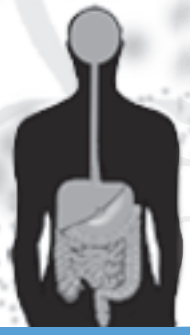
Spring 2015

A publication of the University of North Carolina Center for Functional GI & Motility Disorders

Digest

Our mission is to advance the biopsychosocial understanding and care of patients with functional GI & motility disorders through research, training and education.

IN THIS ISSUE:



State of the Science Article Review on Fecal Incontinence From the NIDDK: Prevalence and Origins of FI

In August 2013, international experts on fecal incontinence (FI) came together at the National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] "Developing a Clinical Research Agenda for Fecal Incontinence." Since then, Dr. William Whitehead has collaborated with several physicians, surgeons, and expert faculty in the field of fecal incontinence and pelvic floor disorders to assist in writing two articles; one discussing the epidemiology, pathophysiology, and classification of FI [1] and the second discussing treatment options for fecal incontinence.[2] The lead author of the first article was Adil Bharucha, MD, of the Mayo Clinic in Rochester, MD.

Anatomy of a Bowel Movement

There are many physiological features in our body that help us stay continent of stool. The three major muscles involved in keeping both men and women continent of stool are the internal anal sphincter, external anal sphincter, and the puborectalis muscle. The internal anal sphincter is made up of involuntary smooth muscle and is responsible for a majority of the muscle strength to hold back stool. The external anal sphincter is made up of voluntary striated muscle and is responsible for the remaining muscle strength needed to hold back stool. This is the muscle you squeeze when actively trying to hold back a bowel movement. The third muscle used to stay continent is the puborectalis muscle. This muscle is shaped like the letter "U" and supports the rectum. When resting, the puboretalis muscle holds constant tension on the rectum to prevent stool from "sliding" down. This muscle is voluntarily controlled and can be further contracted to hold back stool or it can be relaxed, along with the external anal sphincter, to have a bowel movement.

What can cause FI?

There is no one reason why an individual develops FI, but several factors can increase the risk for developing it. Several independent risk factors include diarrhea, cholecystectomy (gall bladder removal), current smokers, rectocele, stress urinary incontinence, increased body mass index, advanced age, increased number of comorbid diseases, obstetrical injury or surgery that damaged the anal sphincter, and decreased physical activity.[1] Diarrhea and constipation are the risk factors that are easiest for patients to modify. African American women have lower rates of FI than white women and African American men have equal rates as white men. [7, 8] Individuals that reported the highest rates of FI are those with chronic illness, those receiving care in their homes, and those in long-term care facilities.[6].

Obstetrical trauma and advanced age are singled out in the State of the Science paper as they are identified as significant risk factors for FI. Pregnancy or labor were not identified as factors that increased risks, but 3rd degree (injury to the external anal sphincter) and 4th degree

Continued on Page 14

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DIGEST is a quarterly publication of the UNC Center for Functional GI & Motility Disorders, a center of excellence within the Division of Gastroenterology and Hepatology, School of Medicine, University of North Carolina at Chapel Hill.

The Center's director is **William E. Whitehead, PhD**, Professor of Medicine and Gynecology.

Over the past decade, the UNC Center for Functional GI and Motility Disorders has enjoyed significant grant support from a number of private foundations and corporations. These grants have ranged from sponsorships of specific events (symposia or CME courses) to unrestricted grants in support of fellowships and the Center's education and training effort. Support for the Digest Newsletter is provided by Takeda Pharmaceuticals North America, Inc.

Thank you for your support!

We would like to extend our gratitude to those who have donated to the UNC Center.
If you would like to donate to the Center, please see page 18 and we will recognize your contribution in the next edition of the Digest.

Donations

Trisha Bundy donated to support gastroparesis awareness.

DIGEST

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Digestive Disease Week: Accepted Publications and Presentations

DDW 2015

Center faculty and investigators will be well represented in presentations and posters at Digestive Diseases Week 2015
May 16 - 19, located in Washington D.C.

DDW is the premier research and clinical forum for scientists and clinicians within digestive diseases which includes gastroenterology, liver disease and gastrointestinal surgery. The American Gastroenterology Association (AGA) represents gastroenterologists. The UNC Center plays an important role that is spanning this decade in developing programs that focus on research and education for those with functional gastrointestinal disorders.

Saturday, May 16

Abstract Title: Cytokine activation is associated with psychological distress, motility and visceral hypersensitivity in Irritable Bowel Syndrome (IBS)
Session Title: Neuro-Immune Interactions and ENS Disorders
Session Type: Research Forum
Authors: Miranda A. van Tilburg, Olafur S. Palsson, Motoyori Kanazawa, David A. Barrow, William E. Whitehead
Time: 2:30PM EST
Location: 156 (WCC)

Monday, May 18

Abstract Title: Constipation, Pain and Laxatives Panel Discussion
Session Title: Motility Matters: An Interactive Forum to Debate What Progress the Field Has Made
Session Type: Clinical Symposium
Authors: Carlo Di Lorenzo, William E. Whitehead, Klaus Bielefeldt
Time: 10:30AM EST
Location: 143 (WCC)

Tuesday, May 19

Abstract Title: Visceral Hypersensitivity is an Important Etiological Factor in the Presence and Severity of Abdominal Bloating Symptoms in Patients with Irritable Bowel Syndrome (IBS)
Session Title: Sensory Neurobiology
Session Type: Research Forum
Authors: Yehuda Ringel, Olafur S. Palsson, Tamar Ringel-Kulka, William E. Whitehead
Time: 2:15PM EST
Location: 158 (WCC)

Sunday, May 17

Abstract Title: Results of a large RCT testing the effect of Cognitive Behavior Therapy on school absences, quality of life and flares in pediatric IBD
Session Title: Pediatric IBD: Clinical and Translational Studies
Session Type: Research Forum
Authors: Rona Levy, Shelby L. Langer, Joan Romano, Lloyd A. Mancl, Tasha Murphy, Lynn S. Walker, Miranda A. van Tilburg, Melissa M. DuPen, Shara I. Feld, Bisher Abdullah, William E. Whitehead
Time: 10:00AM EST
Location: 145A (WCC)

Monday, May 18

Abstract Title: Constipation, Pain and Laxatives Panel Discussion
Session Title: Motility Matters: An Interactive Forum to Debate What Progress the Field Has Made
Session Type: Clinical Symposium
Authors: William E. Whitehead
Time: 11:00AM EST
Location: 143 (WCC)

Saturday, May 16

Abstract Title: Men Report More Severe Fecal Incontinence Symptoms than Women: Patients' Perspective
Session Title: Anorectal Dysmotility
Session Type: Poster Session
Authors: Sarina Pasricha, Steve Heymen, Olafur S. Palsson, William E. Whitehead
Time: 9:30AM EST
Location: Hall C (WCC)

Saturday, May 16

Abstract Title: Fecal Incontinence Severity Index Helps to Identify Patients who View Their Symptoms as Severe Enough to Consult a Physician
Session Title: Anorectal Dysmotility
Session Type: Poster Session
Authors: Steve Heymen, Olafur S. Palsson, Sarina Pasricha, William E. Whitehead
Time: 9:30AM EST
Location: Hall C (WCC)

Saturday, May 16

Abstract Title: Fecal Incontinence is Associated with Clinically Significant Psychological Distress
Session Title: Anorectal Dysmotility
Session Type: Poster Session
Authors: Olafur S. Palsson, Steve Heymen, William E. Whitehead
Time: 9:30AM EST
Location: Hall C (WCC)

Saturday, May 16

Abstract Title: What Makes Discussing Fecal Incontinence (FI) with Providers Difficult?
Session Title: Anorectal Dysmotility
Session Type: Poster Session
Authors: Steve Heymen, Olafur S. Palsson, William E. Whitehead
Time: 9:30AM EST
Location: Hall C (WCC)

Sunday, May 17

Abstract Title: Responses of the Guinea Pig Enteric Nervous System to Blood Serum Collected from Patients with the Irritable Bowel Syndrome
Session Title: Irritable Bowel Syndrome: Pathophysiology
Session Type: Poster Session
Authors: Jackie D. Wood, Guo-Du Wang, Xi-Yu Wang, William E. Whitehead
Time: 9:30AM EST
Location: Hall C (WCC)

