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DigestiveHealth Matters

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Highlights in this Issue

INTERNATIONAL FOUNDATION FOR FUNCTIONAL GASTROINTESTINAL DISORDERS

Information. Assistance. Support.

You Can Take Action for Digestive Health

May 13, 2015 *The Functional Gastrointestinal and Motility Disorders Research Enhancement Act* of 2015 (H.R. 2311) was reintroduced in the U.S. House of Representatives, in the 114th Congress, by Rep. F. James Sensenbrenner (WI-5).

This landmark legislation needs your action to obtain Congressional support.

Call or email your House Member. You can find the contact information for your Representative by going to *www.house.gov*.

Ask your Representative to cosponsor H.R. 2311, the revenue-neutral *Functional Gastrointestinal and Motility Disorders Research Enhancement Act* of 2015.

{Save the Date}

Mark Your Calendars!

We invite you to join us on July 21, 2015

for our virtual Advocacy Day to educate members of Congress about functional GI and motility disorders and the widespread effects of these chronic conditions. This year we will make our voices heard through call-ins, emails, and social media. Stay tuned for more details on this annual event!

http://www.iffgd.org/site/about-iffgd/advocacy/bill/

National Institutes of Health (NIH) Support for Gastroparesis Research

In an effort to improve the diagnosis and treatment of patients with gastroparesis, in 2006 the National Institutes of Health (NIH) started the Gastroparesis Clinical Research Consortium (GpCRC). The research is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to focus on the causes (etiology), natural history, and therapy of gastroparesis.

The goals of the consortium are to perform research that will broadly improve understanding of gastroparesis and to provide an infrastructure that can rapidly and efficiently design and conduct clinical trials for effective approaches to improve treatment of patients with gastroparesis.

Gastroparesis is a long-term (chronic), poorly understood condition, which can significantly impact a person's life. While the number of people with gastroparesis is not well-defined, the incidence and severity appear to be rising.

Research progress on gastroparesis has been hindered by challenges such as single research centers, small population base, and limited range of clinical and research techniques available to study. In response to these limitations, the GpCRC was established.

Specific aims of the consortium include:

- Providing an infrastructure for the efficient design and conduct of multicenter clinical studies
- Performing clinical trials to investigate clinical, diagnostic, and therapeutic interventions for gastroparesis
- Creating a collection of patient samples that may be used for further studies of causes and development of the condition

The GpCRC has also successfully established a registry of individuals with gastroparesis to study and clarify disease factors, natural history, clinical course, and other outcomes of the condition. The registry will provide a resource for additional studies. Expansion of the registry is currently ongoing.

About Gastroparesis

Gastroparesis (also called delayed gastric emptying) is a disorder characterized by the presence of certain long-term symptoms together with delayed stomach (gastric) emptying in the absence of any observable obstruction or blockage. The delayed stomach emptying is confirmed by a test.

The condition affects many people who may exhibit a wide range of symptoms of differing severity. Symptoms usually occur during and after eating a meal.

Symptoms that are characteristic of gastroparesis include:

- Nausea and/or vomiting
- Retching (dry heaves)
- Stomach fullness after a normal sized meal
- Early fullness (satiety) – the inability to finish a meal

Bloating, as well as stomach discomfort or pain, is also noted by some persons with gastroparesis, particularly as symptoms become more severe. Weight loss due to decreased appetite and heartburn may also occur.

The cause of gastroparesis is not well understood but may result from damage to the nerves, muscle, pacemaker cells, or other cells of the stomach that are important for normal function. Such damage may be caused by diabetes, which is relatively common in patients with gastroparesis. Gastroparesis can also occur after stomach surgery for other conditions. There are rare reasons for gastroparesis, such as thyroid disorders or from a side effect of some medications. In many patients, a cause of the gastroparesis cannot be found and the disorder is termed *idiopathic* gastroparesis.

The treatment for gastroparesis in an individual depends on the severity of symptoms. Treatments are aimed at managing symptoms over a long term. Treatment approaches may involve one or a combination of dietary and lifestyle measures, medications, and/or procedures that may include surgery.

Persons who experience symptoms of gastroparesis should talk to their doctor to find out what is wrong. If gastroparesis is diagnosed, the doctor can work with the patient to develop a treatment plan best suited for his or her needs. Patients should let their doctor know about all other drugs or supplements they take, both prescription medications and over-the-counter agents.

GpCRC Centers and Activities

The Gastroparesis Consortium Clinical Centers include:

- California Pacific Medical Center
- Johns Hopkins School of Medicine
- Stanford University
- Temple University
- Texas Tech University – El Paso
- University of Louisville
- University of Michigan
- Wake Forest University
- The Data Coordinating Center is located at the Johns Hopkins University, Bloomberg School of Public Health

Current studies underway in the NIH Gastroparesis Consortium include:

- The Gastroparesis Registry 2 – patients are followed periodically and information is gathered at regular intervals about their disorder
- The Aprepitant for the Relief of Nausea in Patients with Chronic Nausea and Vomiting of Presumed Gastric Origin (APRON) Trial – aims to determine if treatment with the study drug (aprepitant) or placebo results in symptomatic improvement of nausea in patients with chronic nausea and vomiting of presumed gastric origin
- A study that aims at understanding the changes in stomach tissue that occur in gastroparesis to help come up with better ways to treat patients

Additional treatment trials are planned to study the effects of promising drugs and devices to control symptoms and improve the quality of life.

