11th Postgraduate Course on

Gastrointestinal Motility & Neurogastroenterology in Clinical Practice

August 25, 2016

San Francisco, CA

Hyatt Regency San Francisco

This educational activity is jointly provided by
ANMS and University of Kansas Medical Center Continuing Education.

ACKNOWLEDGMENTS

The American Neurogastroenterology and Motility Society
gratefully acknowledges the generous support of
independent medical educational grants
from the following companies:

Benefactors

Ironwood Pharmaceuticals

Primary Sponsors

Medtronic

Takeda Pharmaceuticals International, Inc., U.S. Region

Sponsors

AstraZeneca

LABORIE

Mederi Therapeutics Inc

Sandhill Scientific

Welcome

On behalf of the planning committee, the American Neurogastroenterology and Motility Society is pleased to welcome you to our 11th Postgraduate Course on Gastrointestinal Motility & Neurogastroenterology in Clinical Practice.

The goal of this postgraduate course is to discuss recent scientific and clinical advances regarding the pathophysiology and treatment of common disorders affecting GI neuromuscular function. The postgraduate course will familiarize and update participants on the current indications, methods and interpretation of commonly used GI motility tests, and will review the clinical management of upper and lower gastrointestinal disorders that alter motility. Course attendees will receive "real-time" demonstrations on current procedures to assess GI neuromuscular function resulting in improved understanding of the tests but also lead to a standardized approach for performing these procedures. Participants will learn how to choose between various approaches to optimally assess upper and lower disorders of GI neuromuscular function. Through the use of case-based presentations attendees will learn how to treat patients based on the outcome of these tests using an evidence-based approach that follows national and international practice guidelines.

We look forward to sharing these exciting developments in neurogastroenterology and motility with you.

Course Planning Committee: Ronnie Fass, *Chair*, William D. Chey, Laurie Keefer, Miguel Saps, Gregory S. Sayuk, William J. Snape, Jr.

Registration • Market Street Foyer

Wednesday, August 24 ..... 3:00 pm – 6:00 pm

Thursday, August 25..... 7:00 am – 5:00 pm

Speaker Information

If your talk has changed from what you uploaded previously, please see the AV technician in the room where you are speaking **4 hours before your talk**.

Note

Wi-Fi is not available in any of the meeting rooms.

Exhibits • Grand Ballroom Foyer

Thursday, August 25..... 7:30 am – 5:00 pm

Lunch • Waterfront, Atrium Level • Visit Exhibits

Thursday, August 25.....11:40 am – 12:50 pm

Reception • Waterfront, Atrium Level

Thursday, August 25..... 5:15 pm – 6:30 pm

Procedure for Program Evaluation and Continuing Education Certificate

All participants are required to sign an attendance roster.

Each attendee will be e-mailed a link to log into our new KUMC CE portal to complete the evaluation and print your own certificate. If you do not receive a KUMC e-mail in your inbox by Wednesday, August 31, 2016 (end of day), check your spam/junk mailbox. You may also contact contactce@kumc.edu if you did not receive it and the KUMC CE office will send you another e-mail.

SPEAKERS

MODERATORS

COURSE PLANNING COMMITTEE

Ronnie Fass, MD, *Chair*
William D. Chey, MD
Laurie Keefer, PhD
Miguel Saps, MD
Gregory S. Sayuk, MD, MPH
William J. Snape, Jr, MD

MEETING COORDINATOR

Lori Ennis

CONTINUING EDUCATION PLANNING COMMITTEE

Monya Floyd
Program Manager
Continuing Education & Professional Development
University of Kansas Medical Center

Jan Foecke, MS, RN, ONC
Assistant Dean for Community Affairs
Director of Nursing Continuing Education
University of Kansas School of Nursing

PROGRAM-AT-A-GLANCE

Wednesday, August 24, 2016	
3:00 pm – 6:00 pm	**Registration** • Market Street Foyer
3:00 pm – 6:00 pm	**Exhibit Set-Up** • Grand Ballroom Foyer

Thursday, August 25, 2016		
7:00 am – 5:00 pm	**Registration** • Market Street Foyer	
7:00 am – 7:45 am	Continental Breakfast • **Visit Exhibits** • Grand Ballroom Foyer	
7:45 am – 8:00 am	**Welcome & Opening Remarks** • Grand Ballroom	
8:00 am – 9:10 am	**Practical approaches to common functional bowel disorders** Grand Ballroom	
9:10 am – 10:20 am	**Developments in the diagnosis and treatment of esophageal disorders** Grand Ballroom	
10:20 am – 10:40 am	Break • **Visit Exhibits** • Grand Ballroom Foyer	
10:40 am – 11:40 am	**Live demonstrations: 3D esophageal high-resolution manometry and impedance manometry** Grand Ballroom	
11:40 am – 12:50 pm	Lunch • Waterfront, Atrium Level • **Visit Exhibits** • Grand Ballroom Foyer	
1:00 pm – 1:45 pm	**Live demonstrations: two anorectal cases - 3D HDM and HRM** Grand Ballroom	
1:45 pm – 5:15 pm	**Three Concurrent Sessions**	
1:45 pm – 2:45 pm	Concurrent Session 1 **Advances in the management of gastric function disorders** Grand Ballroom A	Concurrent Session 1 **Is it IBS or something else?** Grand Ballroom BC
2:45 pm – 3:45 pm	Concurrent Session 2 **Interpreting esophageal function tests and understanding the results** Grand Ballroom A	Concurrent Session 2 **Holistic management of functional GI disorders** Grand Ballroom BC
3:45 pm – 4:15 pm	Break • **Visit Exhibits** • Grand Ballroom Foyer	
4:15 pm – 5:15 pm	Concurrent Session 3 **The why, when and what in pediatric testing and management** Grand Ballroom BC	Concurrent Session 3 **The application of brain–gut therapies to upper functional and motility disorders** Grand Ballroom A
5:15 pm	Adjourn	
5:15 pm – 6:30 pm	**Reception** • Waterfront, Atrium Level	

This page has been left blank intentionally.

