



The Upper GI Tract and Its Common Functional and Motility Disorders

By: IFFGD Staff, the International Foundation for Functional Gastrointestinal Disorders (IFFGD), Milwaukee, WI

As a whole, the digestive system can be understood as a food processor. Its job is to receive food and break it down into essential elements, making them available to the body so that it can function and develop. The process of digestion is carried out by different parts of the gastrointestinal (GI) tract, which each have a unique function to perform. The GI tract is divided into four distinct parts: the esophagus, stomach, small intestine, and large intestine (colon). These parts are separated from each other by special muscles called sphincters, which regulate the movement of food from one part of the GI tract to another.

When motility or sensations of one or more parts of the GI tract are not appropriate for performing the correct function, they cause symptoms such as bloating or vomiting that are associated with sensations such as pain, bloating, and fullness. This article describes some common disorders affecting the upper GI tract (the esophagus and stomach), symptoms that can result from abnormal motility or sensation, and treatment approaches.

GERD

Gastroesophageal reflux disease, or GERD, develops when the back-flow (reflux) of stomach contents causes symptoms. GERD is often characterized by symptoms, with or

without tissue damage, that result from repeated or prolonged exposure of the lining of the esophagus to acidic or non-acidic contents of the stomach.

GERD is often accompanied by symptoms such as heartburn or regurgitation. But, sometimes there are no apparent symptoms, and the presence of GERD is revealed only when complications become evident.

Various methods to effectively treat GERD include lifestyle measures, the use of medications, such as antacids, H2 blockers, or proton pump inhibitors (PPIs), or surgical or endoscopic procedures. GERD is a chronic disease for which long-term medical therapy is usually effective.

Functional Dyspepsia

Functional dyspepsia is a common disorder that affects up to 30% of the general population.

Symptoms of dyspepsia include upper abdominal pain or discomfort and frequently include symptoms of burning, pressure, or fullness often, but not necessarily, related to meals. Other common symptoms include the early feeling of fullness (satiety), nausea, belching, and bloating.

Treatment for functional dyspepsia usually includes dietary changes, eradication of *H. pylori* infection if present, and a

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GERD Awareness Week is November 20–26, 2016 and takes place each year during the week of Thanksgiving.

Learn more about GERD on IFFGD's dedicated website
www.aboutGERD.org.

The Upper GI Tract and Its Disorders

combination of acid-lowering medications, prokinetic and antiemetic agents to manage nausea and other symptoms, and centrally acting therapies, such as certain antidepressants. Hypnotherapy has also been shown to improve symptoms of functional dyspepsia in some people.

Gastroparesis

Gastroparesis is a disorder characterized by the presence of certain long-term symptoms together with delayed stomach emptying in the absence of any observable obstruction or blockage.

There are a number of things that may contribute to or cause gastroparesis. In the majority of people with the condition, the cause is unknown, termed “idiopathic.” Other possible causes include long-standing diabetes, as a complication of some surgical procedures, following the use of certain medications, or in association with other illnesses, such as systemic illnesses, neurologic diseases, or connective disorders.

The signs and symptoms of gastroparesis may differ among persons with the condition, however, chronic symptoms that are

characteristic of gastroparesis include nausea and/or vomiting, retching (dry heaves), stomach fullness after a normal sized meal, and early fullness. Bloating, as well as stomach discomfort or pain, are also noted by some individuals with the condition, particularly as symptoms become more severe.

Treatments for gastroparesis are aimed at managing or reducing symptoms, maintaining quality of daily living, and minimizing related problems in the long-term. Treatment approaches may involve one or a combination of dietary and lifestyle modifications, medications, and/or procedures such as enteral nutrition, parenteral nutrition, gastric electrical stimulation (GES), or others.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a rare disease in children and adults characterized by food-related reactions.

The primary symptoms are nausea, vomiting, difficulty swallowing, reflux, abdominal or chest pain, reduced appetite, and/or food impaction (food which gets stuck in the esophagus).

Last month IFFGD took part in the **American Gastroenterological Association (AGA) 2016 Drug Development Conference, Clinical Endpoints in Upper GI Disorders.**

This meeting brought together researchers, clinicians, industry leaders, members of the U.S. Food and Drug Administration (FDA), and patient advocates to communicate what is currently known in the field of upper GI disorders and to provide input into the design and conduct of future clinical trials. Meetings such as this one can help to elevate the research profile of these conditions, share insight into ways to improve research into effective therapies, and, ultimately, improve the lives of all those living with a functional GI or motility disorder.

Treatment may include diet modification and medications. Most cases require steroid therapy to induce remission.

