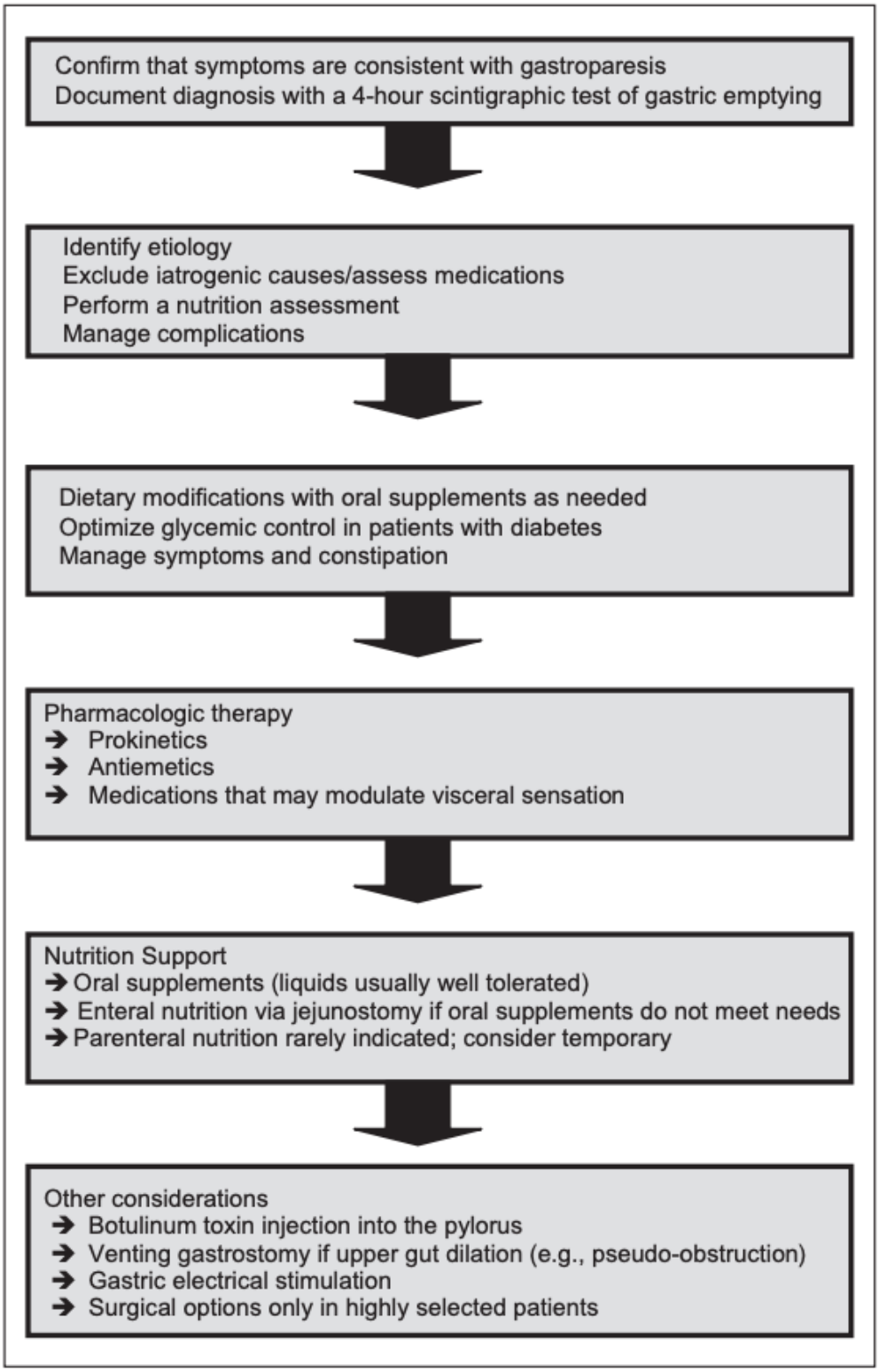
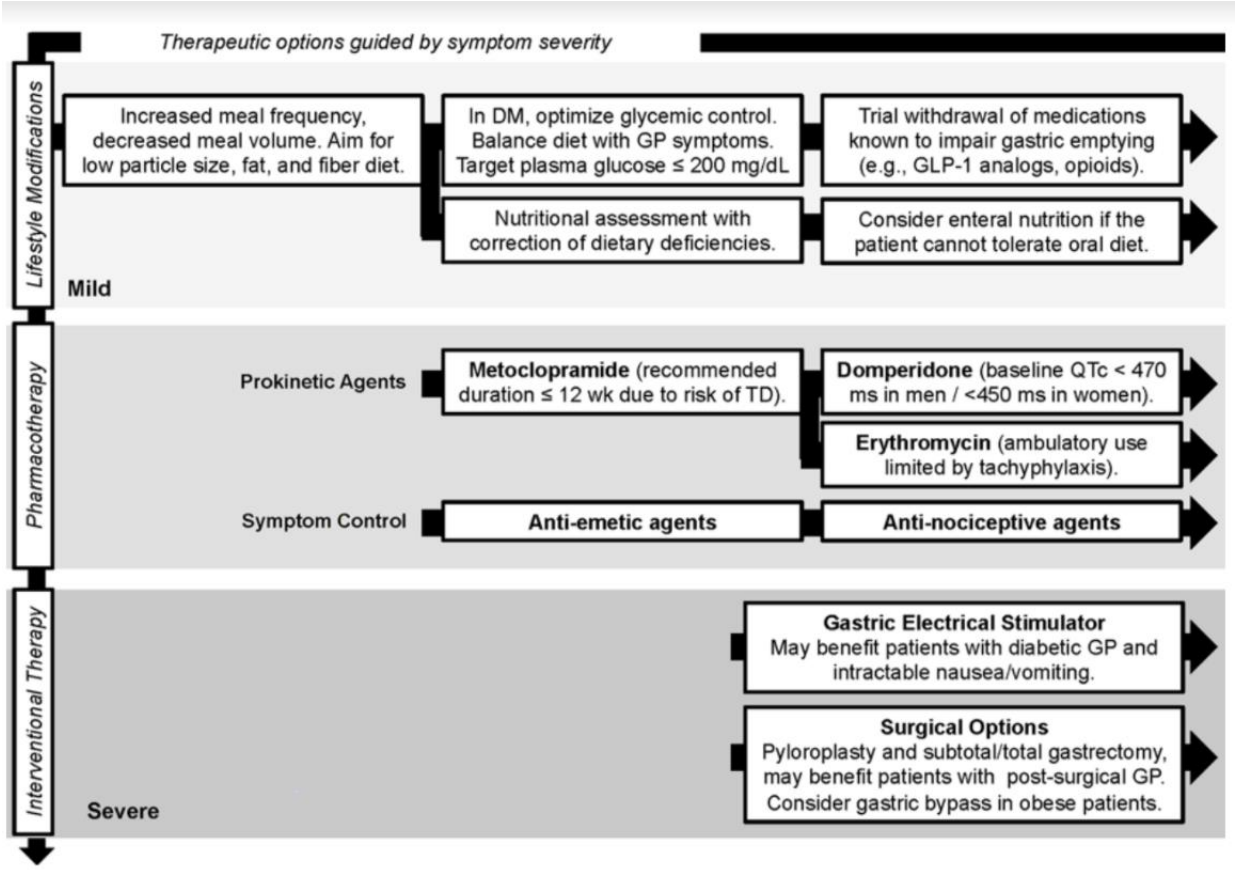