Wednesday, August 24, 2016

3:00 pm–6:00 pm	**Registration** • Market Street Foyer
3:00 pm–6:00 pm	**Exhibit Set-Up** • Grand Ballroom Foyer

Thursday, August 25, 2016

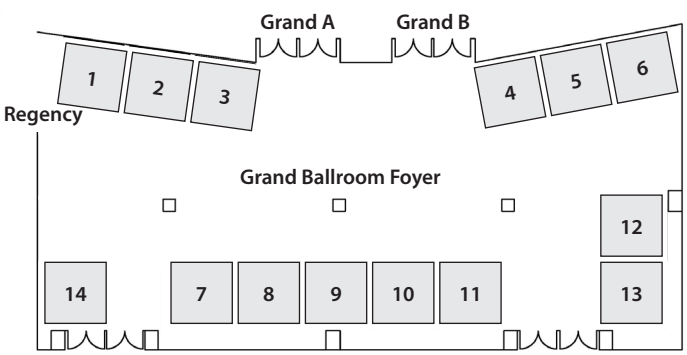
7:00 am–5:00 pm	**Registration** • Market Street Foyer	
7:00 am–7:45 am	Continental Breakfast • **Visit Exhibits** • Grand Ballroom Foyer	
7:45 am–8:00 am	**Welcome & Opening Remarks** • Grand Ballroom *John Wiley, President, ANMS*	
8:00–9:10 am	**Practical approaches to common functional bowel disorders** • Grand Ballroom Moderator: *Adil Bharucha*	
8:00–8:20 am	**Dealing with constipation and dyssynergic defecation** *Satish Rao*	
8:20–8:40 am	**Irritable bowel syndrome and evidence-based therapeutic approach** *Madhusudan Grover*	
8:40–9:10 am	**Fecal incontinence management: Medical or surgical?**	
8:40–8:50 am	**Medical management of fecal incontinence** *Adil Bharucha*	
8:50–9:00 am	**Surgical management of fecal incontinence** *Andreas Kaiser*	
9:00–9:10 am	**Discussion:** *Adil Bharucha, Andreas Kaiser*	
9:10–10:20 am	**Developments in the diagnosis and treatment of esophageal disorders** • Grand Ballroom Moderator: *Ronnie Fass*	
9:10–9:30 am	**Advances in the management of laryngeal, pharyngeal and pulmonary manifestations of GERD** *Michael Vaezi*	
9:30–9:50 am	**Treatment of esophageal hyper- and hypomotility disorders** *Joel Richter*	
9:50–10:10 am	**Functional esophageal disorders – How to incorporate Rome IV into my clinical practice?** *Ronnie Fass*	
10:10–10:20 am	**Discussion**	
10:20–10:40 am	Break • **Visit Exhibits** • Grand Ballroom Foyer	
10:40–11:40 am	**Live demonstrations: 3D esophageal HRM and impedance manometry** • Grand Ballroom Discussants: *Albert (Arjan) Bredenoord, Ronnie Fass, C. Prakash Gyawali, Marcelo Vela*	
10:40–11:25 am	**Case 1 • 3D esophageal HRM** **Presenters:** *Nikhil Agarwal, Mimi Lin, Satish Rao, William Snape*	**Case 2 • Impedance manometry** **Presenters:** *Nikhil Agarwal, Mimi Lin, Satish Rao, William Snape*
11:25–11:40 am	**Discussion**	
11:40 am–12:50 pm	Lunch • Waterfront, Atrium Level • **Visit Exhibits** • Grand Ballroom Foyer	
1:00–1:45 pm	**Live demonstrations: two anorectal cases – 3D HDM and HRM** • Grand Ballroom Discussants: *Darren Brenner, Ronnie Fass, Ajay Kaul*	
1:00–1:30 pm	**Case 1 • Constipation** **Presenters:** *Nikhil Agarwal, Mimi Lin, Satish Rao, William Snape*	**Case 2 • Fecal Incontinence** **Presenters:** *Nikhil Agarwal, Mimi Lin, Satish Rao, William Snape*
1:30–1:45 pm	**Discussion**	

PROGRAM

Thursday, August 25, 2016

1:45–2:45 pm **Concurrent Sessions 1**	Concurrent Session 1 • Grand Ballroom A **Advances in the management of gastric function disorders** Moderator: *William Hasler*	Concurrent Session 1 • Grand Ballroom BC **Is it IBS or something else?** Moderator: *Brooks Cash*
1:45–2:05 pm	**Delayed and rapid gastric emptying: Clinical and management implications** *Henry Parkman*	**Masqueraders of IBS-D – the latest on celiac disease, non-celiac wheat intolerance, microscopic colitis, IBD, bile acid diarrhea, and diverticular disease** *Brooks Cash*
2:05–2:25 pm	**Nausea, vomiting, rumination and regurgitation – how to sort them out and what is the management?** *Albert (Arjan) Bredenoord*	**Opioid-induced constipation** *Anthony Lembo*
2:25–2:45 pm	**Gastric function abnormalities – using the new Rome IV criteria to manage your patients** *William Hasler*	**Clinical considerations in IBS-M – is it a real entity or are mixed patients really just IBS-C or D?** *Baharak Moshiree*
2:45–3:45 pm **Concurrent Sessions 2**	Concurrent Session 2 • Grand Ballroom A **Interpreting esophageal function tests and understanding the results** Moderator: *John Pandolfino*	Concurrent Session 2 • Grand Ballroom BC **Holistic management of functional GI disorders** Moderator: *William Chey*
2:45–3:05 pm	**Esophageal high-resolution manometry** *Arash Babaei*	**Dietary therapies for upper FGID** *Bethany Doerfler*
3:05–3:25 pm	**Reflux monitoring: pH and impedance–pH** *Marcelo Vela*	**FODMAPs & IBS: An update** *William Chey*
3:25–3:45 pm	**Classification of esophageal motor disorders: Implications for diagnosis and treatment** **Case discussions** Presenter: *John Pandolfino* Discussants: *C. Prakash Gyawali, Benson Massey*	**Complementary and alternative medicine therapies for functional gastrointestinal disorders** *Jasmine Zia*
3:45–4:15 pm	Break • **Visit Exhibits** • Grand Ballroom Foyer	Break • **Visit Exhibits** • Grand Ballroom Foyer
4:15–5:15 pm **Concurrent Sessions 3**	Concurrent Session 3 • Grand Ballroom BC **The why, when and what in pediatric testing and management** Moderator: *Manu Sood*	Concurrent Session 3 • Grand Ballroom A **The application of brain-gut therapies to upper functional and motility disorders** Moderator: *Gregory Sayuk*
4:15–4:35 pm	**Esophageal testing: When, why, and how?** *Rachel Rosen*	**Gut-directed hypnotherapy: How to customize it for your practice** *Sarah Kinsinger*
4:35–4:55 pm	**Functional dyspepsia and gastroparesis. Two sides of the same coin or distinct entities?** **Case discussions** Presenter: *Joseph Croffie* Discussants: *John Fortunato, Samuel Nurko*	**How to convince a patient *without* pathologic acid that they *do not need their PPI*** *Laurie Keefer*
4:55–5:15 pm	**Challenging problems and new techniques - What to do when everything fails?** **Case discussions** Presenter: *Bruno Chumpitazi* Discussants: *Ajay Kaul, Manu Sood*	**Psychopharmacology augmenting the benefits of antidepressants in patients with FGID** *Gregory Sayuk*
5:15 pm	Adjourn	
5:15–6:30 pm	**Reception** • Waterfront, Atrium Level	