Learn More

Visit the GpCRC website at *https://jhuccs1.us/gpcrc/open/patients/patientlinks.htm* for more information on the consortium. For gastroparesis information, visit our IFFGD website at *www.aboutGastroparesis.org*.

Primary Sources

https://www.niddkrepository.org/studies/gpcrc/. (Accessed 05.05.15)

http://jhuccs1.us/gpcrc/open/patients/GpCRC.brochure.10oct14.pdf. (Accessed 05.05.15)

Medical News Update

NIDDK Establishes Office of Nutrition Research

In August 2015 the NIH National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) will establish the Office of Nutrition Research. This office will replace the NIH Division of Nutrition Research Coordination (DNRC). The new office will assist in leading a diverse group of offices within the NIH that will be responsible for planning new initiatives in NIH nutrition research. It will also be closely associated with the nutritional sciences grant funding programs in the NIDDK.

NIH, the National Institutes of Health, is the center for all federally-funded biomedical research in the U.S. It conducts medical research; supports the research of non-federal scientists operating in universities, medical schools, hospitals, and research institutions throughout the country and abroad; helps in the training of researchers; and fosters communication of cutting-edge medical information. The NIDDK is the NIH's largest funder of nutrition research. Access NIH at *www.nih.gov* and NIDDK at *www.niddk.nih.gov* to learn more about all that they are responsible for.

New Test for Diagnosing Gastroparesis

In April 2015, the U.S. Food and Drug Administration (FDA) approved a new non-invasive test of delayed gastric emptying to aid in the diagnosis of gastroparesis. Known as the Gastric Emptying Breath Test (GEBT), it can be performed in any clinical setting.

Gastroparesis is a disorder that slows or stops the movement of food from the stomach to the small intestine in the absence of any observable obstruction or blockage.

The GEBT is conducted over a four-hour period after an overnight fast. It is designed to show how fast the stomach empties solids by measuring carbon dioxide in a patient's breath. Unlike scintigraphy, which uses a small amount of radioactive material to track gastric emptying, the GEBT uses no radioactive emitting material. Scintigraphy is considered the standard of care for measuring gastric emptying.

The safety and effectiveness of the GEBT was studied in 115 participants prior to FDA approval. All participants were tested with both the GEBT and gastric scintigraphy. The GEBT results agreed with scintigraphy results 73-97% of the time when measured at various time points during the test.

People with hypersensitivity to Spirulina, egg, milk or wheat allergens should avoid the GEBT. The test also should not be administered to people with certain lung diseases or conditions that cause small bowel malabsorption.

Source: *FDA News Release*. April 6, 2015.

Mesalazine Lacks Effectiveness for Individuals with IBS-D

Researchers looked at an anti-inflammatory drug, mesalazine, to see if it would be useful for the treatment of diarrhea predominant irritable bowel syndrome (IBS-D). They found that the drug may improve symptoms in a subset of people with post-infectious IBS (PI-IBS).

The randomized placebo-controlled study included 136 individuals with IBS-D. Thirteen of these had PI-IBS.

Source: Lam C, et al. *Gut*. 2015 March.

Registry Launched for Eosinophilic Gastrointestinal Diseases

The Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) has announced the launch of a new contact registry for eosinophilic gastrointestinal diseases (EGIDs), including eosinophilic esophagitis, eosinophilic gastroenteritis, and others. These are chronic inflammatory conditions believed to be triggered by food-related allergic hypersensitivity, which can lead to gastrointestinal symptoms.

Funded by the NIH, the goal of the registry is to provide an international database of contact data collected from patients and their families to CEGIR researchers for use in recruiting participants for new EGID studies. Individuals included in the registry will receive notifications of upcoming research studies for which they may be eligible, as well as research updates, advocacy information, and opportunities to contribute to researcher training. The registry is online at: *www.rdcrn.org/CEGIR*.

Gut-Focused Hypnotherapy an Effective Treatment for IBS

A study in the United Kingdom (U.K.) looked at the effectiveness of a gut-directed hypnotherapy technique in 1,000 patients with irritable bowel syndrome (IBS) whose symptoms were not adequately treated by conventional management strategies, such as dietary approaches and medications. The researchers concluded that the hypnotherapy relieved a wide range of symptoms, as well as improved quality of life and mood, safely and without side effects.

This therapy can be a helpful addition to conventional treatment measures, such as education, dietary and lifestyle changes, and drug therapy, in the treatment of IBS.

The patients received 12 weekly sessions of one-on-one gut-focused hypnotherapy from therapists at Wythenshawe Hospital, Manchester, U.K. who were trained and experienced using the technique. A study is ongoing to see if similar results can be achieved in a shorter time.

Source: Miller V, et al. *Aliment Pharmacol Ther*. 2015 March.

Functional Gastrointestinal Disorders and BMI

A prospective population-based cohort study of 35,447 individuals over the age of 18 found several significant relationships between body mass index (BMI) and risk for various functional gastrointestinal disorders (FGIDs). In adult females, high BMI was associated with an increased risk for functional diarrhea, and both high and low BMI were found to have a positive relationship with functional dyspepsia. In adult males, low BMI was found to be a risk factor for irritable bowel syndrome (IBS). Additionally, the study revealed significant overlaps in FGID diagnoses among participants, particularly between functional dyspepsia and IBS and functional constipation.

This analysis is part of the Nutrinet-Sante online study, which was originally launched in France in 2009 but is still ongoing. For more information (in French) or to participate, go to *www.etude-nutrinet-sante.fr.*

Source: Le Pluart D, et al. *Aliment Pharmacol Ther*. March 2015.

