

About Functional GI Disorders, Microbes, and Brain-Gut Interactions

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There are many exciting developments and discoveries being made about the connection between our gut (digestive system) and our brain and how it affects our health, as well as the role microbes play in this connection. Emeran Mayer, M.D., explores these developments and their implications in his new book, *The Mind-Gut Connection: How the Hidden Conversation Within Our Bodies Impacts Our Mood, Our Choice, and Our Overall Health*.

We sat down for a conversation with Dr. Mayer at the 2016 Gut Microbiota for Health World Summit* and talked briefly about what these developments mean for people with functional gastrointestinal (GI) disorders.

Q. Dr. Mayer, what does the term “microbiota” mean?

A. The microbiota (or the microbiome if we include their functional capacities, as well) refers to the collective community of microorganisms, or microbes, that live on or within different parts of our bodies, like the skin, mouth, and the gut. The gut microbiota is made up of trillions of bacteria and other microorganisms that play important roles in helping maintain our health. Among other things, a healthy gut microbiota helps with digestion, with

maintaining our immune system, and with protecting us from dangerous microbes. Conversely, an imbalance or a loss of diversity of species may open us up to a range of symptoms. An obvious example is diarrhea associated with antibiotics.

Q. We have heard at this conference about the growth of knowledge of brain-gut connections and the role of microbes, but still there is caution expressed about relying on much of this information until more and better science backs it up. What can we reliably tell people about developments in this area?

A. There are three things I would point out. One, there is definitely some connection between what the gut microbes produce and brain activity, function, and structure.

Secondly, the most important phase of establishing this connection in people likely begins early in life, prenatally in pregnant women and postnatally for the first 3 years of life, when the pattern and content of gut microbes in an individual are set. An imbalance of the microbiome in early life may have long lasting effects, and could influence brain-gut interactions that make a person more vulnerable to a functional GI disorder.

The third thing is that in adults, diet has an effect on an individual’s gut microbes. The

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In celebration of 25 years of supporting the functional GI and motility disorders patient community, we are pleased to launch our newly redesigned family of websites. Check them out beginning at IFFGD.org.

Functional GI Disorders, Microbes, and Brain-Gut Interactions

microbes produce different *metabolites* in response to what they are fed. These metabolites may have an effect on the nervous system both in the gut (the enteric nervous system) and in the brain. Diet becomes an important factor, not only for its direct effect on us, but also for what it does to the microbes, what they produce, and how these metabolites affect the nervous system.

Microbial metabolites are substances produced by our gut microbes by fermenting food components that the human intestine cannot process or absorb. It is estimated that there are hundreds of thousands of these metabolites produced in the gut, and that up to 40% of the metabolites measurable in our blood originate from the gut microbiota.

negative effects on our gut microbiota and their diversity. This would be a particular concern if such diets are prescribed for pediatric patients. Moreover, it appears that a healthy balanced microbiota also can alleviate symptoms. Looking ahead for people with functional GI disorders, like IBS or dyspepsia, it will be important to find out what the optimal diet for individual patients should be. There is new evidence which suggests that the benefits to a particular diet depend on the individual gut microbial composition of the person. We need a better understanding of what a particular diet does to our gut microbes, to the metabolites, and how do these substances affect the nervous system in the gut and at the level of the brain.

involves a diet with an optimal composition of complex carbohydrates, and protein and fats. I think the Mediterranean or similar diets probably comes closest with a high proportion of complex carbohydrates from plant based foods, minimal animal fat, a relatively small amount of protein mainly from fish and chicken, and little refined sugars. Interestingly, studies have shown there are also regional differences of the health benefits of this diet, suggesting that other lifestyle and social factors may play a role.

Stress or state of mind is a factor as well. So for example, we know that feeling anxious or angry or sad while eating affects various gut functions such as contractions and secretion. In addition, we know that stress can affect the behavior of gut microbiota directly. You will have a different set of microbes if you are acutely stressed or chronically affected by these emotions. It seems that a balanced mind and a reasonable diet go hand in hand, because if you always feel stressed, no matter what you eat, you will not have the same benefits.

Q. So then our diet can have either a positive or a negative effect on our gut microbiota. There was some concern expressed at this conference about the low FODMAP diet. Can you explain the concern?

A. The low FODMAP diet reduces consumption of dietary fibers that support beneficial microbes in our gut. In the short term, a diet like this may alleviate symptoms for some individuals with irritable bowel syndrome (IBS), as the bacteria produce less gas as a product of digestion, but in the long term these diets are difficult to maintain, and they may even have

Q. How will we find that out?

A. There are now studies going on with a technique called metabolomics, which is able to analyze stool, blood, and urine samples to identify the thousands of molecules that come from the bacteria. This approach will make it possible to study how the metabolomics profile of a person changes when he or she is put on a particular diet, and to determine if these changes are associated with an improvement in symptoms. I believe this is going to be a renaissance of serious science about food and nutrition for health, but we are just beginning.