EXHIBIT FLOOR PLAN • GRAND BALLROOM FOYER



Exhibitor	Table No.
Cairn Diagnostics	2
Crospon	1
IM HealthScience.	7
LABORIE	11
Mederi Therapeutics Inc	8
Medtronic	5 and 6
NeuroGASTRO 2017	12
Pelvalon	13
Renew Medical, Inc.	14
Rome Foundation.	4
Salix Pharmaceuticals, Inc.	9
Sandhill Scientific	3
Torax® Medical, Inc.	10

EXHIBITOR SCHEDULE

Set up: Wednesday • 3:00 pm – 6:00 pm (optional)*

Tear down: Sunday • beginning at 12:00 pm

***Exhibitors, please note: The exhibit area is not secure.**

If you have items that need to be secured, you may move them into the meeting staff room, which is nearby, or take them to your room.

EXHIBITOR HOURS

Thursday, Friday, Saturday: 7:30 am – 5:00 pm

Sunday: 7:30 am – 12:00 pm

Cairn Diagnostics

For many patients and physicians, the pathway to a definitive diagnosis can be complex, slow and frustrating. The mission of Cairn Diagnostics is to develop tests that eliminate complexity and create a safer, faster and clearer path to diagnosis.

Cairn's FDA-approved ^{13}C-Spirulina Gastric Emptying Breath Test (GEBT) offers a non-radioactive, non-invasive test for measuring the rate of solid phase gastric emptying in adults and is validated against the method of gastric scintigraphy.

The Cairn GEBT can be administered right in the physician's office and does not require imaging equipment, specialized training or radioactive material. Results are easy to interpret, enabling rapid and accurate diagnosis of gastroparesis by avoiding the need for expensive, time-consuming referrals and scintigraphy.

For more information, visit www.cairndiagnostics.com

Crospon

Crospon's EndoFLIP® system provides measurements of diameter and compliance within the esophagus and stomach to assist in assessment and surgical management of functional GI disorders. The EsoFLIP® dilation catheter incorporates the EndoFLIP® technology.

IM HealthScience (IMH)

IM HealthScience (IMH) was founded in 2012 by a group of senior pharmaceutical executives as a science driven and patient centric company whose mission is to research, develop and make available state of the art medical foods for gastrointestinal conditions such as Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD).

IMH is a family company rooted in the all too forgotten adage that the patient comes first and doing the right thing will always win out in the long term.

As a small, private organization, IMH is committed to putting patients before profits. IMH is also committed to bringing cutting edge life science and world class clinical research to the medical foods industry.

LABORIE

LABORIE takes great pride in improving patients' lives through innovations in pelvic floor and gastroenterology diagnostic and treatment options. LABORIE's GI product line includes Ambulatory Impedance-pH recorders for diagnosing GERD and advanced manometry solutions for esophageal and anorectal manometry studies.

For more information on LABORIE's global product platform and educational course offerings please visit www.laborie.com.

Mederi Therapeutics Inc

Mederi Therapeutics manufactures innovative radiofrequency (RF) therapies for GI disorders − Stretta for the treatment of GERD, and Secca for bowel incontinence. These safe, effective treatments fill the void between failed conservative therapies and invasive and expensive alternatives, like surgery or implants. Stretta and Secca use controlled, delivery of RF

energy to the muscle at either end of the digestive tract, remodeling the muscle tissue, improving motility, symptoms and quality of life for chronic sufferers. Stretta and Secca therapies are minimally invasive, outpatient, promote rapid recovery, and are now available in more than 35 countries.

800 Connecticut Ave, Suite 1E01, Norwalk, CT 06854
Tel: 203-930-9900, Website: www.mederi-inc.com

Medtronic

At Medtronic, we're committed to Innovating for Life by pushing the boundaries of medical technology and changing the way the world treats chronic disease. Our portfolio includes PillCam™ Capsule Endoscopy, Bravo™ pH Monitoring, MansoScan™ High Resolution Manometry, SmartPill™ Motility Monitoring, the Barrx™ RF Ablation System, bnx™ EUS Fine Needle Aspiration System, InterStim® Sacral Neuromodulation System and Enterra® Gastric Electrical Stimulation System.

NeuroGASTRO 2017

NeuroGASTRO is a well-established European event that brings together leading experts and emerging young investigators actively involved in neurogastroenterology, digestive motility and functional gastrointestinal diseases from Europe and from all around the world to discuss cutting-edge research. The APC Microbiome Institute and University College Cork are delighted to welcome NeuroGASTRO 2017 to Cork, August 24–26, 2017. The APC Microbiome Institute is recognized as one of the leaders in the field of microbiome science. Cork is the international gateway to Ireland's Wild Atlantic Way with Cork International Airport serving over 50 international destinations. Cork also boasts the second largest natural harbour in the world and is the Food Capital of Ireland, home to the famed English Market and the best artisan food producers in the country. Don't just take our word for it – as Lonely Planet themselves said 'Everything good about Ireland can be found in County Cork'.