Figure 2: Suggested Therapeutic Options for Gastroparesis.[11]



DM indicates diabetes mellitus; GP, gastroparesis; GLP, glucagon-like peptide; TD, tardive dyskinesia.

Table 2: Nutritional Analysis of Aggravating and Tolerated Foods[13]

	Amount (g)	Carb (g)	Protein (g)	Fat (g)	Fiber (g)	Sodium (mg)	Water (g)
Foods aggravating							
Orange juice	100	13	0.2	0	0.2	2	86.2
Fried chicken (breast)	100	6	23	12	0.1	657	55.5
Cabbage (boiled)	100	5.5	1	0	2	8	92.6
Oranges	100	11.5	0.7	0.21	2.4	0	87.1
Sausage (pork)	100	0.65	14.3	31	0	731	47.1
Pizza (cheese)	100	33	11.4	9.7	2.3	598	43.2
Peppers (sweet, raw)	100	4.6	0.86	0.17	1.7	3	93.9
Onions (boiled)	100	10	1.4	0.2	1.4	3	87.9
Tomato juice (can)	100	3.5	0.85	0.3	0.4	10	94.2
Lettuce (romaine)	100	3.3	0.6	0.3	2.1	8	94.6
Coffee (brewed)	100	0	0.12	0	0	2	99.3
Salsa	100	7	1.5	0.2	1.4	430	89.7
Broccoli (boiled)	100	7.2	2.4	0.41	3.3	41	89.3
Bacon (pork)	100	1.3	12.6	40	0	662	44.2
Roast beef (deli-style)	100	0.64	18.6	3.7	0	853	73.7
MEAN		7.15	5.97	6.55	1.15	267.2	78.6
Foods tolerated							
Saltines	100	76	8.2	9	2.5	1021	2.5
Gelatin (with water)	100	14.2	1.2	0	0	75	84.4
Graham crackers	100	76.2	7	10	3.4	659	3.6
Applesauce (sweetened)	100	17.5	0.16	0.17	1.2	2	82
Popsicles (brand)	100	19.7	0	0.24	0	13	80
White rice (cooked)	100	28.6	2.4	0.21	0.3	0	68.6
Potato (baked with skin)	100	21.2	2.5	0.13	2.2	10	74.9
Salmon (pink)	100	0	20.5	4.4	0	75	75.5
Clear soup (chicken broth)	100	0.44	0.64	0.21	0	371	97.8
White fish (whiting)	100	0	18.3	1.3	0	72	80.3
Pretzels (salted)	100	80.4	10	2.9	3.4	1240	3.1
Sweet potato (unprepared)	100	20.1	1.6	0.1	3	55	77.3
Tea (black, brewed)	100	0.3	0	0	0	3	99.7
Ginger ale	100	8.8	0	0	0	7	91.2
White bread	100	49.4	8.9	3.3	2.7	490	36.4
MEAN		27.52	5.43	2.13	1.25	272.9	63.8