FDA Launches Mobile App to Track Drug Shortages

The U.S. Food and Drug Administration (FDA) has launched an application (app) for mobile platforms to increase public access to information about prescription drug shortages. The app provides real-time information about current drug shortages, resolved shortages, and discontinuations of drugs. Drugs can be searched for by generic or brand name or by therapeutic category.

The app is available for free download by going to the FDA webpage, *www.fda.gov/Drugs/DrugSafety/DrugShortages/*, or in the iTunes store (for iOS) and the Google Play store (for Android) by searching "FDA Drug Shortages."

Self-Applied Acupressure for Functional Constipation

In a randomized clinical study, individuals with functional constipation who were taught how to apply external pressure (acupressure) to the perineum (the area between the anus and the genitals), in addition to standard therapies, reported improved quality of life and bowel function compared with individuals who used only standard treatments. Standard therapies included increased dietary fiber intake, stool softeners, and exercise. A total of 91 people completed the study.

The UCLA researchers suggest that education in perineal self-acupressure, which only takes a few minutes to learn, should be included among other first-line treatments for functional constipation.

Source: Abbott R, et al. *J Gen Intern Med.* November 2014.

A Cautious Approach to the Low-FODMAP Diet

A review of published research looked at food intolerance associated with GI symptoms such as increased intestinal gas, abdominal pain, bloating, or diarrhea. Among the findings was increasing evidence that, for some people, a low FODMAP diet approach may be helpful in functional GI disorders when food intolerance is suspected.

However, there are cautions.

- Measures used in various FODMAP research studies to date are not consistent
- The dietary eliminations should be short-term
- Certain gut microorganisms thought to be beneficial have been noted to be significantly decreased after 4 weeks of a low FODMAP diet
- Nutritional adequacy may be reduced
- The diet must be undertaken with the supervision of an experienced dietician (often a registered dietician, or RD)

FODMAPs are a group of carbohydrates found in many common foods. The diagnosis of FODMAP intolerance is based on a short-term (3–4 weeks) diet to reduce or exclude suspected foods to look for symptom improvement, followed by a gradual reintroduction to establish individual tolerance. The study concluded that it is essential to work with a dietician experienced in food intolerance in order to maintain adequate nutrition, minimize impact on the gut microbiota, and avoid unnecessary dietary restrictions.

Source: Lomer MCE. *Aliment Pharmacol Ther*. 2014 Dec.

Hiatal Hernia and Dyspeptic Symptoms in Children

In a survey of 111 children undergoing upper endoscopy (EGD), presence of hiatal hernia was found to be associated with symptoms of heartburn and regurgitation but not other symptoms commonly described for gastroesophageal reflux (GER) or dyspepsia in children older than 4 years of age. Moreover, no association was found between presence of hiatal hernia and esophagitis.

The results of this study suggest that in children, presence of hiatal hernia represents a risk factor for only limited symptoms.

Source: Scarpato E, et al. *J Pediatr Gastroenterol Nutr*. December 2014.

Effect of Exercise on the Gut Microbiome and Health

Researchers of a case-controlled study of 40 Irish athletes and 46 controls found that individuals who engaged in vigorous exercise had greater gut microbial diversity than those who did not. High diversity of gut microorganisms appears to be linked to decreased intestinal inflammation and improved immune function among other things.

Results of this study suggest that exercise has a beneficial effect on the gut microbiome. However, further investigation is needed to tease apart the effects of exercise from other variables, including diet, in promoting the diversity of gut microbes.

Source: Clarke SF, et al. *Gut*. December 2014.

Visceral Abdominal Fat May Increase Risk of IBS-D

A case-controlled study of 336 individuals found that while overall body mass index (BMI) does not appear to be related to irritable bowel syndrome (IBS), abdominal fat deposits and waist circumference were both predictors of a higher risk of diarrhea predominant IBS (IBS-D).

From these findings the authors concluded that abdominal obesity, and not general obesity, represents a risk factor for IBS, especially IBS-D.

Source: Lee CG, et al. *Am J Gastroenterol*. January 2015.

Unhealthy Eating Behaviors and Functional Dyspepsia

A survey in China of 1,341 individuals with functional dyspepsia (FD) found that those with FD were more likely to engage in unhealthy eating behaviors, including skipping meals, eating extra meals, and consuming large amounts of sweets and gas-producing foods, than healthy individuals. Moreover, these behaviors among individuals with FD were found to be risk factors for more difficult to treat (refractory) FD.

Source: Jiang SM, et al. *J Dig Dis*. December 2014.

Location of Diverticular Disease and IBS

A Japanese study of 1,009 individuals concluded that the location of diverticular disease is associated with a risk of irritable bowel syndrome (IBS). Diverticular disease occurring in the left-sided and bilateral sections of the colon, but not on the right side, was associated with a higher risk of IBS.

Clarifying the specific changes associated with left-sided diverticular disease could provide a better understanding of causes of IBS.

Source: Yamada E, et al. *Am J Gastroenterol*. December 2014.

FDA Approves Generic Version of Nexium for GERD

The U.S. Food and Drug Administration (FDA) has approved the first generic version of Nexium (esomeprazole magnesium) to treat gastroesophageal reflux disease (GERD) in adults and children aged 1 year and older. Esomeprazole is a proton pump inhibitor (PPI) that works by blocking the site of acid production in a particular cell group in the stomach (parietal cells).