Pelvalon

More than 20 million women in the U.S. suffer from loss of bowel control, sometimes called accidental bowel leakage (ABL) or fecal incontinence (FI). This debilitating condition can be caused by pregnancy, childbirth, nerve or muscle damage in the pelvic region, and gastrointestinal disorders such as irritable bowel syndrome (IBS). The Eclipse System is an innovative, non-surgical therapy that offers immediate results for women with this condition. Founded in 2010, Pelvalon's groundbreaking technology originated from Stanford University's Biodesign program, a collaboration between the schools of medicine and engineering. The Eclipse System has recently been made available via a limited commercial rollout in select centers of excellence in Illinois, Michigan, Alabama, California, and North Carolina.

Renew Medical, Inc.

Renew Medical announces the US launch of the Renew® Insert, an innovative silicone rectal insert device now available by prescription for patients with Accidental Bowel Leakage (ABL), otherwise termed fecal incontinence. Renew Inserts are safe, easy-to-use and reduce ABL by 82% with high patient satisfaction.

Renew Inserts softly and comfortably fit the body and seal the rectum from the inside. Renew Inserts provide reliable and discreet internal protection that give your patients the confidence to live a normal and active life.

Rome Foundation

Rome Foundation is an independent not for profit 501(c)3 organization that supports activities to create scientific data to assist in the diagnosis and treatment of Functional GI Disorders. We seek to legitimize and update our knowledge of the Functional GI Disorders by bringing together scientists and clinicians to classify and critically appraise the science of gastrointestinal function and dysfunction. The Mission of the Rome Foundation is: To improve the lives of people with Functional GI Disorders.

The goals of the Rome Foundation are to:
Promote clinical recognition and legitimization of FGIDs, Develop a scientific understanding of their pathophysiological mechanisms, and Optimize clinical management for patients with FGIDs

Salix Pharmaceuticals, Inc.

For over 20 years, Salix Pharmaceuticals, a wholly-owned subsidiary of Valeant Pharmaceuticals International, Inc. has been committed to providing solutions for the management of many chronic and debilitating conditions. Salix currently markets products to U.S. healthcare providers in the areas of gastroenterology, hepatology, internal medicine, primary care, infectious disease, and allergy/immunology.

Sandhill Scientific

Sandhill Scientific continues to be a recognized global leader in GI diagnostics. Our long and rich history in the GI space has produced some of the innovations used today to help enhance the diagnostic yield of reflux and manometry. Since Sandhill introduced impedance/pH technology, it has set the standard for Total Reflux Monitoring. Our Ultima motility platform has the capability of connecting to High Resolution Impedance Manometry (HRiM®) and multiple configurations of High Resolution Anorectal Manometry (HRAM) catheters. Zvu®, our new software platform and the latest innovation from Sandhill, enhances the user experience by providing the tools to allow quick, accurate analysis. The tie that binds all of this together is Sandhill University, which provides the most comprehensive training and education options to meet all of your clinical needs.

Torax® Medical, Inc.

Torax® Medical develops and markets products designed to restore human sphincter function. Our technology platform, magnetic sphincter augmentation, uses attraction forces to augment weak or defective sphincter muscles to treat gastroesophageal reflux disease and fecal incontinence.

Program Overview

The goal of this postgraduate course is to discuss recent scientific and clinical advances on the pathophysiology and treatment of common functional gastrointestinal and motility disorders. The postgraduate course will familiarize and update participants on the current indications, methodology, and interpretation of new and commonly used GI motility tests and will review the clinical management approaches for upper and lower gastrointestinal motility and functional gastrointestinal disorders. Course attendees will receive practical demonstrations on current and new procedures that will facilitate not only better understanding of the tests but also a standardized approach for performing these procedures. They will learn how to choose between various modalities for optimally assessing esophageal or gastric or colonic disorders and their function. Through the case-based presentations they will learn how to treat patients based on the outcome of these tests using an evidence-based and logical approach and following national and ANMS practice guidelines.

Multiple formats will be used including didactic lectures, panel discussions and case-based presentations, real-time live video demonstrations and information from society-based practice guidelines will be covered.

Target Audience

This program is intended for gastroenterologists in academic and clinical practice, GI fellows, nurses, physician assistants, technicians and medical assistants involved in adult and pediatric GI motility testing and research and for those caring for patients with neurogastroenterology & motility disorders as well as pharma and device manufacturers involved in this field.

Course Objectives

- Discuss recent scientific and clinical advances on the pathophysiology and treatment of common functional gastrointestinal and motility disorders
- Describe current indications, methodology, and interpretation of new and commonly used GI motility tests.
- Review the clinical management approaches for upper and lower gastrointestinal motility and functional gastrointestinal disorders.
- Use a standardized approach for performing current and new procedures.
- Choose between various modalities for optimally assessing esophageal, gastric and colonic disorders and their function.
- Develop patient treatment plans based on the test results using an evidence-based and logical approach and following guidelines
- Use the latest pharmacology and therapeutic advances in a broad spectrum of GI motility and functional bowel disorders including treatment strategies and approaches to gastroesophageal reflux disease, dysphagia, gastroparesis, cyclic vomiting, irritable bowel syndrome, constipation, fecal incontinence, and gas and bloating.
- Examine the animal models of visceral pain and their utility in translating to human studies
- Review emerging genetic, epigenetic and pharmacogenomic approaches applicable to functional gastrointestinal disorders
- Discuss emerging technologies and their application to functional GI disorders.
- Determine the role of microbiota in functional gastrointestinal disorders
- Discuss the diagnosis and management of upper and lower functional gastrointestinal and motility disorders in children and adults
- Discuss current clinical research outcome measures and development of novel biomarkers in functional gastrointestinal and motility disorders

Program Outcomes/Desired Results

- Understand basic mechanisms of functional and GI motility disorders.
- Identify common symptoms and presentations of GI Motility disorders.
- Evaluate various diagnostic modalities including motility tests, breath tests, radiological imaging and others.
- Determine which tests are most appropriate for diagnosis of possible motility disorders in specific patients.
- Improve ability of correct interpretation of test results for patients with GI motility disorders.
- Advise patients of the test(s) chosen and explain the methodology for optimally assessing esophageal or gastric or colonic function.
- Develop a treatment plan using an evidence-based approach and using the ANMS and other national/society practice guidelines.
- Assess various options beyond CAT scan and endoscopic procedures for patients who complain of abdominal pain, dysphagia, nausea and vomiting, gas and bloating, constipation or stool leakage.
- Discuss medical and non-medical therapeutic options for neurogastroenterology and motility disorders.