Q. How would you summarize what each of us can do now on our own to take steps aimed at optimizing our own health?

A. It is important to know that functional GI disorders are not psychological diseases; but we also have to realize that the brain plays an important role. The brain communicates constantly with the microorganisms inside each of us. These microbes have a

We can each take care with what, when, and how we eat to promote healthy diversity in our gut microbiome.

Q. Is there any diet advice you can pass on to people now?

A. In my book, I don't give any advice in terms of diets for weight loss, but focus on the published evidence regarding the benefits of diets for brain health. This advice

cooperative relationship with us, not only playing a role in digestion, but also interacting and communicating with our own cells, with our gut and our brain. Gut microbes may provide a link to helping maintain a balance between the brain and the gut.

We can each take care with what, when, and how we eat to promote healthy diversity in our gut microbiome. We can seek to maintain a positive emotional state and as much as possible, relax and enjoy mealtimes. There are many simple forms of stress reduction that can be employed such as regular exercise, abdominal breathing, or progressive muscle relaxation.

The workings of the gut can be disturbed by altered states of mind or by extreme or unhealthy diets. Eating a reasonable diet, reducing stress, and working toward a balanced body and mind are steps we can all take to improve well-being.

*The 2016 Gut Microbiota for Health World Summit, organized by the American Gastroenterological Association (AGA) and the European Society of Neurogastroenterology & Motility (ESNM), took place in Miami, FL from March 5–6, 2016.

Emeran Mayer, M.D. is Professor of Medicine and Executive Director of the G. Oppenheimer Center for Neurobiology of Stress and Resilience at UCLA in Los Angeles, CA. Dr. Mayer is a member of the Board of Directors of IFFGD. His book, *The Mind-Gut Connection: How the Hidden Conversation Within our Bodies Impacts our Mood, Our Choice, and Our Overall Health*, is available at Amazon.com.

Medical News from DDW 2016

The following are a selection of research studies presented as abstracts at digestive disease week (DDW), an annual international conference for medical professionals.

The data and conclusions presented here should be considered preliminary until published in a peer-reviewed journal.

Gastroparesis

The online community-based survey, developed by IFFGD with the help of gastroenterologists, of 1,423 adult patients with gastroparesis aimed at understanding patients' experiences with gastroparesis reported the following:

- The average time from symptom onset to a positive diagnosis of gastroparesis was 6.8 years.
- Patients with gastroparesis have a decreased quality of life (as assessed with SF-36 quality of life measures, particularly the physical health component).
- When gastroparesis symptoms became severe, troubling symptoms included nausea (52%), stomach pain (46%), vomiting (30%), and bloating (25%).
- Many patients expect their health to get worse over time as a result of their gastroparesis (47%).
- A majority of patients reported that they are not satisfied with the current treatment options available (64%) and many want specific treatments for gastroparesis (48%).

A large number of patients find out about treatments not only from their

physician but also using the Internet, including social media.

Another study of the IFFGD survey data looked at determining what specific symptoms contribute to the impaired quality of life in community patients with gastroparesis. Focusing on nausea, vomiting, early fullness (satiety), and upper abdominal pain in patients with gastroparesis may improve quality of life.

A survey of 173 patients with gastroparesis concluded that poor quality of life is consistently present in the condition. Other factors in addition to symptoms of gastroparesis that contribute to poor quality of life included symptoms of irritable bowel syndrome (IBS) and gastroesophageal reflux disease (GERD); psychological factors of anxiety and depression; patient-related factors such as weight, smoking, and drinking; unknown cause; and sudden onset of symptoms.

All Functional Digestive Disorders (FDDs)

Looking at patient data from the Nationwide Inpatient Sample (NIS) in the US between 1993 and 2013, researchers found that hospitalizations for FDDs increased from 24,544 to 197,660 per year and that the average cost per discharge increased from \$6,445 to \$24,094 despite a relatively stable length of stay. Constipation and abdominal pain were the most common FDD discharge diagnoses. IBS was more common in females. Abdominal pain and IBS discharges were most frequent in the 18–44 year age group. Gastroparesis and dyspepsia were most common in the 45–64 year age group, while constipation discharges were most frequent in the 65–84 year age group.