Monday, May 18

Abstract Title: Decreased concentration of whole blood serotonin in IBS with diarrhea
Session Title: Irritable Bowel Syndrome: Pathophysiology
Session Type: Poster Session
Authors: Motoyori Kanazawa, Olafur S. Palsson, Miranda A. van Tilburg, Lisa M. Gangarosa, Shin Fukudo, William E. Whitehead
Time: 9:30AM EST
Location: Hall C (WCC)

Monday, May 18

Abstract Title: Non-gastrointestinal Pain is Increased in Irritable Bowel Syndrome (IBS) but Does Not Account for Abdominal Pain
Session Title: Irritable Bowel Syndrome: Pathophysiolog
Session Type: Poster Session
Authors: Olafur S. Palsson, Steve Heymen, William E. Whitehead
Time: 9:30AM EST
Location: Hall C (WCC)

Monday, May 18

Abstract Title: The feasibility and acceptability of esophageal-directed hypnotherapy for functional heartburn
Session Title: GERD: Innovative and Pharmacologic Therapies
Session Type: Poster Session
Authors: Megan E. Riehl, John E. Pandolfino, Olafur S. Palsson, Laurie Keefer
Time: 9:30AM EST
Location: Hall C (WCC)

Monday, May 18

Abstract Title: Validating a Rome III Infant/Toddler Questionnaire
Session Title: Pediatric Functional and Motility Disorders
Session Type: Poster Session
Authors: Miranda A. van Tilburg, Audra Rouster, David Silver, Gerard Pellegrini, John Gao, Paul E. Hyman
Time: 9:30AM EST
Location: Hall C (WCC)

Monday, May 18

Abstract Title: Efficacy of ONO-2952, a Novel and Selective Antagonist of Translocator Protein: Results of a Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Phase II Study (RESTORE-4)
Session Title: Irritable Bowel Syndrome: Clinical
Session Type: Poster Session
Authors: William E. Whitehead, Toshiya Nabata, Kevin Duffy, John Sharpe, Mark Bruce
Time: 9:30AM EST
Location: Hall C (WCC)

State of the Science Article Review on Fecal Incontinence From the NIDDK: Treatment options and the future of FI research

In August 2013, international experts on fecal incontinence (FI) came together at the National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] for a workshop entitled "Developing a Clinical Research Agenda for Fecal Incontinence." Since then, Dr. William Whitehead has collaborated with several physicians, surgeons, and expert faculty in the field of fecal incontinence and pelvic floor disorders to assist in writing this article discussing treatment options for fecal incontinence.[2] This article is intended to present a consolidated overview of their findings.

Management and Care for FI

Approximately 70% of patients who have FI do not consult their physicians about the problem and use protective pads or protective underwear as well as diet modification to self-manage the condition. [2,3] For those who do seek care, the most common initial treatments are conservative. Examples include dietary supplements to regulate stool consistency, prescribed medications, education for patients on the physiological reasons why they are experiencing FI, suggestions regarding changes in the patient's behavior or routine to prevent an accident, and exercises the patients can do outside the physician's office to strengthen the anal sphincter and puborectalis muscles.[2] If the patient does not respond to conservative treatment, the next level of treatment options includes biofeedback, electrical stimulation, surgical interventions, bulking agents, and non-surgical devices. If a patient continues to fail the prescribed treatments, other surgical interventions include sphincteroplasty, injectable bulking agents around the anal canal, and implanted devices.

Dietary Supplements and Medications

Dietary supplements and medications are intended to make the stool either softer or firmer, depending on if the patient has constipation or diarrhea. An individual who is constipated may not think that the condition can increase risks for incontinence, but in some cases it can – especially in geriatric populations. Overflow incontinence is caused when an individual has a fecal impaction (large amount of stool in the rectum). This dilates the anal sphincter and allows loose stool to seep out.

For patients with constipation, using laxatives, enemas, and suppositories may help patients soften their stools for easier defecation. Patients with diarrhea may find increasing dietary fiber, fiber supplements, and anti-diarrheal medication may help to create a firmer stool consistency. [2] Patients should always consult their physician when adding a new medication, herb, or supplement to ensure it will not adversely interact with any other medications.

Behavioral Changes, Education, and Exercises

Behavioral changes can be recommended by the provider to help reduce the risk of having an accident. These include pelvic floor exercises to strengthen the muscles, squeezing the sphincter muscles prior to exertion, attempting to not squeeze abdominal muscles while trying to hold back a bowel movement, and setting a toileting schedule to minimize sudden urgency accidents. A toileting schedule involves an individual setting up a routine to attempt to have a bowel movement at specific times each day. Conservative treatment of FI, which usually includes a combination of patient education about the physiology of continence and defecation, pelvic floor exercises to improve muscle strength, and fiber supplements or medications to normalize stool consistency, can be expected to reduce the frequency of FI by about 50-60%. However, only about one in five patients achieves continence with conservative treatments alone.

Biofeedback

Biofeedback is an educational technique which is used to teach patients with FI how to contract their pelvic floor muscles without simultaneously contracting their abdominal wall muscles or their gluteal (butt) muscles. Using these other muscles increases the risk of an accident. Biofeedback is also used to help patients learn to recognize the sensation of gas or stool in the rectum and squeeze their pelvic floor muscles when this sensation occurs. This sensory training is designed for patients with neurological injuries that have caused decreased ability to sense rectal fullness. A third type of biofeedback is used to help patients who have FI following strong contractions of their rectum that overwhelm their ability to hold back a bowel movement. This training involves desensitizing them to distention of the rectum with a balloon. Biofeedback training requires specialized equipment that measures pressures in the anal canal or rectum. It usually involves 5-6 one-hour sessions in the clinic with a nurse or physical therapist who acts as a coach. The success of biofeedback depends on the skill of the nurse or physical therapist who does the training, but in the best studies, at least 75% of the patients report substantial improvement and 50% report a cure.

Electrical Stimulation

When used as the primary treatment, eletrical stimulation of the anal canal is not very beneficial.[1,2] However, combining electrical stimulation with biofeedback was reported by one investigator to be effective if the patient practices daily at home for 3-6 months.[8] Further studies of this approach are needed. Sacral nerve stimulation is a surgical procedure where an electrode is implanted next to the sacral nerve. The purpose of this procedure

is to stimulate the nerves for the external anal sphincter and cause the muscles to contract. The intervention is completed in 2 steps. The first step is a temporary testing phase to ensure that the electrode is placed in the correct location and that the patient has a reduction of at least 50% of FI episodes. If the testing phase yields positive results, the surgeon will permanently implant the device under the skin. Sacral nerve stimulation produces long-term reductions in about 75% of patients and continence in 40%. Tibial nerve stimulation can be delivered through a needle inserted near the nerve or by a metal plate taped to the skin over the nerve to elicit contraction of the sphincter muscle. However, tibial nerve stimulation was not as successful as sacral nerve stimulation at reducing FI episodes.[2]

Other Surgical Interventions

There are multiple surgical interventions available to patients who do not find adequate relief from the previously mentioned treatments. Sphincteroplasty is performed by overlapping or putting end to end the torn sphincter muscles and sewing them together. If the physician notices a tear affecting the anal sphincter directly after childbirth, a sphincteroplasty can be performed fairly quickly after delivery. However, if undetected during delivery, any problems associated with tears in the muscle could go unnoticed and untreated until FI episodes begin later in life.[2] Roughly 67% of patients who had a sphincteroplasty reported a short term outcome of "good" or "excellent" outcomes but that was reduced to 51% after 5 years.[5,6] Treatment with radiofrequency lesions causes scar tissue to build up on the area between the rectum and anus to bulk up the muscle, thereby creating a smaller passage and increased resistance for stool to pass through. [2]

Bulking Agents

An inactive substance may be injected in multiple areas around the anal canal with the aim of reinforcing the resting muscle tone and resistance to stool passing. There are multiple agents that can be used as a bulking agent including silicone elastomers, carbon-coated zirconium beads, ceramic beads, and dextranomer microspheres. [2,9] A multicenter study conducted with dextranomer involved 136 patients and found that 52.2% met the milestone of reducing episodes by ≥50% at month 6, 57.4% at month 12, and 52.2% at month 36. [12] The same study also reported 100% reduction of FI episodes of 5.9% month 6, 11.0% at month 12, and 13.2% at month 36.

Additional surgical interventions include the artificial bowel sphincters in which an inflatable ring is implanted around the anal canal that can be inflated by a hand pump to hold back stool or deflated to have a bowel movement. Magnetic beads could also be implanted around the anal canal to increases resistance to stool. When an individual pushes or strains to have a bowel movement, the beads separate and the individual can have a bowel movement.