Course Goal

The goal of this course is to familiarize and update participants on the current indications, methodology, interpretation, and proper use of clinical GI motility tests. In addition, this course will provide an in-depth discussion on the pathophysiology and treatment of GI motility and functional bowel disorders. In addition, the adoption by learners of the national and ANMS practice guidelines on diagnosis and treatment will increase their competence and lead to improved and optimal patient care.

Accreditation Statement

All participants are required to sign attendance rosters at the beginning of the day. A certificate of completion will be provided to all activity participants based on completion of the program evaluation, documentation of actual attendance time, meeting minimum attendance requirements specific to the activity, and payment in full. If you are not paid in full (check received before meeting), a link to complete evaluation and get your certificate will be emailed to you upon receipt of payment.

Physicians This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the University of Kansas Medical Center Office of Continuing Medical Education and American Neurogastroenterology and Motility Society. The University of Kansas Medical Center Office of Continuing Medical Education is accredited by the ACCME to provide continuing medical education for physicians.

The KU Medical Center Office of Continuing Medical Education designates this live activity for a maximum of 7.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses Up to 7.10 contact hours will be awarded to all individuals based on documentation of actual attendance time, meeting minimum attendance requirements specific to the activity, and payment in full.

University of Kansas School of Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

Disclosure of Relevant Financial Arrangements

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME) and the American Nurses Credentialing Center (ANCC), the University of Kansas Medical Center Continuing

Education & Professional Development must ensure that the health and well being of the public is more important than any economic interest, and that activity content is effective in improving practice, independent of commercial interests, and based on valid content. Individuals with control over the content of this activity are required to disclose to the learners any relevant financial relationships within the past 12 months with any proprietary entities producing, marketing, re-selling, or distributing healthcare goods or services related to the content of the activity (with the exemption of non-profit or governmental organizations and non-healthcare related companies). This includes any relevant financial arrangements involving their spouse/partner. Relevant financial relationships may include employment, management position, independent contractor (including contracted research), consulting, speaking and teaching, membership on advisory committees or review panels, board membership, etc. The intent of this disclosure is not to prevent an individual with a relevant financial relationship from being a planning committee member, a teacher, or an author of CME/CNE having control of, or responsibility for, the development, management, presentation, or evaluation of the CME/CNE activity, but rather to assist the provider in the identification and resolution of conflict of interest prior to the activity and to provide the learners with the information they need to determine whether these interests or relationships influenced the content of the activity.

The following presenters and planning committee members have disclosed relevant financial relationships with the following commercial entities producing healthcare goods or services related to the content of their presentations.

Adil E. Bharucha, MBBS, MD receives consulting fees from Allerfan, Forum Pharmaceuticals. He receives royalties from Medspira, and has a pending patent from Medtronic.

Albert J. Bredenoord, MD is on the speaker's bureau for Medical Measurements Systems.

Brooks D. Cash, MD receives consulting fees from Valeant Pharmaceuticals.

William D. Chey, MD receives consulting fees from Nestlé.

Bethany Doerfler, MD is on the speaker's bureau for Nutricia North America

Madhusudan Grover, MD provides research support for the following: DongA, Takeda Pharmaceutical, and Sucampo.

C. Prakash Gyawali, MD is a contracted researcher for Medtronic.

William L. Hasler, MD receives honoraria for being on the Allergan Advisory Board. He receives research grants from Rhythm Pharma and Medtronic.

Andreas M. Kaiser, MD receives royalties from McGraw-Hill.

Anthony Lembo, MD receives consulting fees from the following: Ironwood, Salix, Valeant, Forest Research Labs, Prometheus, Allergan, and Alkermes. He is a contracted researcher for Prometheus.

John E. Pandolfino MD, MSCI receives consulting fees from the following: Medtronic, Inc. and Ironwood. He is on the speaker's bureau for the following: Sandhill Scientific and AstraZeneca.

Satish S.C. Rao, MD, PhD receives consulting fees from the following: Forest Labs, Hollister, Ironwood Pharma, Sucampo Pharma, and Vibrant. He receives honoraria as a member of the Data Safety Monitoring Board for American Medical Systems. He has stock in In Control Medical, and he has research grants from the following: Sun Sweet Corp, Forest Labs, Synergy Pharma, Salix, Ventrus Labs, Covidien, and Vibrant.

Gregory S. Sayuk, MD, MPH is on the speaker's bureau for Allergan and Ironwood, and receives consulting fees from Synergy Pharma and Synthetic Biologics.

Manu R. Sood, MD receives a salary from AbbVie. He receives consulting fees from QOL Scientific, and he has stock options with the following: Abbott Labs and AbbVie.

Marcelo F. Vela, MD, MSCR receives consulting fees from the following: Medtronic, Inc., Torax, and Sandhill Scientific.

The following presenters and planning committee members do not have any relevant financial relationships with any commercial entity producing healthcare goods or services related to the content of their presentations or related to the content of the activity.

Nikhil Agarwal, MD
Arash Babaei, MD
Bruno P. Chumpitazi, MD, MPH
Joseph M. Croffie, MD, MPH
Lori Ennis
Ronnie Fass, MD
Monica Floyd
Jan Foecke, MS, RN, ONC
John E. Fortunato, MD
Ajay Kaul, MD
Laurie Keefer, PhD
Sarah Kinsinger, PhD
Mimi S. Lin, MD
Benson Massey, MD
Baharak Moshiree, MD
Samuel Nurko, MD, MPH
Henry P. Parkman, MD
Joel E. Richter, MD
Rachel Rosen, MD, MPH
Miguel Saps, MD
William J. Snape, Jr, MD
Michael F. Vaezi, MD, PhD
Jasmine Zia, MD

Resolution of Conflict of Interest

A conflict of interest, or a potential for bias, exists if an individual/entity in a position to benefit financially from the success of a continuing education activity is also in a position to influence its content, design, or implementation. For this continuing education activity, conflict of interest was resolved and successful resolution of conflict of interest will be validated through the implementation of the following mechanisms.