Conclusion

As we learn more about the functioning of the upper GI tract in these disorders and gain information on how affected individuals are impacted, a better understanding of these conditions and future directions for effective treatments will emerge.

GERD
Awareness
Week

The week of
Thanksgiving,
November

aboutGERD.org

Gastroesophageal reflux disease, or GERD,
is more than simple heartburn.

Learn the symptoms and see your doctor
to get the help you need.



National GERD Awareness Week

The 17th Annual GERD Awareness Week is November 20–26, 2016. Gastroesophageal reflux disease, or GERD, is a very common disorder. Each year around the week of Thanksgiving, IFFGD encourages people experiencing symptoms, which may be GERD-related, to consult their physicians and to learn more about the condition.

GERD Awareness Week, with sponsorship from IFFGD, is listed on the U.S. National Health Observances calendar. Health observances are days, weeks, or months devoted to promoting particular health concerns. Health professionals, teachers, community groups, and others can use these special times to sponsor health promotion events and stimulate awareness of health issues.

GERD is More Than Simple Heartburn: Tips on When to See a Doctor

Occasional heartburn is quite common, especially after eating large meals during the holiday season. But, not all heartburn is the same. It is important to distinguish simple, occasional heartburn from long-standing heartburn that keeps recurring. Frequent, worsening, or persistent heartburn signals that it's time to see your doctor or healthcare provider to receive an accurate diagnosis and the right treatment. An underlying condition such as gastroesophageal reflux disease (GERD) could be the cause.

GERD affects one in five or more adult men and women in the U.S. While the disease usually can be treated effectively, its symptoms often are unrecognized or misunderstood.

GERD occurs when stomach contents flow back (reflux) into the food pipe (esophagus). Repeated reflux can irritate the lining of the esophagus, cause uncomfortable symptoms, and possibly lead to complications such as tissue damage in the esophagus or difficulty swallowing. Most people with GERD have mild symptoms, with no visible evidence of tissue damage and little risk of developing complications.

Chronic heartburn is the most frequently reported symptom. Because heartburn is so common, it may be self-treated or ignored. But self-treatment may delay effective treatment.

It is time to see a doctor if your heartburn:

- persists or becomes more severe,
- happens at night and wakes you from sleep,
- occurs two or more times a week,
- has been occurring for five years or more, or
- creates pain that interferes with daily activities.

Regurgitation (refluxed material into the mouth) is another common symptom of GERD. Other symptoms may occur, such as trouble swallowing, sore throat, or hoarseness in the morning. Sometimes there are no apparent symptoms, and the presence of GERD is not revealed until complications appear.

A diagnosis of GERD should be made by a doctor. Symptoms usually can be reduced and may require a combination of approaches.

"Once diagnosed, GERD can be treated and, in most cases, people can begin to lead far more comfortable lives," said Nancy Norton, President of the International Foundation for Functional Gastrointestinal Disorders (IFFGD). Often treatment involves dietary and other lifestyle changes. A doctor may also recommend medications, which can reduce the amount of acid the stomach produces. Other treatments may include surgery or endoscopic procedures to help prevent reflux.

Most people with GERD have a form of the disease that can be controlled. But GERD may lead to complications if left untreated. See a doctor to have symptoms checked and to develop an effective treatment plan for GERD.

Learn more about GERD by visiting the IFFGD web site at: www.aboutGERD.org.



Medical & Research News

Family Environments May Play Roles Equal to Genetics in Some Diseases

Researchers who examined the medical histories of a large group of people and their families from the United Kingdom (UK) – including both blood and adoptive relatives – concluded that family history of disease may be as much the result of shared lifestyle and surroundings as inherited genes.

Looking at incidences of 12 common diseases, the results show that not only genetic but also familial environmental factors make substantial contributions to a person's risk of some diseases, pointing out the need to identify environmental factors that contribute to diseases and how to modify them to reduce disease risk.

The researchers used data from self-reported personal and family history of disease in 1,555,906 white European participants and relatives from the UK Biobank database of volunteers' health.

Source: Munoz M, et al. *Nature Genetics*. July 2016.

Psychological Therapies Found to Reduce Symptoms of IBS

A review of existing randomized controlled research studies, involving data from 2,209 individuals with irritable bowel syndrome (IBS), concluded that psychological therapies, including cognitive, relaxation, and hypnosis treatments, are effective in improving gastrointestinal (GI)

symptoms in adults with IBS. About half of participants were assigned to a psychotherapy and half to control conditions (such as treatment as usual, education, sham treatments). On average, individuals who received psychotherapy had a greater reduction in GI symptoms after treatment than 75% of individuals assigned to a control condition and effectiveness was maintained after both short-term (less than 6 months) and long-term (6–12 months) follow-up periods.