Devices used outside the body include anal plugs and vaginally inserted device. The vaginal device is a balloon that can be inflated and deflated and pushes against the back of the vagina to depress on the rectum. This decreased the space in the rectum and increases resistance for stool to pass.[2]

Regenerative Medicine

The science of growing new tissues is constantly evolving and new discoveries are made each year. Stem cells have been used to grow new smooth muscle and there is possible uses to recreate or improve a damaged internal anal sphincter.[11] There has also been innovations that involve the harvesting cells from the anal canal and intestine. These cells go through a bioengineering process and are then transplanted back into the area around the anus. In animal models, the new tissue was able to incorporate fully back into the animal, establish new blood flow, and function similar to healthy tissue.[10]

1. Bharucha AE, Dunivan G, Goode PS, Lukacz ES, Markland AD, Matthews CA, Mott L, Rogers RG, Zinsmeister AR, Whitehead WE, Rao SSC, Hamilton RA. Epidemiology, Pathophysiology, and Classification of Fecal Incontinence: State of the Science Summary for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Workshop. Am J Gastroenterol. 2015: 110; 127-136.
2. Whitehead WE, Rao SSC, Lowry A, Nagle D, Varma M, Bitar KN, Bharucha AE, Hamilton FA. Treatment of Fecal Incontinence: State of the Science Summary for the National Institute of Diabetes and Digestive and Kidney Diseases Workshop. Am J Gastroenterol. 2015: 110; 138-146.
3. Johanson JF, Lafferty J. Epidemiology of fecal incontinence: the silent affliction. Am J Gastroenterol. 1996: 91;33-6.
4. Yu SWB, Rao SSC. Anorectal physiology and pathophysiology in the elderly. 2014: 30(1); 95-106
5. Madoff RD. Surgical treatment options for fecal incontinence. Gastroenterology. 2004: 126; S48-S54.
6. Glasgow SC, Lowry AC. Long-term outcomes of anal sphincter repair for fecal incontinence: a systematic review. Dis Colon Rectum. 2012: 55; 482-90.
7. Abbas MA, Tam MS, Chun LJ.
8. Norton C, Gibbs A, Kamm MA. Randomized, controlled trial of anal electroical stimulation for fecal incontinence. Dis Colon Rectum. 2006 49; 190-6.
9. Hussain ZI, Lim M, Stojkovic SG. Systematic review of perianal implants in the treatment of faecal incontinence. Br J Surg. 2011: 98; 1526-36.
10. Reghaven S, Miyasska EA, Gilmont RR, et al. Perianal implantation of bioengineered human internal anal sphincter constructs intrinsically innervated with human neural progenitor cells. Surger: 2014: 155; 668-74.
11. Singh J, Rattan S. Bioengineered human IAS reconstructs with functional and molecular properties similar to intact IAS. AM J Physiol Gastrointest Liver Physiol. 2012: 303; F713-G722.
12. Mellgren A1, Matzel KE, Pollack J, Hull T, Bernstein M, Graf W; Nasha Dx Study Group. Long-term efficacy of NASHA Dx injection therapy for treatment of fecal incontinence. Neurogastroenterol Motil. 2014 Aug;26(8):1087-94

Gastroparesis: An Update for Patients and their Doctors
Kenneth L. Koch, MD

Dr. Kenneth Koch, MD is a Professor of Internal Medicine and Section Chief in Gastroenterology at Wake Forest School of Medicine in Winston-Salem, North Carolina. Dr. Koch specializes in GI motility disorders, particularly gastroparesis, gastric dysrhythmias, and unexplained nausea and vomiting.

Introduction

Gastroparesis is defined as delayed gastric emptying of a standard test meal in the absence of mechanical obstruction. The symptoms typically associated with gastroparesis are early satiety, prolonged fullness, abdominal discomfort, nausea, and vomiting (1). These symptoms are common and are reported in other disorders such as gastroesophageal reflux disease, chronic cholecystitis, small bowel bacterial overgrowth, postprandial distress syndrome, dyspepsia, and irritable bowel syndrome. Thus, the assessment of symptoms associated with gastroparesis and the treatment of gastroparesis can become difficult for patients and their doctors.

In this review, new information regarding the pathophysiology of gastroparesis will be described, information that is leading to a better understanding of gastroparesis. There are two causes of gastroparesis that are reversible, and these will be described in detail. Few medications are available to treat the symptoms associated with gastroparesis, but several pharmaceutical companies are dedicated to bringing their compounds through the FDA for patients with this noxious and debilitating disease, gastroparesis.

How does the normal stomach work?

The stomach is a muscle, an extremely complicated muscle that has a pacemaker and a nervous system. Stomach smooth muscle, nerves, and pacemaker rhythms must work in harmony to receive the food we eat, then mix the food into the proper consistency (a milling process), and carefully empty the milled food into the duodenum and small intestine (2).

Receiving

As food enters the stomach from the esophagus, gastric relaxation or accommodation of the volume of food must occur. During this "reception" of food, the stomach changes from a contracted state during fasting to a relaxation state to accommodate the volume of food that is ingested. Relaxation of the upper part of the stomach called the fundus requires nitric oxide, a neurotransmitter that relaxes the smooth muscle.

Milling (Grinding)

The body and antrum of the stomach produce very gentle rhythmic contractions that form peristaltic, moving pressure waves that gently break down the ingested solid foods (Figure 1). The foods are milled with gastric acid by the peristaltic waves into particles that are one to two millimeters (about 1/16 of an inch) in diameter. This milling of the ingested food results in chyme, the term for the fine food particles in gastric juice. Chyme is the suspension of milled nutrients that is ready for gastric emptying.

Emptying

Gastric emptying occurs when peristaltic waves roll towards the pylorus and empty chyme into the duodenum. The pylorus is a valve or sphincter that regulates the outflow volume of chyme from the stomach. This important function of the pylorus must be coordinated. That is, the pyloric sphincter remains open to some degree as the peristaltic wave approaches in order that a small volume of chyme can be emptied in a highly controlled fashion into the duodenum and small bowel.

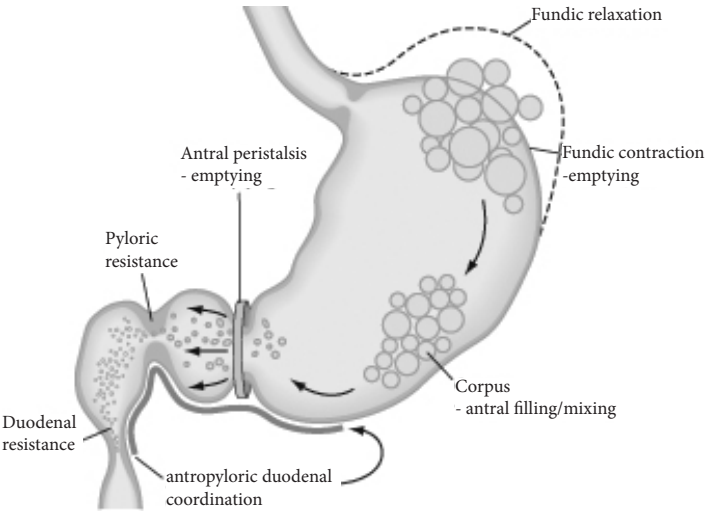

Figure 1. Work of the stomach after a solid meal is ingested. Note that there is fundic relaxation, milling and mixing of the corpus and antral areas of the stomach, peristalsis in the antrum that also results in the emptying of small particles of food to the pylorus and into the duodenum. The pylorus offers resistance to the flow of the gastric contents and helps to regulate the rate of gastric emptying. (Modified from Ref 2.)

