Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *Diabetic Gastroparesis*
-May 2018-

Background:

The National Pharmacy & Therapeutics Committee (NPTC) reviewed the pharmacotherapeutic management of gastroparesis at the May 2018 meeting. It was the initial review of the subject matter for the NPTC. Following the clinical review, **no modifications were made to the National Core Formulary.**

Gastroparesis is a syndrome of objectively delayed gastric emptying in absence of obstruction and cardinal symptoms[1-3]. Most patients experience nausea, vomiting, early satiety, postprandial fullness, bloating and upper abdominal pain. Gastroparesis occurs in ~24 of every 100,000 persons, and is more prevalent in women and patients with diabetes[2,3]. Patients with diabetes >10 years or microvascular disease are more likely to experience gastroparesis[3,4]. About 5% of T1DM patients and 1% of T2DM patients are effected[3,5].

Three types of etiologies for gastroparesis exist; idiopathic, diabetic and postsurgical[1,3]. Idiopathic gastroparesis, the most common type, is often seen in young/middle aged women who do not exhibit any underlying signs of abnormality but still have delayed gastric emptying with symptoms usually resolving. Diabetic gastroparesis is the second most common etiology and is the most recognized. Lastly, postsurgical gastroparesis, a result from various types of surgeries, is the least common and symptoms resolve. There are many contributors to delayed gastric emptying which include vagal nerve and enteric nervous system abnormalities, disease-related causes, medications and alterations in glycemic control[1-3]. Medications such as opioids, anticholinergics, tricyclic antidepressants, and GLP-1 receptor agonists, along with acute hyperglycemia, have been linked to delayed gastric emptying[1,3].

Discussion:

The treatment of gastroparesis includes supportive care (nutritional support, glycemic control, antiemetics and analgesics), medication management (prokinetics), gastric electrical stimulation and surgery[1,3,6]. Prokinetic therapy is the mainstay of treatment including medications such as metoclopramide and erythromycin[1,3,6-8]. Long-term management should not include combination therapy, but rather focus on drug holidays or cyclic therapies to minimize drug exposure and extend drug effectiveness.

Medications for gastroparesis all have limited duration of use due to tolerability and severe adverse effects affecting the central nervous (CNS) and cardiovascular systems[1-3,6]. *Metoclopramide, the only FDA approved medication for the treatment of gastroparesis, has a limited use to less than 12 weeks due to CNS effects including tardive dyskinesia*[1,2,3,6-8]. Domperidone, available only in Canada, carries the risk of sudden cardiac death and ventricular arrhythmias and should be used for the shortest duration possible. Erythromycin use is limited to less than four weeks due to risk of QTc prolongation and tachyphylaxis. Drug interactions are common among all agents, especially those who exhibit metabolism through the CYP450 pathway[1-3,6,7]. Many of these interactions are contradictions to use or require dose adjustments. Medications profiles should be closely reviewed prior to beginning any agent and reviewed throughout treatment for adverse effects and appropriate monitoring.

The most recent guidelines for the management of gastroparesis are from the 2013 American College of Gastroenterology. The guidelines recommend using metoclopramide at the lowest effective dose while monitoring for early signs of CNS adverse effects. Domperidone and erythromycin can also be used for metoclopramide failures. The 2018 American Diabetes Association briefly mentions gastroparesis in its most recent guidelines. Emphasis is placed on appropriate diagnosis, supportive care, and withdrawing offending agents prior to beginning medication therapy. In severe cases, metoclopramide is indicated for no longer than five days due to weak levels of evidence regarding its benefits and the risk for serious adverse effects. The 2017 American Association of Clinical Endocrinologists and the American College of Endocrinology do not specifically address the treatment or symptom management of gastroparesis in their most recent guidelines. They do suggest patients taking GLP-1 receptor agonists may experience

delayed gastric emptying and should be monitored. The 2015 NICE Type 2 Diabetes guidelines suggest alternating erythromycin and metoclopramide compared to domperidone, despite domperidone having the greatest effectiveness, due to the increased safety risks of the medication.

Evidence for the use of prokinetics is based on trials from up to three decades ago[1,3,6]. These trials were not designed with large patient populations or daily response outcome measurements. Much of the treatment is based on trial and error and patient reported responses.

The efficacy of metoclopramide for gastroparesis has been assessed in four placebo-controlled trials, two active comparator controlled and open-label studies[1,3,6]. Overall, studies showed symptom improvement and an increase in gastric emptying with use. The majority of patients were insulin-dependent with varying durations of diabetes. No trials were conducted for more than 4 weeks, all had small sample sizes and the majority were open-label. Additionally, most studies did not report adverse effects.

The efficacy of domperidone for gastroparesis has been assessed in five placebo-controlled trials and open-label studies[1,3,6]. Overall, domperidone was effective in improving gastric emptying and improving symptom control. The majority of patients were insulin-dependent with varying durations of diabetes. Most studies focused on adverse effects and one study focused on quality of life improvement. Although many of these studies were of small sample size and short duration, one study did have an extended duration of greater than 1 year in examining symptom severity and frequency, both favoring domperidone.

The efficacy of erythromycin for gastroparesis has been assessed in two placebo-controlled trials and several open-label studies[1,3,6]. Most trials showed improved gastric emptying with erythromycin but many did not assess or find a benefit in symptom improvement. Adverse effects were not mentioned in most studies and all were of short duration. The majority of patients were insulin-dependent with varying durations of diabetes. Other macrolides, such as azithromycin and clarithromycin, accelerate gastric emptying however there were no randomized controlled trials comparing these drugs with placebo or other drugs. If used, consider the potential for tachyphylaxis, cardiac risk and antibiotic resistance.

A double blind, multicenter, randomized controlled trial examining domperidone compared to metoclopramide for diabetic gastroparesis showed that both domperidone (38.9%) and metoclopramide (41.1%) reduced symptom scores but these were not significant[1,3]. Additionally, metoclopramide showed greater incidence and severity of adverse effects, specifically to the CNS, and higher rates of treatment discontinuation. A single blind, cross over study of metoclopramide vs. erythromycin for diabetic gastroparesis showed that both agents had significant reductions in symptom scores[1,3]. Both the half-life and meal retention at 60 and 90 minutes had significant improvements compared to baseline but did not differ significantly between treatment groups.

Findings/Conclusions:

Gastroparesis is a syndrome of delayed gastric emptying that most commonly affects females and those with diabetes. Clinical guidelines recommend the short-term use of prokinetics, with metoclopramide the only FDA approved treatment, in addition to symptom control and supportive care. Evidence for treatment is several decades old and provides little guidance on favorable or effective treatment options. Side effect profiles of medications should be considered, as many medications warrant discontinuation or dose adjustments due to adverse effects. New treatments are under development but not approved by FDA.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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