Source: Laird KT, et al. *Clin Gastroenterol Hepatol*. December 2015.

Relamorelin Found to Reduce Symptoms in Adults with Diabetic Gastroparesis

In a 4-week randomized, double-blind, Phase 2 clinical study involving 204 adults with diabetic gastroparesis, the drug relamorelin was found to be better than placebo in accelerating gastric emptying and reducing vomiting. No overall safety concerns were identified.

Source: Lembo A, et al. *Gastroenterology*. July 2016.

Swallowed Flonase Effective for Long-Term Management of EoE in Children

A prospective, single-center study of 54 children (80% male) between the ages of 2 and 17 years with active eosinophilic esophagitis (EoE) that looked at long-term safety (up to around 24 months) of swallowed fluticasone (Flonase) concluded that swallowed fluticasone is

effective as a long-term management therapy for children with EoE, without growth impediment or serious side effects.

Source: Andrae DA, et al. *Am J Gastroenterol*. August 2016.

Treatment Approved by F.D.A. for Fecal Incontinence

The U.S. Food and Drug Administration (FDA) has approved the surgically implanted FENIX Continence Restoration System to treat fecal incontinence in certain individuals who are not candidates for, or who have not previously been helped by, medical or other surgical treatment options. The FENIX System consists of a ring of titanium beads with magnetic cores designed to support a weak sphincter muscle with the aim of reducing incontinence events. The FDA reviewed data for the FENIX System through the humanitarian device exemption (HDE) process. The system was studied over a 12 month period in 35 adults who failed conventional medical therapy for treating fecal incontinence. Among patients who have failed other fecal incontinence therapies, the results suggest that some could benefit from the device. Adverse events identified in the clinical trial for the FENIX System include pain, infection, impaction or defecatory disorder, device erosion, device removal/re-operation, and bleeding. Find more details at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm477914.htm.

Nausea and Vomiting in Gastroparesis

Among 159 patients with gastroparesis (107 idiopathic) enrolled in the National Institute of Diabetes and Digestive and Kidney Disorders (NIDDK) Gastroparesis Registry asked to complete questionnaires assessing nausea and vomiting in gastroparesis and their influence on quality of life, nausea was found to be present in essentially all patients (96%) with gastroparesis regardless of cause and was found to be more prevalent, more severe, and occurred more frequently in individuals with diabetic gastroparesis. Diabetic patients more often experienced vomiting in the morning before eating, during the night, and when not eating.

These observations suggest that, while nausea was present in nearly all patients regardless of cause, the characteristics of vomiting differ between individuals with diabetic and idiopathic gastroparesis

Source: Parkman HP, et al. *J Neurogastroenterol Motil.* June 2016.

An Association, But Not a Clear Link, Has Been Observed Between Rosacea, and Certain Gastrointestinal Disorders

A nationwide study in Denmark of 49,475 individuals with rosacea (an inflammatory facial skin condition) and 4,312,213 controls found an association between rosacea and the incidence of certain GI disorders, including IBS, celiac disease, and Crohn's disease. While no causal link is known, the authors suggest that clinical suspicion of these conditions should be considered in patients with rosacea and GI symptoms.

Source: Egeberg A, et al. *Brit J Dermatol.* August 2016.

C. difficile Infection May Be a Risk Factor for IBS

Among 205 individuals with *Clostridium difficile* (*C. difficile*) infection with no pre-infection history of IBS, 25% (n = 52) developed IBS over 6 months following infection. Mixed diarrhea and constipation predominant IBS (IBS-M) was the most common diagnosis, followed by IBS with diarrhea (IBS-D). Longer duration of *C. difficile* infection (greater than 7 days), high anxiety scores, and higher body mass index (BMI) were found to be independent risk factors for the development of post-infectious IBS.

Source: Wadhwa A, et al. *Aliment Pharmacol Ther.* July 2016.

Preliminary Results Announced for OIC Treatment

Positive results were reported from a randomized, double-blind, placebo-controlled Phase 3 clinical trial of investigational drug naldemedine in 547 patients with opioid induced constipation (OIC) following use of opioids for chronic, non-cancer pain. Naldemedine was found to significantly increase spontaneous bowel movements better than placebo over a study period of 12 weeks. The drug was well-tolerated, with diarrhea and abdominal pain being the principal side effects.

Source: American Academy of Pain Medicine (AAPM) 2016 Annual Meeting. Poster #192.