The coordinated peristaltic contractions occur in the stomach because they are electrically paced. The stomach has an electrical rhythm (a pacemaker) that paces the peristaltic waves described above, much like the heart has a paced rhythm for normal cardiac function. In the human stomach, the normal pacemaker rhythm is 3 cycles per minute (cpm) (Figure 2). The 3 cpm rhythm originates from specialized

cells in the stomach wall termed the interstitial cells of Cajal or ICCs. The ICCs impart their pacemaker frequency onto the smooth muscle cells of the stomach, which do the work of mixing and emptying described above. The ICCs and the smooth muscle are also influenced by nerves in the stomach itself. These nerves are nerves of the enteric nervous system, the nervous system within the GI tract. These enteric nerves cause contraction or relaxation of the smooth muscle to mill

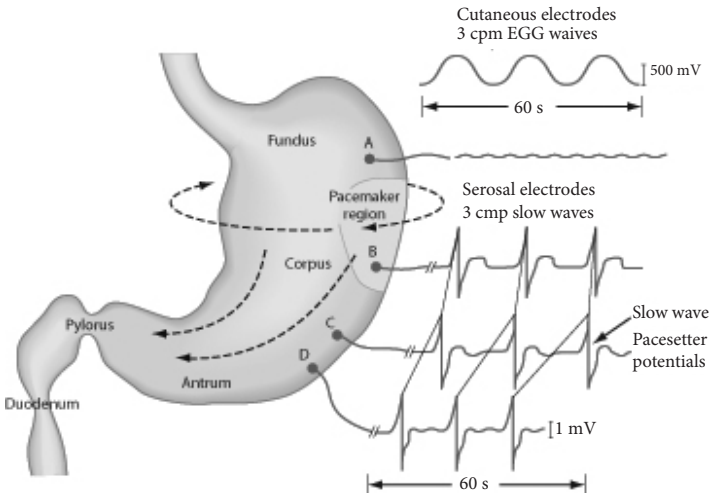

Figure 2. Electrical control of stomach work functions. The stomach has a pacemaker region between the fundus and the corpus areas shown on the greater curvature of the stomach. Electrodes recording electrical activity are illustrated to record the gastric slow waves or pacesetter potentials. The normal pacesetter potential is 3 cycles per minute. The fundus does not have these electrical slow waves. The slow waves coordinate the regular 3 cpm peristalsis required for gastric emptying. (Modified from Ref 2.)

and empty the various foods we ingest. The stomach is also controlled by the autonomic nervous system, a level of control that will not be discussed in this review.

Finally, when the stomach's nerve and muscle and pacemaker components are all performing in harmony, the ingestion of food "feels good." In fact, it feels beyond good. There is pleasure associated with the comfortable feelings during and after a meal, a pleasure that is increased further when food is ingested in the company of family and good friends.

What happens in gastroparesis?

In gastroparesis, everything described above can go wrong!

What happens in gastroparesis?

In gastroparesis, everything described above can go wrong!

Receiving

In gastroparesis, the stomach does not relax normally to receive and accommodate the ingested food. Thus, after a very small amount of food many patients feel extremely full and cannot finish even half of a sandwich, a symptom termed early satiety. The normal 3 cpm pacemaker rhythm may be replaced in many cases by electrical dysrhythmias or gastric dysrhythmias termed tachygastrias, and bradygastrias, and mixed dysrhythmias, and various conduction defects (3). In the setting of dysrhythmias, there is often a sense of nausea (4).

Milling

In the presence of dysrhythmias, the body and antrum of the stomach cannot regularly produce rhythmic 3 per minute peristaltic waves. The normal 3 cpm rhythm is replaced by dysrhythmias. Thus, the efficiency of gastric contractions and emptying are decreased. The presence of dysrhythmias reflects the depletion of ICCs, the pacemaker cells (4, 5).

Emptying

The severity of the delay in gastric emptying is quite variable. In the Gastroparesis Consortium, severe gastroparesis is defined as greater than 35 percent of a test meal (Egg Beaters® sandwich) remaining after four hours of gastric work (6). On the other hand, mild gastroparesis is considered 10 to 20 percent of the meal remaining after four hours. (Normal emptying is defined as 0 to 9 percent of the test meal remaining in the stomach after 4 hours.) In a minority of patients with gastroparesis, the main abnormality in gastroparesis is the dysfunction of the pylorus. The pylorus may go into spasm or inappropriately close during a peristaltic wave, resulting in delayed gastric emptying (7, 8).

After ingesting a meal the patient with gastroparesis oftentimes feels nausea and fullness for hours. Twenty percent of patients have abdominal pain as their primary symptom (6). In severe cases, recurrent vomiting occurs. The vomitus typically contains chewed food because the muscle work of the stomach is weak and the milling function can no longer be performed. In some cases, dehydration and weight loss occurs and requires emergency department visits for fluids or admission to the hospital for supplemental nutrition with enteral feedings.

Thus, patients with gastroparesis feel bad after ingesting food in contrast to the comfortable sensations described above for the healthy stomach. The symptoms associated with gastroparesis, such as early satiety, prolonged fullness, abdominal discomfort, nausea, and vomiting, are worse after eating. The symptoms are also depressing and difficult to treat. Loss of the social aspects of dining also becomes onerous, and patients frequently feel depressed about the situation and often say "I want my life back."

What is new about the causes of gastroparesis?

Studies from the Gastroparesis Clinical Research Consortium indicate that the major abnormality in gastroparesis is depletion of the ICCs in the stomach wall (5). Patients with gastroparesis have less than five ICCs per high-power field (3, 5). If less than 5 ICCs are present, then gastric dysrhythmias are usually present and the normal 3 cpm rhythm is decreased. If greater than 5 ICCs per high-power field are present, then the normal 3 cpm rhythm is recorded more frequently. The second abnormality is in the neurons of the enteric nervous system (5). The neurons are deformed or missing processes. These neural abnormalities are worse in patients with idiopathic gastroparesis compared with diabetic gastroparesis. Finally, there is an inflammatory infiltrate located around the enteric neurons and ICCs that

are harmful to the numbers and functions of the ICCs and neurons in the stomach wall (5).

Thus, abnormalities of the ICCs and nerves of the stomach wall result in gastric dysrhythmias that reduce the efficiency of gastric peristalsis and result in delayed gastric emptying to variable degrees. The loss of ICCs and neurons may also play a role in the inability of the stomach to relax and accommodate meals, contributing to the symptoms described above.

What if I have the diagnosis of gastroparesis?

There are actually six different forms of gastroparesis, at least by general categories (2). Each patient should know what sort of gastroparesis he or she has. Six types of gastroparesis are listed in Table 1. Two types of gastroparesis are reversible and should be considered. The first is gastroparesis due to obstruction at the pylorus or duodenum (9). Obstruction can be due to either mechanical or neuromuscular abnormalities of the pylorus. Mechanical obstruction of the stomach means that scar tissue, perhaps from chronic ulcer disease, for example, has formed at the pylorus and created an obstruction to outflow of the chyme. Cancers of the stomach or duodenum can also cause obstructive gastroparesis. Rarely, this outflow obstruction can be due to a cancer that is located in the duodenum just beyond the pylorus. These diseases that cause mechanical obstruction can be excluded by endoscopy or abdominal CT scan.

Table 1. Six types of gastroparesis and frequency

1.	Diabetic gastroparesis (type 1 and 2)	30%
2.	Idiopathic gastroparesis*	40%
3.	Postsurgical gastroparesis (antrectomy, vagotomy, fundectomy, fundoplication)	20%
4.	Obstructive gastroparesis (pyloric dysfunction-mechanical or spasm)	10%
5.	Ischemic gastroparesis	<1%
6.	Miscellaneous causes	<1%

** post-viral; drug induced; degenerative or inflammatory processes of enteric nerves, interstitial cells of Cajal, and smooth muscle.*

The other type of pyloric obstruction of the stomach is due to spasm or poor coordination of the pylorus during gastric emptying (7, 8). Pyloric dysfunction has been described in idiopathic and in diabetic gastroparesis. In these gastroparesis patients, the normal 3 cpm electrical activity was recorded with the electrogastrogram (EGG), an electrical recording of the stomach like an EKG recording for the heart. The finding of normal 3 cpm EGG activity is surprising in gastroparesis and indicates that the numbers of ICCs are normal—yet gastric emptying is delayed. These two findings (normal 3 cpm electrical rhythm and gastroparesis) define a subset of gastroparesis wherein the delayed emptying is actually due to pyloric neuromuscular dysfunction. In these patients, balloon dilation of the pylorus, botulinum toxin A injection of the pylorus, and even pyloroplasty may be appropriate treatments for this subtype of obstructive gastroparesis (10).

A rare but reversible form of gastroparesis is due to decreased blood flow to the stomach due to narrowing of the celiac and superior mesenteric arteries, the arteries that provide blood to the stomach and intestine. Bypassing or stenting the narrowed arteries result in improved symptoms and better gastric emptying (11).