- Relevant financial relationships were disclosed and resolved prior to everyone's participation in the planning, development, and implementation of this activity.
- Prior to participating in this activity, everyone in a position to influence its content, design or implementation received our terms and conditions regarding conflict of interest expectations and they agreed to comply.
- Speakers were selected based upon a review of their qualifications and an assessment of their ability to present the best available evidence accepted in health care practice.
- Clinical content was validated by a review of the activity for fair balance and bias, appropriate patient treatment recommendations, and whether scientific studies cited in the activity conform to standards accepted by the scientific community.
- Oversight will be maintained by monitoring the planning, development, and implementation of this continuing education activity.
- Disclosure of relevant financial relationships will be provided to the participants prior to the activity.
- Participants will evaluate the activity's success in resolving conflict of interest and providing an activity free of bias.

Product Disclosures

Unless otherwise announced prior to the session, this activity does not include any information about off-label use of a product for a purpose other than that for which it was approved by the Food and Drug Administration (FDA).

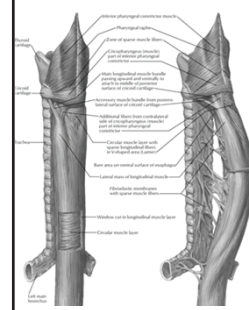
Esophageal High-Resolution Manometry

Arash Babaei, MD
Gastroenterology and Hepatology
Medical College of Wisconsin
August 25, 2016

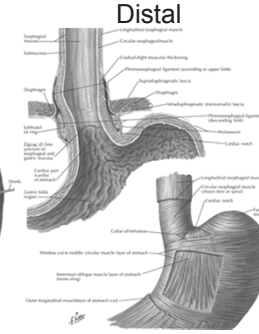
ANMS 11th Postgraduate Course on Gastrointestinal Motility
San Francisco, California, USA

Esophagus

Proximal

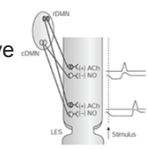


Distal



Esophageal Peristalsis

- Definition: "coordinated and aborally propulsive sequential contraction of the muscle layer"
- Sequence of peristalsis is triggered by the "central pattern generator" of brainstem
- "Peristalsis in smooth muscle is physiologically regulated as a wave of inhibition followed by a wave of excitation"



Goyal & Shaker GI Motility online

Diagnostic Assessment of Esophageal Motor Function

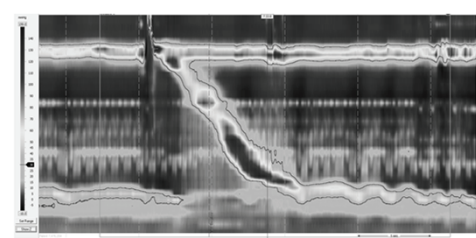
- Dysphagia
  - Normal esophagogastroscopy and/or esophagram
- Preoperative assessment of peristaltic function
  - Fundoplication
  - Myotomy
  - Bariatric procedures
  - Other
- Gastroesophageal reflux disease (GERD)
  - Lung transplant evaluation
  - Placement of the ambulatory reflux monitoring catheter
- Non-cardiac chest pain

Basic Principles

- Carefully follow manufacturer's recommendation for pre-procedure calibration or post-procedure correction (when required)
- Catheter tip must be placed across the esophagastric junction (EGJ)
- Several swallows at least 20-30 seconds apart (usually ten wet swallows are recommended)
- The reference normative data is mostly obtained in recumbent position (supine or decubitus)
- Normal range of peristaltic pressure parameters for various systems may be different

High-resolution Manometry

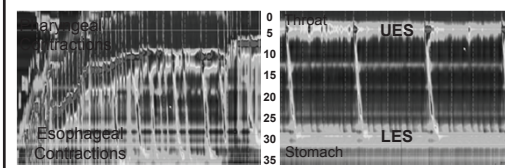
- It is more time-friendly, operator-friendly and interpreter-friendly than conventional manometry
- The cost of equipment is unfriendly!



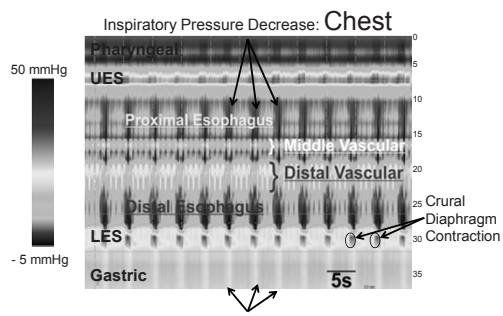
Peristalsis and Deglutitive EGJ Relaxation

INITIAL ASSESSMENT

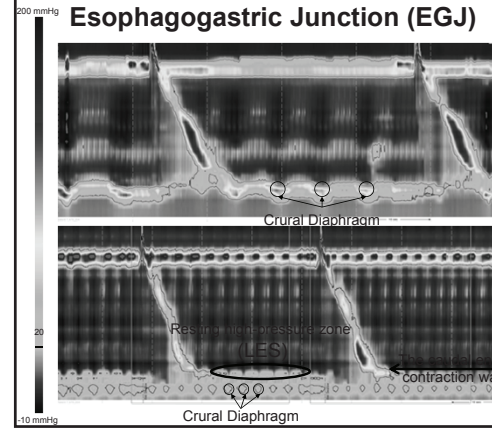
Placement : Upper and Lower Esophageal Sphincters



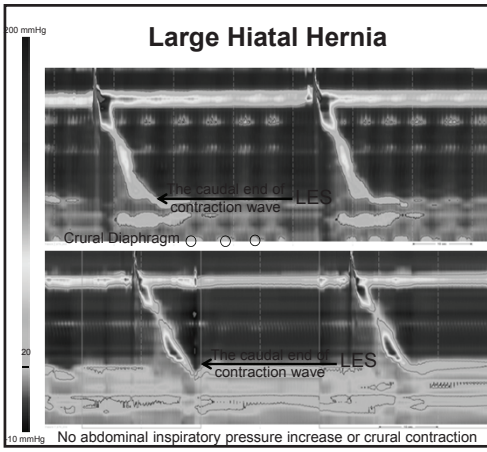
Pressure Compartments & Landmarks



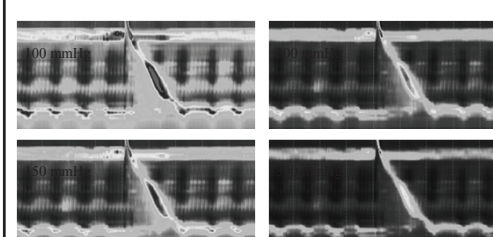
Esophagogastric Junction (EGJ)