New Breath Test for Gastroparesis

A new non-invasive, non-radioactive Gastric Emptying Breath Test (GEBT) approved in 2015 by the FDA has recently become available. The GEBT, conducted over a four hour period after an overnight fast and a special meal, is designed to show how fast the stomach empties solids by measuring carbon dioxide in a patient's breath. Researchers compared diagnostic results from both GEBT and the conventional gastric scintigraphy test and found that GEBT results agree with scintigraphy results 73–97 percent of the time when measured at various points during the test.

Mirtazapine Found to Reduce Some Symptoms of Functional Dyspepsia 5

Results of a randomized, double-blind, placebo-controlled pilot study of 34 mostly female (n = 29) patients with functional dyspepsia who have experienced weight loss greater than 10% of their original body weight found the antidepressant drug mirtazapine to improve symptoms of early feeling of fullness (satiation), quality of life, GI-specific anxiety, nutrient tolerance, and unintentional weight loss better than placebo over eight weeks. The principal side effect of the drug was drowsiness. Further research is necessary to confirm the safety and efficacy of mirtazapine for functional dyspepsia with weight loss.

Source: Tack J, et al. *Clin Gastroenterol Hepatol.* March 2016.

IFFGD Industry Council

Formed in 1998, the IFFGD Industry Council facilitates communication with the Council participants – helping us make the needs of people with functional GI and motility disorders known to the companies with the means and interest to develop treatment products and services. While we do not endorse any specific product or company, we thank the IFFGD Industry Council participants for helping support the mission of IFFGD.

- QOL Medical, LLC
- Shire
- Ironwood Pharmaceuticals, Inc.
- Allergan

Congenital Sucrase-Isomaltase

Deficiency (CSID) – CSID is a genetic disorder that affects a person's ability to digest certain sugars. Symptoms usually begin in childhood and typically include stomach cramps, bloating, excess gas production, and diarrhea. Recent studies suggest that CSID may be more common than currently estimated. Newer genetic tests and more accurate noninvasive breath tests may lead to more accurate prevalence studies and diagnosis of less typical cases. Learn more at IFFGD.org/other-disorders/congenital-sucrose-isomaltase-deficiency-csid

Linaclotide for IBS-C or Chronic Idiopathic Constipation – Linaclotide (Linzess/Constella) is a prescription drug to relieve symptoms in people who have irritable bowel syndrome with constipation (IBS-C), or chronic idiopathic constipation. In studies, patients taking linaclotide experienced improvement in multiple symptoms including pain or discomfort, bloating, and bowel function. Learn more at IFFGD.org/news/industry-treatment-news/linaclotide-linzess

Participants Sought for Linaclotide Study for IBS-C in Children –

Participants sought for a multicenter, randomized, double-blind, placebo-controlled safety and efficacy study of a range of linaclotide doses administered orally to children, ages 7 to 17 years, with IBS-C. The purpose of this study is to evaluate the safety and efficacy of linaclotide for the treatment of **IBS-C in children ages 7–17 years**. For more information on this Phase II study, visit www.marco-polostudies.com or phone 888-609-3456.

Participants Sought for Linaclotide Study for Functional Constipation in Children –

Participants sought for a multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety and efficacy study of a range of linaclotide doses administered orally to children, ages 6 to 17 years, who fulfill modified Rome III Criteria for child/adolescent functional constipation. The purpose of this study is to evaluate the safety and efficacy of linaclotide for the treatment of **functional constipation in children ages 6–17 years**. For more information on this Phase II study, visit www.marco-polostudies.com or phone 888-609-3456.

Eluxadoline for IBS-D –

Eluxadoline (Viberzi) is a drug FDA approved in 2015 for treatment in adult men and women of diarrhea and abdominal pain associated with diarrhea predominant irritable bowel syndrome (IBS-D). It works by decreasing bowel activity. Learn more at IFFGD.org/news/industry-treatment-news/eluxadoline

Teduglutide for Short Bowel Syndrome (SBS) –

Teduglutide (Gattex®/Revestive®) is a drug for the treatment of SBS, a rare condition related to poor absorption of nutrients. It typically occurs in people who have had half or more of their small intestine removed who may then need to use

parenteral nutrition (PN) and intravenous (IV) fluids, the slow infusion of a solution of nutrients and fluids into a vein. Gattex works by regenerating cells in the intestinal lining, slowing down transit through the gut and increasing blood flow, and allowing for increased nutrient absorption. In studies, the drug was associated with achieving and maintaining clinically meaningful reductions in PN and IV fluid volume in adult subjects with SBS. Learn more at IFFGD.org/news/industry-treatment-news/Gattex

Participants Sought for Study of Teduglutide for Treatment of

Pediatric SBS – Participants sought for a SBS research study for children up to 17 years of age on PN. The aim of the study is to increase absorption of nutrients which may result in decreased PN support. For more information on this Phase III study email clinicaltransparency@shire.com, and refer to its ClinicalTrials.gov identifier: NCT02682381.