IBS

A study of 530 IBS patients and 337 controls showed a higher number of chronic medical conditions among the immediate families of individuals with IBS. Illness burden in the family was also found to be associated with the IBS patients' own co-morbidities. Of the chronic conditions found among families, migraine, tension headache, back pain, and insomnia were the most frequent.

Overlap between IBS and functional dyspepsia was found to be frequently unrecognized in a study of 391 patients. Patients with unrecognized IBS and functional dyspepsia overlap were found to have more severe symptoms compared with either functional dyspepsia or IBS patients.

4 IBS with Diarrhea (IBS-D)

A study of 171 individuals with IBS-D found that those who followed a low FODMAP diet experienced improvements in abdominal symptoms compared to a control diet. The authors found benefits for bloating were identified within 2 weeks of initiation and concluded that their data suggest that a 2–4 week trial with the low FODMAP diet is sufficient to determine clinical response.

IBS with Constipation (IBS-C)

A large population-based online survey of 30,000 people in Japan found that abdominal bloating is the most common and bothersome symptom in patients with IBS-C. Overall, IBS-C patients experienced a high degree of anxiety in their daily lives and considered bowel habit to be an indicator of general health more than controls.

Rome IV Released at DDW

This May the Rome Foundation, a nonprofit professional organization, unveiled the fourth edition of their comprehensive diagnostic criteria for functional digestive conditions at Digestive Disease Week (DDW) in San Diego, California. The release of Rome IV – *Functional Gastrointestinal Disorders; Disorders of Gut-Brain Interaction* – comes almost 10 years after the publication of the third edition of the criteria.

The Rome Foundation has played a pivotal role in creating diagnostic criteria and contributing to the discovery and application of new knowledge in the field of functional gastrointestinal disorders (FGIDs). Rome IV is a collection of the knowledge accumulated since Rome III was published 10 years ago.

It expands upon previous editions in a number of ways, including:

- Updating the basic and clinical literature.
- Offering new information on gut microenvironment; gut-brain interactions; how genes affect a person's response to drugs (pharmacogenomics); and biopsychosocial, gender, and cross-cultural understandings of FGIDs.
- Reducing the use of imprecise and occasionally stigmatizing terms when possible.
- Using updated diagnostic algorithms.
- Incorporating information on the patient illness experience, and physiological subgroups or biomarkers that might lead to more targeted treatments.

Notably, Rome IV adopts a definition for FGIDs that is affirmative and reflective of current scientific knowledge:

Functional GI disorders are disorders of gut-brain interaction. They are a group of disorders classified by GI symptoms related to any combination of the following:

- Motility disturbance,
- Visceral hypersensitivity,
- Altered mucosal and immune function,
- Altered gut microbiota, and
- Altered central nervous system processing.

Rome IV lists the 33 adult and 20 pediatric FGIDs, including descriptions of their respective anatomic domains, pathophysiology, diagnostic features, and treatment aspects.

Other diagnostic tools, including supplements for pediatric and primary care practitioners, accompanied the release of Rome IV. Together, these tools will help healthcare professionals in all clinical settings better identify and treat FGIDs and ultimately, improve the lives of people living with these conditions.



Medical & Research News

High Prevalence of Functional GI Disorder Diagnoses in Pediatric Outpatient Clinic

Over half (52%) of 976 pediatric patients admitted to an outpatient gastroenterology clinic were positively diagnosed with one or more functional gastrointestinal (GI) disorders using Rome III criteria. In patients younger than 4 years, functional constipation (29%), infant regurgitation (13%), and cyclic vomiting syndrome (CVS: 10%) were the most prevalent. In patients ages 4 to 18 years, the most common diagnoses were irritable bowel syndrome (IBS: 36%), abdominal migraine (19%), functional constipation (17%), and CVS (8%).

Source: Rouster AS, et al. *J Pediatr Gastroenterol Nutr.* October 2015.

IBS Associated with Vitamin D Deficiency

The authors of a randomized, double-blind pilot study of 51 individuals with IBS found to have low levels of vitamin D suggest that the impact of IBS on quality of life may be heightened by vitamin D deficiency, which is commonly associated with low quality of life. They suggest that individuals with IBS might benefit from screening and possible supplementation.

Source: Tazzyman S, et al. *BMJ Open Gastroenterol.* November

National Survey Finds GI Disorders Continue to be Source of Substantial Burden and Cost

A national survey in the US of data on symptoms and diagnoses, hospitalizations, emergency department visits, and mortality of GI, liver, and pancreatic diseases from the years 2007 through 2012 found that these conditions remain a source of considerable burden and health care cost. Notable findings include:

- Nearly 1 million discharge diagnoses of functional GI and motility disorders were made (mostly for constipation) from emergency departments.
- The most common GI symptoms prompting ambulatory visits were abdominal pain (more than 27 million), bleeding (more than 3.6 million), constipation (more than 3 million), and anorectal symptoms (more than 2.5 million).
- The most common GI diagnoses in the ambulatory setting included abdominal pain (more than 16.6 million), GERD and reflux esophagitis (more than 7 million), and constipation (more than 3.7 million).
- Hospitalizations for *C. difficile* infection increased by 151% since 2003 with a total cost of more than \$1.1 billion.