Esomeprazole was first approved to treat GERD by the FDA as Nexium in 2001. It is also approved to reduce the risk for gastric ulcers associated with nonsteroidal anti-inflammatory drugs (NSAIDs), treat *H. pylori* infection in association with certain antibiotics, and treat conditions where the stomach produces too much acid (such as Zollinger-Ellison syndrome).

FDA Approves Neurostimulator to Treat Symptoms of Gastroparesis

The U.S. Food and Drug Administration (FDA) has approved a second-generation neurostimulator device (Enterra II) to treat symptoms of nausea and vomiting in people with gastroparesis when other therapies have failed (refractory). The device is implanted under the skin and delivers a mild electrical pulse to stimulate the smooth muscles of the lower stomach. Enterra was first approved by the FDA in 2000. The new device provides physicians with greater system flexibility and ease of use. ■

The Roles of Intestinal Nerves and Serotonin in Gut Function and Dysfunction

By: Gary M. Mawe, Ph.D., Department of Neurological Sciences, University of Vermont, Burlington, VT

Dr. Mawe is the recipient of IFFGD's 2013 Senior Basic Science Research Award. He and his colleagues have made discoveries that provide fundamental information about how the digestive organ systems work, and insight about changes that occur in inflammatory and functional GI and motility disorders.

While the big brain in our head is dealing with abstract thoughts and complicated equations, the "little brain" in our gut is dealing with the everyday, but complex, work of digestion and defecation. Known as the enteric nervous system, nerves in the wall of the intestines control how the gut reacts to an ingested meal, and they regulate the processes of digestion, nutrient absorption, and waste elimination.

The coordinated activities of this nervous system ensure that we efficiently extract the calories that are available from the food and drink that we ingest. When all is well, this process of intestinal motility and secretion occurs behind the scenes at a sub-conscious level. When all is not well, we are quickly reminded that we take our gastrointestinal (GI) tracts for granted. Diarrhea, constipation, vomiting, and abdominal pain can quickly shake us out of our status quo. All of these responses involve the actions of the nervous system of the gut.

My colleagues and I have been studying how nerve cells regulate muscle function in the gut and gallbladder under normal conditions and how the circuitry of the gut is altered under abnormal conditions. We have also been studying how the neurotransmitter serotonin acts as a critical signaling molecule to activate gut reflexes, and how key elements of serotonin signaling are altered by inflammatory bowel disease (IBD) and in irritable bowel syndrome (IBS).

> ***Neurotransmitters are chemicals in the nervous system that help transmit messages.***

Neural regulation of the digestive tract – understanding changes that contribute to IBD and IBS

Other organ systems in our body, such as the heart and bladder, are controlled by neural signals arising in the brain and spinal cord. In the GI tract, neural circuits that are housed entirely within the wall of the intestine are capable of regulating various features of gut function such as motility and secretion.

While these enteric neural circuits can be controlled by signals coming from the brain, they can also function independently. This means that the nervous system of the intestines, the enteric nervous system, has many special features.

These features include:

1. The ability to sense changes within the gut, such as nutrients that would activate digestive responses, or invasive organisms that would activate protective responses such as vomiting and diarrhea

2. The ability to process this information and activate the appropriate gut behaviors, such as moving contents to and fro for digestion, or propelling them along the gut for elimination

3. The ability to excite or inhibit the muscle and glands in a given region of the gut

In states of inflammation, such as Crohn's disease or ulcerative colitis, intestinal motility, secretion, and sensitivity are altered. As nerve cells of the intestines regulate all of these functions, it is likely that changes in how these neurons function contribute to the symptoms that lead to so much suffering in individuals with these conditions.

Discoveries in the biology of the gut nervous system over the past two decades have provided us with a solid understanding of the components that make up gut reflex circuits, and how these neurons function under normal physiological conditions. We are beginning to understand what changes occur in colitis at precise sites along the reflex circuits. We are also starting to determine the mechanisms responsible for these changes. We have discovered that inflammation leads to several changes in the response of nerves, which can disrupt colonic motility.

Interesting discoveries have been made in laboratory studies of inflammation-induced changes in nerves that could have implications for functional GI disorders. We have found that the changes in the physiological properties of neurons brought on

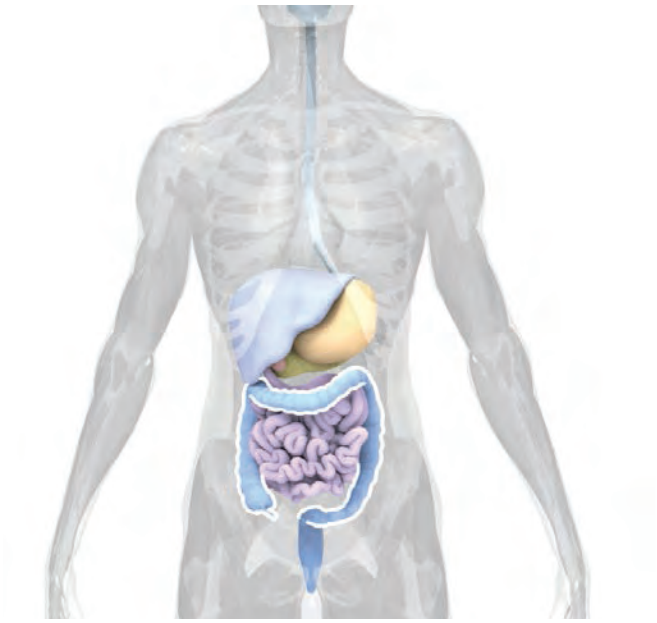
by the inflammatory response persist long after inflammation has resolved. Also, inflammation-induced alterations in gut motility and sensitivity are observed weeks beyond the recovery from inflammation.