A common cause of the non-reversible gastroparesis types is diabetes. Long-standing type 1 or type 2 diabetes may result in the damage to the enteric nerves and loss of the ICCs which results in gastroparesis (3). Operations on the stomach may cause gastroparesis. Whenever part of the stomach is operated upon or removed, such as removal of the body or antrum or fundus or cutting the vagus nerve, the result may be delayed gastric emptying. Gastroparesis may also occur in uncommon diseases such as muscular dystrophy, lupus, and amyloidosis. The largest category of gastroparesis is idiopathic gastroparesis which means we do not know the cause of the gastroparesis (6). Many patients with idiopathic gastroparesis have suffered a severe viral-like gastroenteritis and months later develop chronic symptoms associated with gastroparesis. It is possible the inflammatory response to the virus results in damage to the ICCs and neurons of the stomach and leads to gastroparesis.

How is gastroparesis diagnosed?

The standard test for gastroparesis is a nuclear medicine test. A radioactive isotope is mixed with Egg Beaters® to make an easy-to-eat egg sandwich test meal (12). The patient ingests the sandwich and a picture of the stomach is obtained for one minute each hour for four hours to determine the rate of food emptying. The wireless capsule motility device is a capsule with an acid and pressure sensor. The capsule is ingested with a test meal and a recorder device receives sensor data for five to seven days. Gastric emptying time, as well as the small bowel and colon transit times, can be determined (13). A breath test to measure gastric emptying rates was approved by the FDA in April 2015.

The electrogastrogram or EGG test is much like the EKG test of the heart, but the electrodes are placed on the abdominal surface. After a baseline recording, the patient is asked to drink water over a five-minute period until completely full. The stomach electrical rhythm is recorded for an additional 30 minutes and analyzed to determine if the normal 3 cpm rhythm is present or if there is an abnormal rhythm such as tachygastria or bradygastria or mixed dysrhythmia (14). The volume of water ingested is recorded and reflects the accommodation or capacity of the stomach. On the basis of the gastric emptying and the electrical rhythm results, two categories of gastroparesis can be determined: gastroparesis with gastric dysrhythmia and gastroparesis with normal 3 cpm electrical activity (Figure 3).

What are the current treatments for gastroparesis?

Diet

Proper treatment begins with a credible diagnosis based on carefully performed stomach diagnostic tests and exclusion of or treatment of other diseases (e.g. chronic cholecystitis

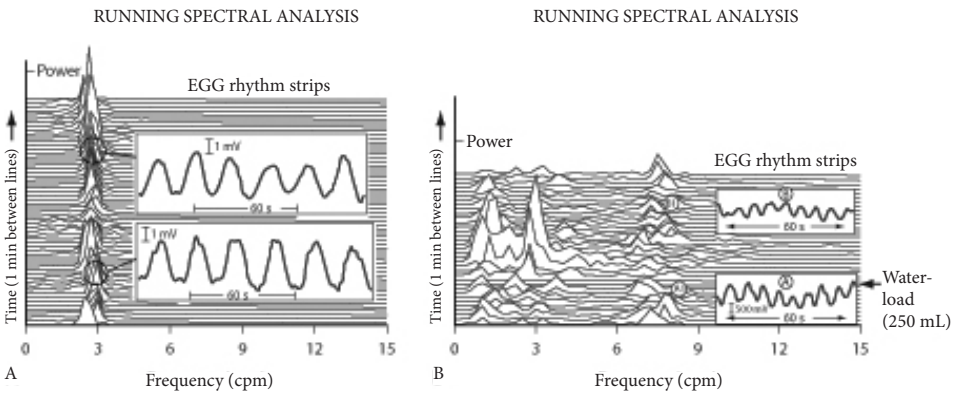

Figure 3. Panel A shows the electrical rhythm in a patient with gastroparesis due to obstruction at the pylorus. Note the normal but high amplitude 3 cpm rhythm. Panel B shows little or normal 3 cpm peaks, but a variety of rhythms in the tachygastria range from 4 to 9 cpm are present. This patient also had gastroparesis but secondary to loss of interstitial cells of Cajal and enteric neurons. (Modified from Ref 2.)

or GERD). Treatment of gastroparesis should begin with extensive dietary counseling. Many patients choose foods that they are accustomed to eating, but foods that are in fact very difficult for the weakened stomach muscle to mill and empty. For example, patients with diabetes are well trained to consume many types of salads. However, lettuce and carrots and other fresh vegetables are extremely difficult for the weak stomach to mill and empty. Therefore, postprandial symptoms are often worsened by some dietary choices. Very few patients with gastroparesis have been referred to a dietician to review the gastroparesis diet (2).

Table 2 lists a gastroparesis diet that has been used for many years (2). Many patients intuitively make changes towards the types of foods listed in Table 2 because these foods are easy for the weakened stomach to mill and empty. These foods are organized into three steps so patients can manage diet changes moving through Steps 1 – 3 throughout their day. Patients make selections depending on how they feel in terms of nausea and fullness.

Step 1 is basically electrolytes in liquids. These liquids are consumed to avoid dehydration on a bad day. Step 2 advances to liquid nutrition. Any calories in a liquid form, such as light soups or thin smoothies, may be better tolerated by the patient with gastroparesis because very little milling is required before emptying the nutrient. Step 3 emphasizes starches, chicken, and fish. Starches are the easiest food to mill (mashed potatoes, for example) when compared with red meats or fatty or fried foods which have increased calorie density and delay gastric emptying. Attention to the types of foods that are ingested not only can improve symptoms after eating but also help maintain nutrition and weight. Because this is a low-protein and low-fat diet, it is not a complete diet. A chewable daily vitamin should also be taken.

Drugs

Few drugs are available to treat gastroparesis in 2015 (1, 2, 11). The only approved drug is metoclopramide (Reglan). While Reglan increases gastric emptying and helps nausea and depression, prolonged use may lead to important side effects like Parkinson's-like symptoms and tardive dyskinesia (uncontrolled tongue movements). Erythromycin is an antibiotic that stimulates strong antral contractions and may be used for patients with gastroparesis. An FDA program is available to obtain domperidone, a drug that is effective for the nausea and early satiety of gastroparesis. The drug is not approved in the United States and thus requires this FDA program.

Table 2. Diet for Nausea and Vomiting in Patients with Gastroparesis

Step 1: Sports Drinks and Bouillon		
DIET	GOAL	AVOID
For severe nausea and vomiting: Small volumes of salty liquids, with some caloric content to avoid volume depletion; Chewable multiple vitamin	1000-1500 mL/day in multiple servings (e.g., 12, 120-mL servings over 12-14 hr); Patient can sip 30-60 mL at a time to reach approximately 120 mL/hr	Citrus drinks of all kinds; highly sweetened drinks
Step 2: Soups and Smoothies		
If Step 1 is tolerated: Soup with noodles or rice and crackers Smoothies with low fat dairy; Peanut butter, cheese, and crackers in small amounts; Caramels or other chewy confection; Ingest above foods in at least six small-volume meals/day; Chewable multiple vitamin	Approximately 1500 calories/day to avoid volume depletion and maintain weight (often more realistic than weight gain)	Creamy, milk-based liquids
Step 3: Starches, Chicken, Fish		
If Step 2 is tolerated: Noodles, pastas, potatoes (mashed or baked), rice, baked chicken breast, fish (all easily mixed and emptied by the stomach) Ingest solids in at least six small-volume meals/day; Multiple vitamin (liquid or dissolvable)	Common foods that patient finds interesting and satisfying and that provoke minimal nausea/vomiting symptoms	Fatty foods that delay gastric emptying; red meats and fresh vegetables that require considerable trituration; pulpy fibrous foods that promote formation of bezoars

Lack of medications to treat symptoms associated with gastroparesis is appreciated by pharmaceutical companies, and there are several companies looking at new drug compounds which include ghrelin agonists, motilin agonists, and 5-HT3 antagonists. These drugs are still undergoing clinical trials.

What about the gastric stimulator?

Enterra (Medtronic) is a device therapy for gastroparesis. The device is programmed to electrically stimulate the stomach at a rate of 12 cpm with a very short burst of electrical charge (330 microseconds) with a certain intensity to help the symptoms associated with diabetic or idiopathic gastroparesis. Several open-label studies have shown that the stimulation decreases vomiting over the course of 12 months, decreases nausea and vomiting, and improves gastric emptying. However, controlled trials with the stimulator off or on have not shown that stimulation is better than the placebo setting. Thus, the device is available by the FDA under the humanitarian device exemption rules. It is used for idiopathic and diabetic gastroparetic patients but with greater efficacy in patients with diabetic gastroparesis (15).