Large Hiatal Hernia



Pressure Topography Color Scale



MANOMETRY ANALYSIS

Swallow:

1) Topographic landmarks:
   - Temporal
     - Swallow onset
     - Termination of contractile wave
   - Spatial
     - Upper esophageal sphincter
     - Transition zone (TZ) location
     - Contraction deceleration point
     - Upper margin of LES
2) Peristalsis pressure metrics:
   - Inhibitory phase (LES relaxation)
     - Integrated relaxation pressure
   - Excitatory phase (esophageal contraction)
     - Distal contractile integral

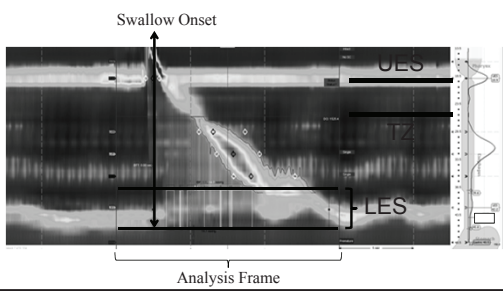
Distal Latency

TOPOGRAPHIC LANDMARKS

1. Onset of swallow
2. Upper esophageal sphincter (UES)
3. Transition zone (TZ)
4. Contraction deceleration point
5. Upper margin of lower esophageal sphincter (LES)
6. Termination of the contractile wave

Swallow and Landmarks

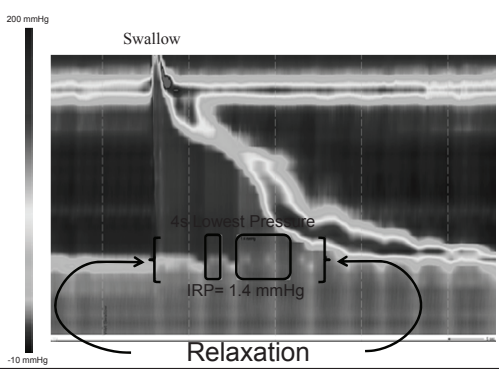
- Verify the main landmarks (UES, TZ, LES)
- Check each swallow event individually



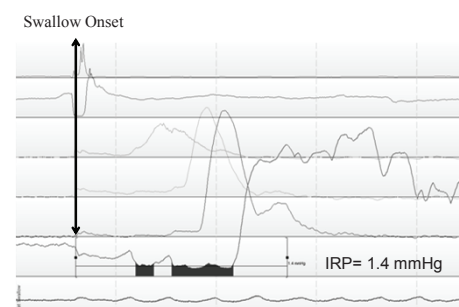
PERISTALSIS METRICS

1) Integrated Relaxation Pressure (IRP) (~ nadir relaxation pressure)
2) Distal Latency (DL) (~ propagation velocity)
3) Distal Contractile Integral (DCI) (~ contraction amplitude)

Deglutitive LES Relaxation

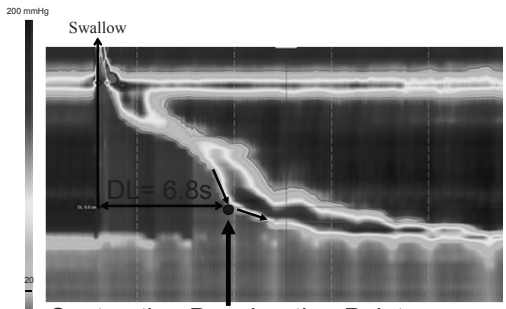


1- Integrated Relaxation Pressure



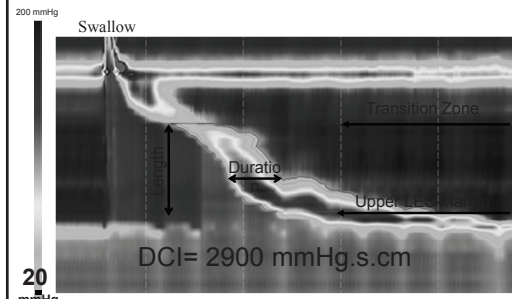
1. Identify relaxation window
2. Average pressure over 4 seconds of lowest LES pressure
3. Referenced to the gastric pressure

2- Distal Latency



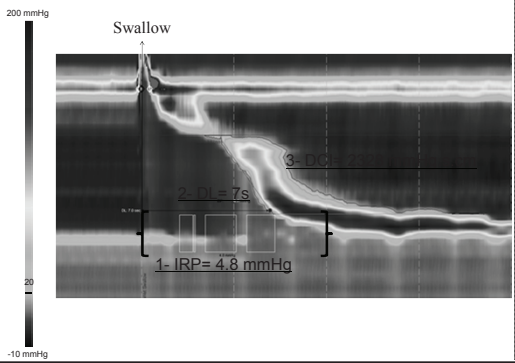
Contraction Deceleration Point

3- Distal Contractile Integral



Pressure Amplitude x Contraction Duration x Length = DCI (mmHg.s.cm)

All Peristaltic Metrics Single-Swallow Analysis



Chicago Classification v3.0

- Major Esophageal Motor Disorders

1. Achalasia
   I. Type 1
   II. Type 2
   III. Type 3
2. EGJ outflow obstruction
3. Absent Contractility (scleroderma esophagus)
4. Distal esophageal spasm (diffuse spasm)
5. Hypercontractile esophagus (nutcracker esophagus)

- Minor Esophageal Motor Disorders

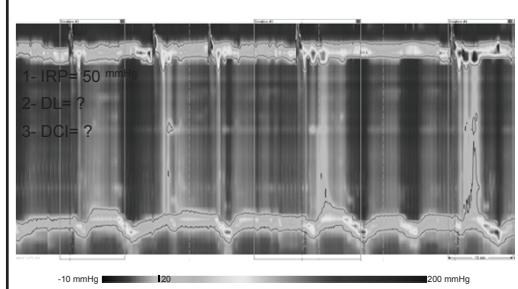
6) Ineffective esophageal motility
7) Fragmented peristalsis