One of the puzzling and frustrating aspects of functional GI disorders like IBS is that there is no test for it, and the GI tracts of individuals with IBS appear completely normal. Our ability to study the electrical properties of single neurons allows us to detect the changes responsible for altered gut function and sensitivity. It is possible that in some forms of IBS, such as post-infectious IBS, a previous inflammatory condition has resulted in persistent changes in the properties of the neurons that supply the gut.

Serotonin signaling in the GI tract

We typically think of serotonin (5-HT) as a neurotransmitter – a signaling molecule – in the brain that influences our state of mind, but most of the body's serotonin is actually located in the GI tract. The majority of serotonin is synthesized by specialized cells in the inner lining of the intestine called enterochromaffin (EC) cells.

Serotonin released by EC cells stimulates receptors on nearby nerve fibers to activate reflexes that are involved in secretion of fluid and coordinated muscle responses that propel ingested food and fluids along the intestines. The serotonin in the intestine is re-absorbed (in a process called reuptake) into cells lining the gut by a protein called the serotonin selective reuptake transporter (SERT). This molecule's function is inhibited by serotonin selective reuptake inhibitors (SSRIs), which are commonly prescribed for the treatment of depression and anxiety disorders.



> "Our ability to study the electrical properties of single neurons allows us to detect the changes responsible for altered gut function and sensitivity."

In the gut, SERT is located on cells throughout the inner lining of the intestines. Studies conducted in our laboratory and others have demonstrated that various aspects of serotonin signaling are reduced in people with IBD or IBS. We have pursued further studies to better understand how SERT activity is regulated.

Current studies in our laboratory are directed towards identifying serotonin related targets in the gut that could be useful for developing safe and effective treatments for functional GI disorders. Recently, we made an interesting discovery related to a type of serotonin receptor called the 5-HT4 receptor. Compounds that activate this receptor (5-HT4 agonists), such as cisapride, tegaserod, and prucalopride, have been developed for the treatment of constipation, and they also appear to relieve abdominal discomfort in constipation-predominant IBS. Unfortunately, previously approved 5-HT4 agonists are not available due to fear of cardiovascular side effects.

We discovered that essentially all of the cells in the inner lining of the colon have this receptor. We also found that the application of 5-HT4 agonists that target just the surface of the colon activates receptors that lead to mucus, serotonin, and fluid secretion. All of these actions could lead to the reduction of constipation and colonic pain. Formulating 5-HT4 agonists to prevent absorption outside the colon may improve treatment effects while avoiding potential side effects.

Conclusions

Each meal that we ingest triggers a highly choreographed series of physiological reflex responses along the GI tract that allow us to gain access to nutrients and to systematically eliminate waste byproducts. Ongoing basic science (lab) research is identifying the key elements of these reflex responses at the molecular, cellular, and tissue levels. Translational research studies aimed at converting these discoveries into practical applications are also being conducted to explain which of these key elements are changing in various GI disorders, and which of these changes have important implications for gut function and sensitivity. Collectively, these investigations are leading to discoveries that are revealing new targets for the treatment of inflammatory and functional GI disorders. ■

IFFGD INDUSTRY COUNCIL

When IFFGD began in 1991 there was little communication between patients living with functional GI and motility disorders and the companies with the means to develop treatment products and services. Subsequently, IFFGD has worked hard to make the needs of our members known – not only to the clinicians who see patients, but also to the researchers and providers of diagnostic and treatment methods and tools.

In an effort to strengthen our voice, in 1998 we formed the IFFGD Industry Council. The Council provides a forum to help ensure that the voice of our membership is heard. We invite participation from companies with a demonstrated interest in these disorders. While we are grateful to our Industry Council members for their support, we do not endorse any specific product or company. IFFGD retains unrestricted control over the planning, content, objectives, methods, and execution of all initiatives and projects.

IFFGD INDUSTRY COUNCIL

Sucampo Pharmaceuticals, Inc. and Takeda Pharmaceuticals USA, Inc.

Salix Pharmaceuticals, Ltd.

QOL Medical, LLC.

NPS Pharmaceuticals, Inc.

Ironwood Pharmaceuticals, Inc.

Ferring International PharmaScience Center US, Inc.

Entera Health, Inc.

Actavis

Seeking Participants with Diabetic Gastroparesis

Purpose of Study: To assess the safety of IW-9179 in individuals with diabetic gastroparesis and its effects on the principal symptoms of diabetic gastroparesis.

Sponsor: Ironwood Pharmaceuticals, Inc.

Study Population: Eligible male and female patients over the age of 18 and with a diagnosis of type 1 or type 2 diabetes mellitus and a diagnosis of diabetic gastroparesis.

Contacts: Find a recruiting location online at *ClinicalTrials.gov*; refer to *ClinicalTrials.gov* identifier: NCT02289846

Linaclotide for Treatment of IBS-C and CIC

Linaclotide, a guanylate cyclase type-C (GC-C) agonist, is a prescription drug used to relieve symptoms of abdominal pain, discomfort, bloating, and bowel symptoms in people who have irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC). It has been shown to be safe and effective in trials. It works by increasing the amount of fluid that flows into the bowel, allowing stool to pass more easily, and reducing abdominal pain.