What is the future for the treatment of gastroparesis?

Progress is being made in understanding gastroparesis, particularly in terms of the mechanism of gastroparesis with the loss of ICCs and neurons. These new insights will help to identify targets for new and effective drug therapies. In patients with gastroparesis and normal 3 cpm rhythm, therapies may be directed toward the pylorus with dilation, botulinum toxin A, and in highly selected cases (pyloroplasty). Studies of acupuncture and acustimulation for decreasing symptoms and increasing normal 3 cpm electrical rhythms and improving gastric emptying are ongoing. Improvement in gastric stimulator parameters and controlled studies are still needed.

The National Institutes of Health also appreciates that gastroparesis is a major problem for patients in the United States and continue to support the Gastroparesis Clinical Research Consortium (GpCRC). The GpCRC was established to further investigate the natural history of gastroparesis and carry out drug and other studies to help alleviate the ongoing suffering related to gastroparesis. By furthering our understanding of the mechanisms of gastroparesis, new insights and new targets for treatment will be developed.

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Additional Resources on Page 15

References

1. Camilleri M, Parkman H, Shafi M, et al. Clinical guideline: Management of gastroparesis. Am J Gastroenterol 2013;108:18-37.
2. Koch KL. Gastric neuromuscular function and neuromuscular disorders. In Sleisenger and Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/ Diagnosis/Management. Eds Feldman M, Friedman LS, Brandt LJ. Elsevier, Inc., Philadelphia, 2015, pp. 811-838.
3. O'Grady G, Angeli TR, Du P, et al. Abnormal initiation and conduction of slow wave activity in gastroparesis, defined by high-resolution electrical mapping. Gastroenterol 2012;143:589-598.
4. Koch KL. Gastric dysrhythmias: a potential objective measure of nausea. Exp Brain Res. 2014;232(8):2553-61.
5. Grover M, Farrugia G, Lurken MS, et al. Cellular changes in diabetic and idiopathic gastroparesis. Gastroenterol 2011; 140:1575-1583
6. Parkman HP, Yates K, Hasler WL, et al. Similarities and differences between diabetic and idiopathic gastroparesis. Clin Gastroenterol Hepatol 2011;9:1056-64.
7. Mearin F, Camilleri M, Malagelada JR. Pyloric dysfunction in diabetics with recurrent nausea and vomiting. Gastroenterol 1986;90:1919-25.
8. Fisher RS. Gastroduodenal motility disturbances in man. Scand J Gastroenterol 1985;109:59-68.
9. Brzana RJ, Bingaman S, Koch KL. Gastric myoelectrical activity in patients with gastric outlet obstruction and idiopathic gastroparesis. Am J Gastroenterol 1998;93:1083-1089.
10. Kundu S, Koch KL. Effect of balloon distention or botulinum toxin A injection of the pylorus on symptoms and body weight in patients with gastroparesis and normal 3 cycle per minute gastric electrical activity. Am J Gastroenterol 2011;106:S35.
11. Liberski SM, Koch KL, Atnip RG, Stern RM. Ischemic gastro¬paresis: Resolution after revascularization. Gastroenterology 1990; 99:252-257.
12. Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low fat meal: Establishment of international control values. Am J Gastroenterol 2000;95:1456-62.
13. Kuo B, McCallum RW, Koch KL, et al. Comparison of gastric emptying of a non-digestible capsule to a radio-labeled meal in healthy and gastroparetic subjects. Aliment Pharmacol Ther 27:186-196, 2008.
14. Koch KL. Electrogastrography for evaluation of patients with suspected gastroparesis. In: Gastroparesis: Pathophysiology, Presentation, Diagnosis and Treatment. Eds. H. Parkman and R. McCallum. Springer, New York, NY, 2011, pp 153-161.
15. McCallum RW, Snape W, Brody F, et al. Gastric electrical stimulation with Enterra improves symptoms from diabetic gastroparesis in a prospective study. Clin Gastroenterol Hepatol 2010;8:947-54.

Research Subjects Needed

Causes of Symptoms Studies

Diagnostic Evaluation of Functional GI and IBS Networks (DEFINE)

The UNC Center for Functional GI and Motility Disorders is looking for eligible subjects to participate in the DEFINE study.

You may be eligible to participate if:

- You have experienced any of the following GI symptoms for at least 3-6 months without a definitive diagnosis:
  - Abdominal pain or discomfort
  - Bloating
  - Constipation
  - Diarrhea
- You have not had any definitive testing for your GI symptoms
- You are at least 18 years of age

Eligible participants may receive up to $214 for time and travel.

The development and validation of a blood test to identify IBS: DEFINE (Diagnostic Evaluation of Functional GI and IBS Networks)
IRB #13-2900

Principal Investigator
Dr. Yehuda Ringel, MD

Contact Information

Charles Mclendon
919-843-1003
aycockmc@email.unc.edu

FDA to hold public meeting on FGIDs: Patient-Focused Drug Development

On May 11, 2015, FDA will conduct a public meeting on Functional GI Disorders Patient-Focused Drug Development. FDA is interested in obtaining patient input on the impact of functional GI disorders on daily life and patients' views on currently available therapies to treat the functional GI disorders, such as irritable bowel syndrome, gastroparesis, chronic persistent symptomatic gastroesophageal reflux despite standard therapeutic interventions, and chronic idiopathic constipation.

Date: May 11, 2015

Time: 1:00 p.m. to 5:00 p.m.

Location: FDA White Oak Campus
10903 New Hampshire Avenue
Building 31, Room 1503 B & C (Great Room)
Silver Spring, MD 20993
Enter at Building 1 to clear security

For additional resources and information regarding registration and attendance, please visit the below online resources.

FDA Website: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm430885.htm

Registration: http://www.eventbrite.com/e/functional-gi-disorders-patient-focused-drug-development-public-meeting-registration-15203090854

Twitter: https://twitter.com/FDA_Drug_Info

Facebook: https://www.facebook.com/FDA?ref=br_tf&rf=110870742267430&no_highlight_redirect=1

State of the Science Article Review on Fecal Incontinence From the NIDDK: Continued from Cover

(injury to the external and internal anal sphincters) tears during delivery were associated with an increased risk.[1] Vaginal delivery in itself, regardless if there was a tear or not, is a risk factor, but it's effect on FI with regards to prevalence is noted several decades after the fact.[1] It is also important to note that a correlation has been identified between the decline of the use of forceps, vacuum extractions, and less frequent use of an episiotomy, with reduced rates of fecal incontinence after a vaginal delivery.[1] The increased prevalence of FI in the elderly may be due to several factors including; dementia, mobility impairment, constipation with overflow incontinence, and increased comorbid diseases. Other risk factors are decreased resting tone of the anal sphincter, decreased ability to voluntarily squeeze the anal sphincter, and decreased sensation in the rectum. Reduced rectal sensation is when an individual has trouble sensing the presence of stool in their rectum. The individual may not feel that they need to have a bowel movement until they pass stool.

Problems associated with comorbid diseases, such as diabetes, can increase the risk for FI. Peripheral neuropathy caused by diabetes has been linked to neurogenic lesions that may affect the ability to squeeze the external anal sphincter. [14] An additional stressor on the pelvic floor muscles includes straining when trying to have a bowel movement. This can stretch the muscles over time and consequentially damage nerves in the pubocretalis muscle. This weakens the puborectalis' ability to squeeze the rectum or maintain appropriate resting tone. [15]

How do you measure the rate of FI?