Table 3: Food Qualities of Aggravating and Tolerated Foods[13]

	Food qualities
Provoking foods	
Orange juice	Acidic
Fried chicken	Fatty
Cabbage	Roughage
Oranges	Acidic
Sausage	Fatty, spicy
Pizza	Fatty, spicy
Peppers	Spicy, roughage
Onions	Roughage
Tomato juice	Acidic
Lettuce	Roughage
Coffee	Bitter, acidic
Salsa	Spicy, acidic
Broccoli	Roughage
Bacon	Fatty
Roast beef	Fatty
Alleviating and tolerable foods	
Saltines	Salty, bland
Jello	Sweet
Graham crackers	Bland, sweet
Applesauce	Sweet
Popsicles	Sweet
White rice	Bland
Potato	Bland, starchy
Salmon	Fatty, bland
Clear soup	Bland, salty
White fish	Bland
Pretzels	Salty
Sweet potato	Sweet, starchy
Tea	Bland
Ginger ale	Sweet
White bread	Bland, starchy

Table 4: Treatments Tried for Gastroparesis Symptoms (*n*=284)[5]

Treatment	*n*	Symptom improvement	Side effects
Metoclopramide	134	43%	35%
Domperidone	76	46%	9%
Erythromycin	63	27%	24%
Botox injection in the pylorus	19	37%	10%
Gastric stimulation	12	45%	16%
Alternatives (ginger, acupuncture, marijuana, acupuncture)	17	–	–
Antiemetics	173	–	–
Ondansetron	47%	–	–
Promethazine	29%	–	–
Scopolamine	14%	–	–
Dronabinol	13%	–	–
Lorazepam	13%	–	–
Prochlorperazine	12%	–	–
Trimethobenzamide	11%	–	–
Meclizine	8%	–	–
Diphenhydramine	5%	–	–
Granisetron	3%	–	–
Opioid medications	***n***	**Morphine Eq[a] (mg)**	
Oxycodone	25	1564	
Methadone	11	1260	
Hydromorphone	11	3180	
Tramadol	8	128	
Fentanyl	7	1290	
Morphine	7	454	

[a]Total daily dose calculated as morphine equivalent in milligrams

Table 5: Novel Drug Effects[19]

Drug class	Antiemetic effects	Prokinetic effects
Drug name		
Dopamine D2-receptor antagonists		
Intranasal metoclopramide	+	+
Domperidone	+	+
Ghrelin agonist		
Relamorelin		+
Motilin agonist		
Camicinal		+
5-HT_3 receptor antagonist		
Granisetron patch	+	
5-HT_4 receptor agonist		
Revexepride		+
Velusetrag		+
DA-6650		+
RQ-00000010		+
VKP10811		+
NK-1 receptor agonist		
Aprepitant	+	
Tradipitant (VLY-686)	+	

Table 6: Mechanisms of Action of Novel Drugs[19]

Drug target/drug name	Mechanism of action
Dopamine D2-receptor antagonists Intranasal metoclopramide, domperidone	Blocks dopamine receptors in the chemoreceptor zone and enhances response to acetylcholine in GI tract leading to enhanced motility and accelerated gastric emptying
Ghrelin receptor agonists Relamorelin	Activates ghrelin receptors leading to prokinetic effects on gastrointestinal motility mediated by vagal signaling and stimulation of the phase III component of the gastric migrating motor complex
5-HT_3 receptor antagonists Granisetron patch	Blocks serotonin leading to inhibition of vagal afferent nerves in the chemoreceptor trigger zone
NK-1 antagonists Aprepitant, tradipitant/VLY-686	Blocks activation of the Neurokinin-1 receptor inhibiting substance P's involvement in emetic reflex
5-HT_4 receptor agonists Revexepride, Velusetrag, RQ-00000010	Activation of 5-HT_4 receptors releases acetylcholine at the myenteric plexus, leading to increased muscular contractions and accelerated transit
Motilin receptor agonist Camicinal	Activation releases motilin which facilitates cholinergic activity in the antrum and initiates phase III contractions of the migrating motor complex

Figure 3: Degree of Gastric Emptying Delay in Patients Prescribed Opioids[5]

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