Linaclotide (Linzess) has been available in the United States to treat IBS-C and CIC in adults aged 18 and older since 2012. It is available in Canada and several European countries with the EU brand name Constella.

Linaclotide should *not* be used in patients 17 years of age or younger or in patients with known or suspected mechanical gastrointestinal obstruction. The most common side effect reported during clinical studies was diarrhea.

Linaclotide is being co-produced in the United States by Ironwood Pharmaceuticals and Actavis. Ironwood has out-licensed linaclotide to Almirall, S.A. for development in Europe; to Astellas Pharma for development in Japan, Indonesia, Korea, the Philippines, Taiwan, and Thailand; and to AstraZeneca in China.

Participants Sought for Congenital Sucrase-Isomaltase Deficiency (CSID) Genetic Prevalence Study in Children with Chronic Diarrhea or Chronic Abdominal Pain

Congenital sucrose-isomaltase deficiency (CSID) is a rare genetic disorder that affects a person's ability to digest the sugars sucrose and maltose. Sucrose is found in fruits, and is also known as table sugar. Maltose is the sugar found in grains.

In this study, clinicians are looking at using two different tests to rule out CSID, which often causes chronic diarrhea and/or abdominal pain. Children 18 years of age or younger experiencing chronic diarrhea or abdominal pain for at least 4 weeks, may qualify to participate in this study.

If your child is eligible, there is the potential for up to three doctor's office visits that could include: having the inside of his/her cheeks swabbed to look for common CSID genetic mutations, taking a breath test, providing a medical history review, and completing a few questionnaires.

Purpose of Study: Determine the prevalence of CSID genetic variants in subjects 18 years of age or younger with a primary symptom of chronic idiopathic diarrhea or chronic abdominal pain without constipation.

Sponsor: QOL Medical, LLC

Collaborators: 19 Medical Centers located throughout the U.S.

Contact: Healther Elser, Ph.D., 919-832-4949, *helser@qolmed.com*. Refer to *ClinicalTrials.gov* identifier: NCT01914003.

Review Article Concludes that Bile Acid Transport Inhibitor Elobixibat is Effective in Treating Chronic Idiopathic Constipation

Elobixibat is a first-in-class compound under investigation by Ferring Pharmaceuticals for treatment of chronic idiopathic constipation (CIC), and for irritable bowel syndrome with constipation (IBS-C).

An article recently published in the journal *Therapeutic Advances in Gastroenterology* reviewed data that examined the mechanisms by which bile acids can affect symptoms in CIC and the role of the drug elobixibat in managing these symptoms. Bile acids are digestive juices that have a stimulating effect in the colon. Elobixibat reduces bile absorption in the small intestine. This stimulates bowel movements by increasing fluid secretions and motility in the colon.

The authors concluded that published research shows that elobixibat significantly affects the symptoms of CIC, with minimal and tolerable side effects.

Medical Food in the Management of Diarrhea

EnteraGam™ is a prescription *medical food* product to help people manage ongoing problems with chronic loose and frequent stools (diarrhea). Medical foods are required to be used under physician supervision as part of ongoing medical care for a specific condition or disease.

EnteraGam is manufactured and distributed by Entera Health, Inc. It is indicated for the clinical dietary management of intestinal disease (enteropathy) in patients who, because of therapeutic or chronic medical needs, have limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients.

The main ingredient in EnteraGam is a specially formulated protein preparation that consists of more than 50 percent of immunoglobulin (molecules involved with immune function). This ingredient, SBI (serum-derived bovine immunoglobulin/protein isolate), is made up of beef serum proteins. The proteins in SBI remain in the intestine and are not absorbed whole.

Review Looks at Effects of SBI on Managing Conditions like IBS-D

A review, which summarizes accumulated data from prior studies, concluded that specially formulated immunoglobulin sources like SBI have multiple effects, which collectively serve to improve and maintain nutrient utilization, including water balance. This aids in the management of intestinal disorders (enteropathy) in patients with chronic loose and frequent stools in conditions like irritable bowel syndrome with diarrhea (IBS-D).

The mode of action appears to be combined effects on inflammation, gut barrier function, and immune balance. The study review, by Petschow et al, was published in August 2014 in the journal, *Digestive Diseases and Sciences*. The authors are employed by Entera Health.

Study Evaluates Impact of SBI in People with IBS-D

Results from a randomized, double-blind, placebo-controlled pilot study enrolling 66 subjects suggest that nutritional therapy with SBI, the ingredient found in EnteraGam – used in addition to traditional medical care – can help manage various symptoms associated with irritable bowel syndrome with diarrhea (IBS-D). The study, by Wilson et al., was published in 2013 in the journal, *Clinical Medicine Insights: Gastroenterology*.

FDA Approves Eluxadoline (Viberzi) for Treatment of IBS-D in Men and Women

On May 27, 2015 the U.S. Food and Drug Administration (FDA) approved eluxadoline (Viberzi™), a new drug treatment for irritable bowel syndrome with diarrhea (IBS-D) in adult men and women. Viberzi is taken orally twice daily with food. The drug activates receptors in the nervous system that can lessen bowel contractions.

Viberzi is a novel drug compound to treat diarrhea and abdominal pain associated with IBS-D. The safety and effectiveness of the drug for treatment of IBS-D were established in two double-blind, placebo-controlled clinical trials in which 2,425 patients were randomly assigned to receive the eluxadoline or placebo. Results showed Viberzi was more effective in simultaneously reducing abdominal pain and improving stool consistency than placebo over 26 weeks of treatment.