How do you measure the prevalence of a disorder that society stigmatizes and where patients feel socially isolated? Patients who experience FI, whether once a month, multiple times a month, or daily may feel a loss in confidence in doing daily household activities, participating in social engagements with friends or family, or traveling. This results in patients not sharing their medical condition with family members and may prevent the patient from seeking care from their physicians.[1] When physicians were asked the importance of screening for FI, they considered it less important than other medical conditions, such as diabetes, alcohol abuse, or urinary incontinence. [9] This is compounded by physicians having limited time to address only the most serious health problems during the visit and not being familiar with the risk factors, treatment options, burden, or prevalence of FI. [10] Caregivers were also under increased stress as the highest ranked burdens were (1) measured hours of care, (2) emotional and physical toll taken for caring for the patient, and (3) contemplating admitting the patient into a long term care facility or nursing home.[1]

Studies have been conducted over the past 20 years to analyze the frequency and severity of FI by asking questions about incontinence episodes, such as if a patient had a FI episode "once per week over the past year" (males 4.5% and females 3.1%] [3], "any FI" (males 12.8% and females 17.8%) [4] and "loss of liquid or solid or mucous stool during the past 30 days" (males 7.7% and females 8.9%). [5] An additional issue is the array of questionnaires used to measure the severity of FI. Currently, there are over 20 different FI severity rating scales that are used in clinical research studies, though some have not been fully validated.[1] An important factor in measuring prevalence of FI is the way questions are asked as well as patients feeling comfortable with the language of the question. A survey conducted online found that women preferred the term "accidental bowel leakage" over "fecal incontinence" when describing accidents. [5] Also, how the interview was conducted (over the phone, in person, the time frame referencing episodes, and the definition of incontinence) all influence how an individual reports their symptoms. This has led to varying accounts for the rates of FI. Fecal incontinence also has a tremendous effect on the quality of life of patients and their caregivers. Patients who experienced FI developed changes to their lifestyle to cope with the episodes. Patients reported on questionnaires that fear or embarrassment of FI resulted in restricted social activities, increased concern over hygiene and body odor, developed a fear of having an accident, and restricted daily exercise or physical activities. [13]

How much economic burden does FI place on the patient?

There isn't a definitive number, but there are multiple costs associated with the disorder. These can include personal hygiene products, physician visits, diagnostic tests, non-surgical treatments, loss of productivity, and potential nursing home admissions.[1] There has been limited research into actual realized costs associated with FI, but of the ones conducted calculated between $3,200 - $4,100 per year.[11,1] This does not account for any surgical interventions. Newer treatments, such as sacral nerve stimulation, end up costing over $20,000 with Medicare and may cost more with private insurance.[12]

Summary

Continued research into the risk factors for FI are necessary to continue improving on and creating new treatments as well as improving health care outcomes for patients. There are still many unanswered questions about FI and as a collective team, UNC, faculty collaborators, NIDDK, and NIH are all pushing for continued support of patients and their caregivers.

1. Bharucha AE, Dunivan G, Goode PS, Lukacz ES, Markland AD, Matthews CA, Mott L, Rogers RG, Zinsmeister AR, Whitehead WE, Rao SSC, Hamilton RA. Epidemiology, Pathophysiology, and Classification of Fecal Incontinence: State of the Science Summary for the National

Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Workshop. Am J Gastroenterol. 2015: 110; 127-136.
2. Whitehead WE, Rao SSC, Lowry A, Nagle D, Varma M, Bitar KN, Bharucha AE, Hamilton FA. Treatment of Fecal Incontinence: State of the Science Summary for the National Institute of Diabetes and Digestive and Kidney Diseases Workshop. Am J Gastroenterol. 2015: 110; 138-146.
3. Talley NJ, O'Keefe EA, Zinsmeister AR et al. Prevalence of gastrointestinal symptoms in the elderly: a population-based study. Gastroenterology. 1992: 102; 895-901.
4. Reilly W, Talley N, Pemberton J, Fecal incontinence: prevalence and risk factors in the community. Gastroenterology. 1995: 108; A32.
5. Brown HW, Wexner SD, Segall MM et al. Accidental bowel leakage in the mature women's health study: prevalence and predictors. Int J Clin Pract. 2012: 66; 1101-8.
6. Nelson RL. Epidemiology of fecal incontinence. Gastroenterology. 2004: 126; S3-S7.
7. Whitehead WE, Borrud L, Goode PS. Et al. Fecal incontinence in US adults: edidemiology and risk factors. Gastroenterology 2009: 137; 512-7.
8. Goode PS, Burgio KL, Halli AD et al. Prevalence and correlates of fecal incontinence in community—dwelling older adults. J Am Geriatr Soc. 2005: 53; 629-35.
9. Kunduru L, Kim SM, Heymen S et al. Factors that affect consultation and screening for fecal incontinence. Clin Gastroenterol Hepatol 2014; S1542-3565:01230-0
10. Bliss DZ, Norton C, Vodusek DB. Raising awareness about fecal incontinence. Neurourol Urodyn. 2010; 29: 612-5.
11. Xu X, Menees SB, Zochowski MK et al. Economic cost of fecal incontinence. Dis Colon Rectum, 2012; 55: 586-98
12. Hetzer FH, Bieler A, Hahnloser D et al .Outcome and cost analysis of sacral nerve stimulation for faecal incontinence. Br J Surg 2006. 93:1411-7
13. Cotterill N, Norton C, Avery KNL et al. A patient-centered approach to developing a comprehensive symptom and quality of life assessment of anal incontinence. Dis Colon Rectum. 2008: 51; 82-7.
14. Bharucha AE, Daube J, Litchy W. et al. Anal sphincter neurogenic inject in asymptomatic nulliparous women and fecal incontinence. Am J Physiol Gastrointest Liver Physiol. 2012; 303:G256-62
15. Bharucha AE, Fletcher JG, Harper CM et al. Relationship between symptoms and disordered continence mechanisms in women with idiopathic fecal incontinence. Gut 2005; 54:546-55.

Additional Gastroparesis Resources

Medical Institutions

University of North Carolina at Chapel Hill
www.med.unc.edu/ibs

Wake Forest University
http://www.wakehealth.edu/Gastroenterology/

Online Resources

UNC's 2014 Patient Day Video Archives
http://www.fgidpatientupdate.com/DCsymposium2014.html

International Foundation for Functional Gastrointestinal Disorders (IFFGD)
http://www.iffgd.org
http://www.dha.org

Crystal Saltrelli, CHC
http://livingwithgastroparesis.com/

http://www.scoop.it/t/gastroparesis-by-trisha-high-bundy

Social Media Advocacy

Twitter
@bundytr5
@melissarvh
@FGIFYI
@WeAreDHA
@IFFGD
#Green4GP

Facebook
https://www.facebook.com/Gastroparesis.FightingForChange.Page?ref=aymt_homepage_panel

https://www.facebook.com/groups/rkh78gastrodaybyday/

FDA approves new gastric device for the treatment of obesity: how it works and potential impacts on the GI system

What is it and how does it work?

On January 14, 2015, the Food and Drug Administration (FDA) approved the EnteroMedics Inc. Maestro Rechargeable System for the treatment of obesity. This has created a lot of discussion as it is the first device to gain FDA approval since the gastric banding procedure in 2007. The device (as seen below) is used to treat patients with morbid obesity or have obesity with one or more medical conditions such as Type II Diabetes, cardiovascular disorders, or high cholesterol. It is designed to provide mild electrical stimuli to the vagus nerve, which is responsible for sending signals from the stomach to the brain regarding hunger and the regulation of gastric emptying. The concept behind the electrical stimulation of the vagus nerve is to "quiet" the nerve signals from the stomach to trick the brain into thinking that the stomach is satisfied and doesn't need more food.[1,2] According to the guidelines set by the FDA[2], individuals may qualify

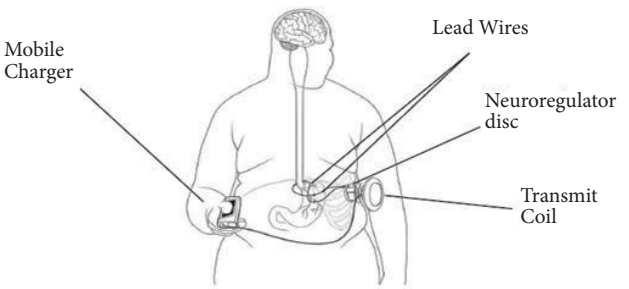

Diagram 1-1 [2]

for this device if they are over the age of 18 and either have a Body Mass Index (BMI) of 40 – 45 or a BMI of 35 – 39.9 with one or more medical condition related to obesity. The device is implanted near the stomach with the electrodes placed near the posterior and anterior vagus nerves. The device uses an external transmit coil that is placed on the skin to recharge it's lithium ion battery.[1] The rechargeable battery has an 8 year battery life and is ***not*** MRI safe. The patient is responsible for monitoring the battery level and recharging. The device also has customizable firmware that allows the physician to change how the device functions.

What adverse events are associated with the device?