Participants Sought for Long-Term Study of SBS –

Participants of any age are being sought for a long-term research study of patients with SBS. For more information email to clinicaltransparency@shire.com, and refer to its ClinicalTrials.gov identifier: NCT01990040.

Study of Oral Budesonide for

Treatment of EoE – Eosinophilic Esophagitis (EoE) is a chronic immune system disease. It can cause inflammation and lead to difficulty swallowing (dysphagia). Participants are sought for a study in adolescents and adults with EoE to measure the histologic response and determine if any reduction in dysphagia is achieved. Learn more at IFFGD.org/news/industry-treatment-news/eosinophilic-esophagitis-study

Diagnostic Gene Studies for Chronic Intestinal Pseudo-Obstruction

By: Aubrey Milunsky, M.D., Founder and Co-Director, Center for Human Genetics, Cambridge, MA

CIPO, with or without frequent bladder involvement, is caused primarily by a mutation in a gene transmitted through a dominant mode of inheritance (an affected person having a 50% risk of passing the disorder to each of his or her children). The disorder can also occur due to a new mutation.

Thus far, the most important gene (ACTG2) discovered with mutations account for 44% of patients with CIPO. Analysis of 111 affected individuals (one from each family) from our studies, combined with those reported in the medical literature, revealed that 49 had a mutation in this gene.

CIPO can be diagnosed prenatally by lab test analysis of this gene which can also enable future prenatal diagnosis and preimplantation genetic diagnosis.

We are seeking a second gene, and welcome families who wish to participate in this research effort. If interested, please email amilunsky@chginc.org for details.

Website for more information: www.chginc.org.

Dr. Milunsky is the Founder and Co-Director of the Center for Human Genetics. He also serves as Adjunct Professor of Obstetrics and Gynecology at Tufts University School of Medicine, Boston, MA.

Common Questions About Chronic Intestinal Pseudo-Obstruction

What is Chronic Intestinal Pseudo-Obstruction?

Chronic intestinal pseudo-obstruction (CIPO) is a relatively rare disorder of gastrointestinal (GI) motility in which the coordinated contraction of muscles that propel food and other contents through the GI tract (peristalsis) becomes altered and inefficient. When this happens, nutritional requirements of the body cannot be adequately met.

What are the signs and symptoms of CIPO?

Symptoms of CIPO vary in their presentation and severity. The most common symptoms include abdominal pain and distension, nausea, vomiting, swallowing difficulty, and constipation. Diarrhea, bladder problems, the premature feeling of fullness (satiation), gastroesophageal reflux symptoms, and weight loss may also be present.

There is no single lab test to diagnose CIPO. Symptoms may mimic or be similar in their presentation to other GI disorders. The diagnosis of CIPO is made on the basis of symptoms, clinical findings, and tests including ruling out the presence of a mechanical obstruction.

What causes CIPO?

The term “pseudo-obstruction” refers to a group of GI disorders with similar characteristics that can have a number of causes. The symptoms of CIPO are caused by a problem in how the smooth muscles of the intestine (visceral myopathy) and the nerves that control the propulsive movements of the intestines (which move stomach contents forward) work. When tests show that the dysfunction is caused by unsynchronized contractions, the disorder is classified as neurogenic (arising from the nerves). If the dysfunction is caused by weak or absent contractions, the disorder is classified as myogenic (arising from the muscles).

How is CIPO treated?

The primary treatment strategy for CIPO is nutritional support to prevent malnutrition and antibiotics to treat any present bacterial infections. Long-term intravenous feeding (TPN) is often required. Surgical procedures are common, and may include removal of a portion of the intestine (e.g. colectomy) or even the removal of the entire intestine, stomach, or other organs.

The challenges of treating CIPO are often multifaceted and involve the patient and family as well as the physician. The physician may suggest a multidisciplinary approach to treatment. A management team might include the child's pediatric gastroenterologist, a pediatric pain management specialist, a behavioral specialist, and others.

*Adapted from IFFGD Publication #843 by William F. Norton, IFFGD, Milwaukee, WI;
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INTERNATIONAL FOUNDATION FOR FUNCTIONAL GASTROINTESTINAL DISORDERS

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.



Visit IFFGD at:

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Articles in *Digestive Health Matters* are in no way intended to replace the knowledge or diagnosis of your doctor. We advise seeing a physician whenever a health problem arises requiring an expert's care.

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