In clinical trials the drug was generally well tolerated. The most common side effects in patients treated with Viberzi were constipation and nausea.

The most serious known risk associated with Viberzi is the risk of spasm in the sphincter of Oddi, the smooth muscle that surrounds the end portion of the common bile and pancreatic ducts, which can result in pancreatitis. In clinical trials, sphincter of Oddi spasm occurred in less than 1% of the patients receiving Viberzi, which usually arose within the first week of treatment and resolved when they stopped taking Viberzi.

Viberzi should *not* be used in patients with a history of bile duct obstruction, pancreatitis, severe liver impairment, or severe constipation, and in patients who drink more than three alcoholic beverages per day.

Viberzi has mixed opioid receptor activity. It is a mu receptor agonist, a delta receptor antagonist, and a kappa receptor agonist.

The FDA has recommended that Viberzi be classified as a controlled substance. Product availability is expected in early 2016.

Teduglutide Granted Orphan Drug Status in Japan

In January 2015 the Japanese Ministry of Health, Labor, and Welfare (MHLW) granted teduglutide (Gattex in the U.S.; Revestive in the E.U.) orphan drug status for the treatment of adult patients with short bowel syndrome (SBS).

Data Supports Long-Term Use of Gattex for Treatment of Short Bowel Syndrome

In June 2014 the U.S. Food and Drug Administration (FDA) approved updated labeling for teduglutide (Gattex) for injection to include long-term data from adult patients with Short Bowel Syndrome (SBS). The revised labeling provides important information for healthcare professionals and patients about long-term use of teduglutide.

The data, published in 2013, demonstrated that there was an increased response to treatment over time in all groups receiving teduglutide. The open-label extension study included 88 adult patients with SBS. Investigators reported that the long-term use of teduglutide in patients with SBS resulted in additional, clinically meaningful reductions in the volume and days per week of parenteral support requirements in this extension study. Thirteen patients in the study achieved complete independence from parenteral support with long-term teduglutide therapy. No new unexpected safety concerns were observed with long-term teduglutide treatment and the product's safety profile remains consistent with the product's label.

The drug works by regeneration of cells in the intestinal lining, slowing down transit through the gut and increasing blood flow, allowing for increased nutrient absorption.

In studies, the drug was associated with achieving and maintaining clinically meaningful reductions in parenteral nutrition (PN) and intravenous (IV) fluid volume in adult subjects with SBS.

Teduglutide was approved by the FDA as Gattex in 2012 for treatment of adult patients with SBS who are dependent on parenteral support. To help ensure that the benefits of the drug outweigh the risks for causing other serious conditions, the drug is approved with a Risk Evaluation and Mitigation Strategy, which patients need to discuss with their doctors. While the researchers found the safety profile to be acceptable, they advise that physicians closely monitor patients beginning the drug for side effects and possible need to adjust dosage.

SBS is a rare condition related to poor absorption of nutrients. It typically occurs in people who have a significant portion of their small intestine removed due to disease or injury. They cannot absorb enough water, vitamins, and other nutrients from food and may then need to use parenteral nutrition and intravenous fluids.

Patients with SBS Sought for Long-term Study

Purpose of Study: This global clinical study has begun enrolling patients with short bowel syndrome (SBS) in order to provide additional long-term data on safety of teduglutide and on the natural history of SBS in patients in routine, real world settings. The information gathered is intended to assist healthcare providers in optimizing their clinical decision making in managing SBS patients.

Enrollment will include SBS patients treated and not treated with teduglutide.

Sponsor: NPS Pharmaceuticals, Inc.

Study Population: Male and female patients of any age with a diagnosis of SBS, including those who have never taken teduglutide, as well those who have or are using teduglutide.

Study Follow-up Duration: 10 years

Contact: NPS Clinical Operations, phone: 908-450-5300, email: *SBSregistry@quintiles.com*; refer to *ClinicalTrials.gov* identifier: NCT01990040

FDA Approves Rifaximin (Xifaxan) for Treatment of IBS-D in Adults

On May 27, 2015 the U.S. Food and Drug Administration (FDA) approved the antibiotic rifaximin (Xifaxan®) 550 mg for treating irritable bowel syndrome with diarrhea (IBS-D) in adult men and women.

The safety and effectiveness of Xifaxan for treatment of IBS-D were established in three double-blind, placebo-controlled trials. In the first two trials, 1,258 patients were randomly assigned to receive Xifaxan or placebo for 14 days, and then followed for a 10-week treatment-free period. More Xifaxan-treated patients reported improvements in abdominal pain and stool consistency than those on placebo.

A third trial evaluated repeat courses of Xifaxan, because patients with IBS-D can develop recurrent signs and symptoms after a single treatment course of Xifaxan. A total of 636 patients with recurrence were randomized to receive either Xifaxan or placebo for two additional 14-day courses separated by 10 weeks. More patients treated with Xifaxan than placebo were responders in abdominal pain and stool consistency in this phase of the study.

Xifaxan works by reducing or altering bacteria in the gut. It is only slightly absorbed in the gut and is generally tolerated well. The most common side effects in patients treated with Xifaxan for IBS-D include nausea and an increase in alanine aminotransferase (ALT), a liver enzyme measured in blood.

If diarrhea does not improve or worsens after treatment with Xifaxan, then evaluation for development of *C. difficile* enterocolitis should be performed. Caution should be used when using Xifaxan in patients with severe liver impairment or when combined with certain other drugs.