There were 503 subjects enrolled in the EMPOWER research study [5] and 239 subjects in the ReCharge study [4]. At 12 months post surgery, the EMPOWER study reported 148 related adverse events, of which 10 were classified as serious adverse events[1,5] and the ReCharge study reported 377 adverse events and 15 serious adverse events [1,4]. An adverse event is any unanticipated medical problem that happened during the study. A serious adverse event is classified by the FDA as, "any adverse event that results in life-threatening injury or death, hospitalization, disability, permanent damage, or required intervention(s) to prevent permanent impairment or damage." There were a total of twelve surgical revisions over the 18 month research study and thirty-six patients had the device surgically removed and withdrawn from the study.

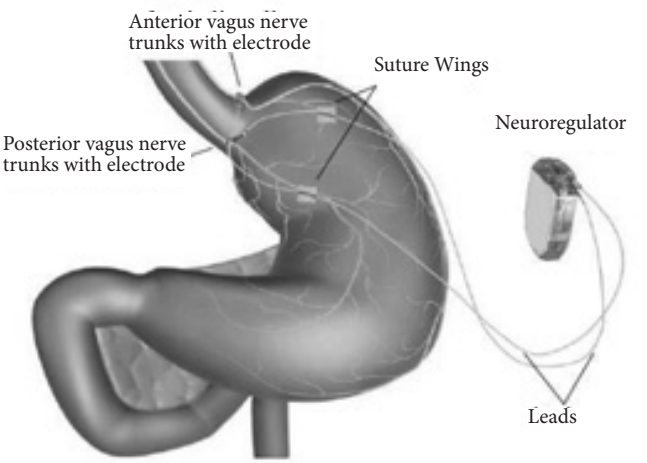

Diagram 1-2 [1]

Most Common AE During Research Study [1,4]		
AE (Most Common)	# VBLOC Pts Affected	# Control Pts Affected
Neuroregulator site pain	59 pts w/69 events	31 pts w/32 events
"Other" pain	37 pts w/42 events	0 pts w/0 events
Heartburn/ dyspepsia	35 pts w/39 events	3 pts w/3 events
"Other" AE	34 pts w/43 events	7 pts w/10 events
Difficulty or discomfort swallowing	13 pts w/13 events	0 pts w/ 0 events
Belching	12 pts w/12 events	0 pts w/0 events
Nausea	11 pts w/14 events	1 pt w/1 event
Chest Pain	9 pts w/9 events	2 pts w/2 events

pt = patient; event = each time an AE was reported.

What does current published research say about it?

The EMPOWER Study[5] and the ReCharge Study[4] are randomized clinical trials that investigated VBLOC© electrical stimulation of the vagus nerve for the treatment of obesity. The conclusions from the EMPOWER Study

state that the device's safety met key goals, but that "… weight loss was not greater in treated compared to controls; clinically important weight loss, however, was related to hours of device use."[5] Results from the ReCharge Study were similar in that the device "…did not meet either the prespecified co-primary efficacy objectives, although weight loss in the vagal block group was statistically greater than in the sham device group."[4] Bariatric surgeons at UNC are not yet ready to fully endorse the procedure and would need to see a nationwide trend of physicians embracing use of the device as well as more uniform weight loss before using it in their practice.

How does it compare with other interventions?

There are multiple FDA approved weight loss devices and surgeries available in addition to the Maestro Rechargeable Device. These include devices such as the Lap-Band gastric banding system, Realize Gastric Band as well as surgical procedures such as Roux-en-Y gastric bypass surgery and Vertical Sleeve Gastrectomy.

As with each medical procedure, there are risks associated with surgery and altering the digestive tract. If the silicone band from the adjustable gastric band slips, this can cause vomiting, heartburn, difficulty swallowing, delayed gastric emptying, esophagitis, or halitosis.[7,8] Other complications that can result from bariatric surgery include GI bleeding, leakage, hernia, dumping syndrome, and nutritional deficiencies.[7,8] Dumping syndrome, which has symptoms of abdominal pain, diarrhea, bloating and nausea can occur from rapid gastric emptying.[8]

Weight gain after Surgery

Weight gain after surgery is possible. There are diets and supplements specifically tailored to meet the nutritional needs of bariatric surgery patients. However, some patients do gain some or all of the weight back. Sensations of satiety seem to play a big role in keeping off weight after the procedure.[9] Other factors that play a role in post operative weight gain are binge eating, loss of control when eating, and eating small amounts of food continuously over the day with lack of control, also known as "grazing."[10] The diagram 1-3 looks at patients over a 10 year time span to monitor the change in Body Mass Index (BMI) over a 10 year period.

Conclusion

As with any surgical procedure, talking with your physician about the benefits and potential complications of any surgery is important. Obesity has a profound effect on the quality of life and overall health outcomes experienced by patients. It is important to research all the options available to you and work with your physician to decide which option would be best suited to you.

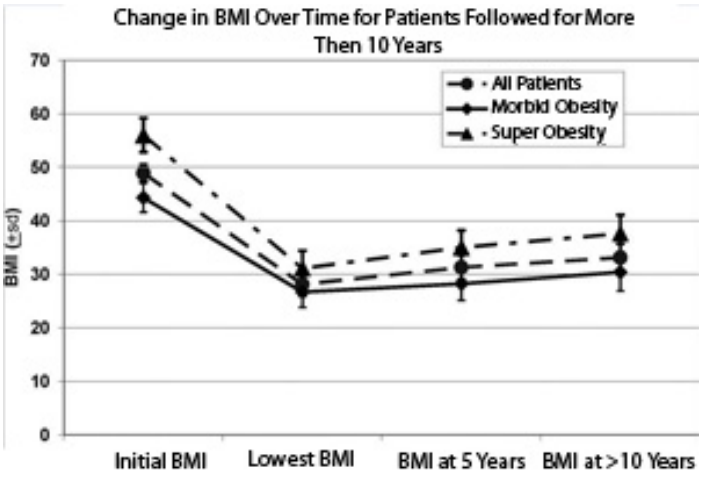

Diagram 1-3 [9]

1. FDA Executive Summary: Premarket Approval P130019. MAESTRO Rechargeable System for VBLOC Therapy. June 17, 2014. Food and Drug Administration. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/UCM401000.pdf

2. EnteroMedics Maestro Rechargeable System - P130019. http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm430696.htm Accessed March 13, 2015.

3. Reporting Serious Problems to the FDA. What is a serious adverse event? http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm. Accessed March 13, 2015.

4. Ikramuddin S, Blackstone RP, Brancatisano, et al. Effect of Reversible Intermittent Intra-abdominal Vagal Nerve Blockade on Morbid Obesity: The ReCharge Randomized Clinical Trial. JAMA. 2014; 312(9): 915-22.

5. Sarr MG, Billington CJ, Brancatisano R, Brancatisano A, Toouli J, Kow L, Nguyen NT, Blackstone R, Maher JW, Shikora S, Reeds DN, Eagon JC, Wolfe BM, O'Rourke RW, Fujioka K, Takata M, Swain JM, Morton JM, Ikramuddin S, Schweitzer M, Chand B, Rosenthal R; EMPOWER Study Group. The EMPOWER study: randomized, prospective, double-blind, multicenter trial of vagal blockade to induce weight loss in morbid obesity. Obes Surg. 2012 Nov;22(11):1771-82. doi: 10.1007/s11695-012-0751-8.

6. Ahnis A, Figura A, Hofmann, T, Stengel A, Elbelt U, Klapp BF. Surgically and Conservatively Treated Obese Patients Differ in Psychological Factors, Regardless of Body Mass Index or Obesity-Related Co-Morbidities: A Comparison between Groups and an Analysis of Predictors. PLoS One. 2015 Feb 13;10(2):e0117460. doi: 10.1371/journal.pone.0117460. eCollection 2015.

7. Mancini MC. Bariatric surgery - An update for the endocrinologist. Arq Bras Endocrinol Metabol. 2014 Dec;58(9):875-88. doi: 10.1590/0004-2730000003413.

8. Tack J, Deloose E. Complications of bariatric surgery: Dumping syndrome, reflux and vitamin deficiencies. est Pract Res Clin Gastroenterol. 2014 Aug;28(4):741-9. doi: 10.1016/j.bpg.2014.07.010. Epub 2014 Jul 10.

9. Christou NV, Look D, MacLean LD. Weight Gain After Short- and Long-Limb Gastric Bypass in Patients Followed for Longer Than 10 Years. Ann Surg. 2006 Nov; 244(5): 734–740.

10. Kofman MD, Lent MR, Swencionis C. Maladaptive eating patterns, quality of life, and weight outcomes following gastric bypass: results of an Internet survey. Obesity (Silver Spring). 2010 Oct;18(10):1938-43.

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