Source: Peery AF, et al. *Gastroenterology.* December 2015.

Patient Experiences of Foods on Gastroparesis Symptoms

A study surveyed 45 individuals with gastroparesis (39 with idiopathic gastroparesis) to identify and characterize foods that may worsen symptoms as well as foods that may help alleviate symptoms. Foods found to *provoke* symptoms tended to be fatty, acidic, spicy, and roughage-based. *Tolerable foods* (not symptom provoking) were generally bland, sweet, salty, and starchy, such as ginger ale, gluten-free foods, potatoes, pretzels, white fish, clear soup, salmon, white rice, popsicles, and applesauce. Saltine crackers, Jello, and graham crackers were reported to moderately improve symptoms.

Source: Wytiaz V, et al. *Dig Dis Sci.* April 2015.

August is Gastroparesis Awareness Month

IFFGD works to focus attention on important health messages about gastroparesis diagnosis, treatment, and quality of life issues. The goals include improving understanding of gastroparesis to help patients and families manage the condition, and encouraging preventive strategies.

If you experience symptoms of gastroparesis talk to your doctor. Find out more on our website at aboutGastroparesis.org.

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

Virtual Advocacy Day 2016

On June 23rd, patients, family members and friends, health care providers, researchers, and members of the public across the U.S. reached out to their House Members of Congress through email, phone, and social media on behalf of *The Functional Gastrointestinal and Motility Disorders Research Enhancement Act of 2015* (H.R. 2311). On this day thousands of Americans shared their unique personal story of how they have been impacted by a functional gastrointestinal (GI) or motility disorder and the daily challenges that come with living with a functional digestive condition.

After hearing from their constituents, H.R. 2311 received 5 new cosponsors:

- David Joyce (OH-14)
- Sean Duffy (WI-7)
- Eliot Engel (NY-16)
- Mark Pocan (WI-2)
- Ron Kind (WI-3)

Thank you to everyone who has taken action for this critical piece of legislation! There are thousands of bills for Congress to consider every session, but only a few become law. Continued contact with your House Members of Congress is essential to help move H.R. 2311 forward through the legislative process.

We are thankful to all of our supporters for making sure that the voices of the digestive health community were heard.

Want to join the conversation on Twitter? Follow IFFGD at @IFFGD and @WeAreDHA and tweet with #HR2311.

Statement for the Record Recognizing Gastroparesis Awareness Month

On July 12, 2016 Senator Tammy Baldwin (WI) introduced a statement for the record on behalf of the millions of Americans affected by gastroparesis recognizing August as Gastroparesis Awareness Month. Below are her remarks.

Statement for the Record

Senator Tammy Baldwin

July 12, 2016

Mr. President, I would like to bring attention to the estimated 5 million Americans suffering from gastroparesis in observance of National Gastroparesis Awareness Month in August.

Gastroparesis is a chronic medical condition in which the stomach cannot empty properly in the absence of any observable blockage. The condition can affect people of all ages, but it is four times more likely to affect women than men. The symptoms of gastroparesis, which include nausea, vomiting, and inability to finish a normal sized meal, can be debilitating and sometimes life threatening. The condition can lead to malnutrition, severe dehydration, and difficulty managing blood glucose levels.

While there is no cure for gastroparesis, some treatments, such as dietary measures, medications, procedures to maintain nutrition, and surgery, can help reduce symptoms. Unfortunately, gastroparesis is a poorly understood condition and so patients often suffer from delayed diagnosis, treatment and management for this disorder. As such, further research and education are needed to improve quality of life for this patient population.

I want to recognize the important efforts of the International Foundation for Functional Gastrointestinal Disorders (IFFGD), an international organization based in my home state of Wisconsin, as well as other patient organizations, in providing education and support to help those affected by gastroparesis.

I urge my fellow colleagues to join me in recognizing August as National Gastroparesis Awareness Month in an effort to improve our understanding and awareness of this condition, as well as support increased research for effective treatments for gastroparesis. Furthermore, I encourage the Department of Health and Human Services to recognize and include Gastroparesis Awareness Month in their list of National Health Observances.

Thank you.

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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www.aboutgastroparesis.org

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