Lubiprostone Study Published Showing Efficacy in Opioid-Induced Constipation

A study published in 2014 in the medical journal *Pain Medicine* examined the efficacy and safety of lubiprostone (Amitiza) for relieving symptoms of opioid-induced constipation (OIC) in chronic non-cancer pain. The study found that patients treated with lubiprostone showed significant overall improvement for abdominal discomfort, straining, constipation severity and stool consistency when compared to placebo. The authors concluded that lubiprostone was effective and well tolerated in OIC patients with chronic non-cancer pain.

Lubiprostone is a prescription drug first FDA approved in 2006 to relieve abdominal pain, bloating, and straining and produce softer and more frequent bowel movements in men and women who have chronic idiopathic constipation (CIC). It is also FDA approved to treat irritable bowel syndrome with constipation (IBS-C) in women who are at least 18 years of age. Lubiprostone works by increasing the amount of fluid that flows into the bowel and allowing the stool to pass more easily.

Two Studies of Lubiprostone in Pediatric Subjects with Functional Constipation

Purpose of study 1: This is a 12-Week study to evaluate the efficacy, safety, and pharmacokinetics of oral lubiprostone as treatment for pediatric patients with functional constipation.

Purpose of study 2: This is a 9-Month study to evaluate the long-term safety, efficacy, and pharmacokinetics of oral lubiprostone as treatment for pediatric patients with functional constipation.

Collaborators: Sucampo Pharma Americas, LLC and Takeda

Participation: Eligible male and female patients aged 6–17 years

Contact: Shadreck Mareya, PhD, phone: 301-961-3400, email: *pedgen@sucampo.com*; refer *ClinicalTrials.gov* identifier: NCT02042183 (study 1) and NCT02138136 (study 2) ■

Amber's Personal Story

Since the creation of her website, *www.eatsandexercisebyamber.com/*, Amber Vesey has taken on the title of IBS Advocate.

IBS – three letters that used to control my life.

I was diagnosed with irritable bowel syndrome, IBS, at the age of 15. During my college years my IBS symptoms spiraled out of control.

Suddenly my stomach was the size of a beach ball and an x-ray showed that my intestines were filled with stool. I didn't understand how I was constipated; I was still going to the bathroom. I was told to take an over-the-counter laxative and thought I had found the solution to my problems. Little did I know that this would be the start of my struggles.

Over the next three years, I had countless endoscopies, biopsies, a colon pressure exam, the Smart Pill test, as well as a slew of blood work, which all came back inconclusive. Slow transit time, a loopy colon, weak sphincter muscles, but nothing that was found to be the root of all my suffering. I cut out dairy, but that didn't make a difference, and despite being diagnosed with Celiac Disease, going gluten free did not alleviate my symptoms.

Slowly, my medication totaled 10 pills a day, yet I was still experiencing extreme bloating and distention, and constipation. I developed unbearable stomach pain that sent me to the hospital twice, only to be sent home with pain killers for "stomach pain, cause unknown" and "colic." I sat teary eyed in my doctor's office saying I couldn't handle living my life like this.

For over three years, I experienced extreme flare-ups. I lost track of the social events declined because I was at home writhing in pain, bloated beyond recognition, or chained to the bathroom. I began to hate my body and became afraid of food because anything I ate would send my intestines into distress.

"I advocate for myself and others with this digestive disorder as much as I can because most people suffer in silence or are unaware of how detrimental a condition like IBS can be."

Desperately seeking relief, one night in 2013 a Google search led me to the IBSOS Clinical Trial, a non-medication type of treatment that gave me hope.

The clinical trial involved a lot of paperwork, self-work and effort on my part. At first, I was skeptical, but after slowly starting to see improvement, I became a believer.

Now, I am not "cured" of my IBS. I still experience symptoms and have to take extra medication from time to time. I have foods I have to avoid, as well as a routine I need to follow to keep my irate intestines appeased. But the frequency of the symptom flare-ups and my *entire* attitude has changed. This is the happiest and healthiest I have ever been.

My changed outlook is what motivates me to be so open about my condition and advocate not only for myself, but others as well. After finishing my last session in the clinical trial I offered to be the face of the trial. I got the opportunity to be on the news, as well as share my story with others, in hopes to help them find relief.

I have Irritable Bowel Syndrome, but it does not have me. I am in control of my life, not my chronic condition. I am beautiful, bloated or not, because my self worth is not set on my reflection. I thrive with my symptoms, not merely survive.

To see Amber's interview on her local news station, visit her Awareness Ambassador story page at DHA.org, *www.dha.org/raise-awareness/stories/1611/amber.*

A clinical study or clinical trial is a research study to answer specific questions about new products, therapies, or new ways of using known treatments.

Amber was enrolled in The Irritable Bowel Syndrome Outcome Study (IBSOS) at the University at Buffalo Behavioral Medicine Clinic at Erie County Medical Center in Buffalo, New York. The study is a seven-year, multi-site clinical trial to test the efficacy of a behavioral self-management treatment for IBS, aimed at changing the interactions between the brain and the gut.

Learn more about clinical trials, including the one that Amber took part in, by visiting our website at *www.giresearch.org/site/studies/*. ■

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Our Unique Mission: The International Foundation for Functional Gastrointestinal Disorders (IFFGD) is a nonprofit education and research organization dedicated to informing, assisting, and supporting people affected by gastrointestinal disorders. IFFGD has been working since 1991 with patients, families, physicians, practitioners, investigators, employers, regulators, and others to broaden understanding about gastrointestinal disorders and support research.

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