Major Esophageal Motor Disorders

1) Achalasia
   I. Type 1
   II. Type 2
   III. Type 3
2) Outflow Obstruction
3) Absent contractility
4) Esophageal spasm
5) Hypercontractile Esophagus

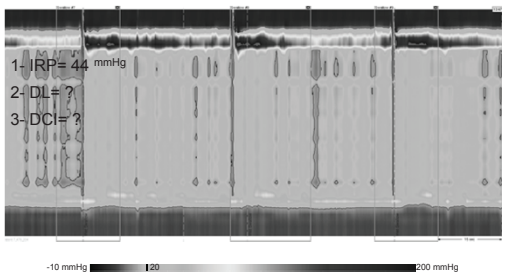
Achalasia Type I

1. Elevated IRP
2. 100% failed peristalsis *(Very low DCI)*



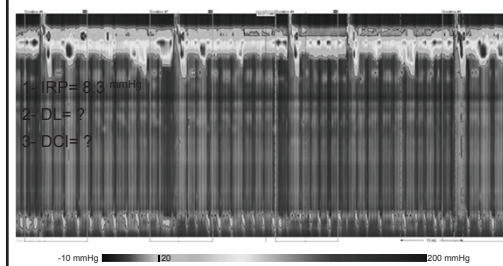
Achalasia Type II

1. Elevated IRP
2. 100% failed peristalsis
   – Esophageal pan-pressurization in >20% of swallows



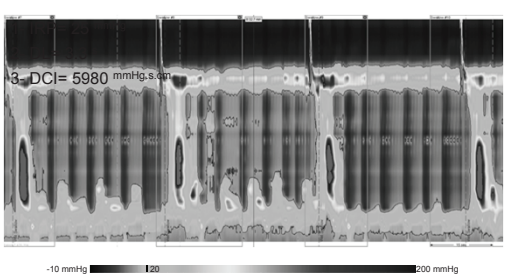
Absent Contractility
(*Scleroderma Esophagus)*

1. Normal IRP
2. 100% failed peristalsis *(Very low DCI)*



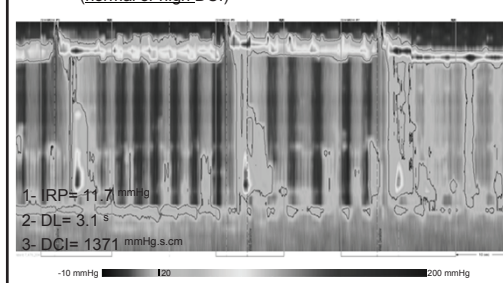
Achalasia Type III

1. Elevated IRP
2. No normal peristalsis, premature >20% of swallows
   – Low DL (normal or high DCI)



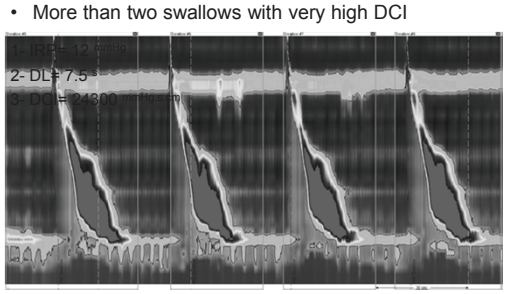
Distal Esophageal Spasm

- Normal IRP
- Premature contractions in >20% of swallows
  – (normal or high DCI)



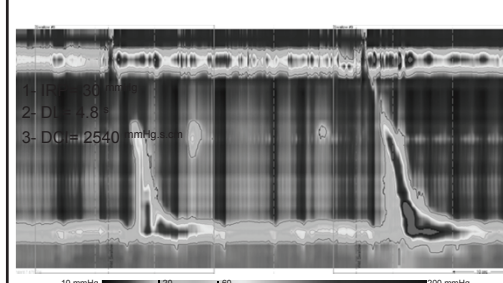
Hypercontractile Esophagus

- Normal IRP and DL
- More than two swallows with very high DCI



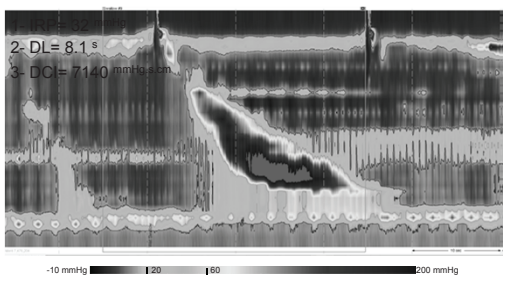
Outflow Obstruction (achalasia?)

1. Elevated IRP
2. Sufficient evidence of peristalsis present



Outflow Obstruction (Hiatus?)

1. Elevated IRP
2. Sufficient evidence of peristalsis present



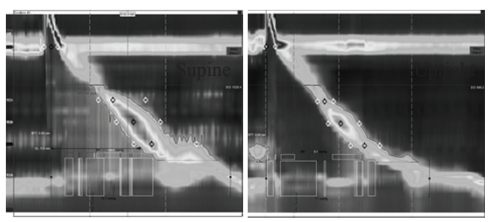
CAVEATS & *PITFALLS*

1) Effect of posture on metrics
2) Bolus presence in wet swallow
3) Esophageal isobaric pressure
4) Pressure artifact

1- Posture Effect

200 mmHg

- Was patient recumbent or gravity also assisted the bolus transport?



20

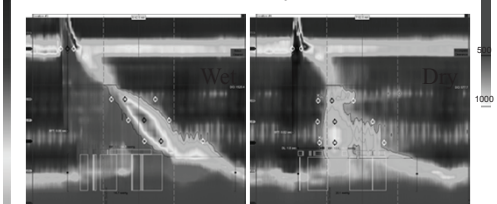
10 mmHg

Supine	Upright
1- IRP= 14.7 mmHg	1- IRP= 7.7 mmHg
2- DL= 5.8 s	2- DL= 6.5 s
3- DCI= 1525 mmHg.s.cm	3- DCI= 688 mmHg.s.cm

2- Presence of Bolus

200 mmHg

- Did patient swallow the bolus as marked by the operator? (Was it really wet swallow?)



20

10 mmHg

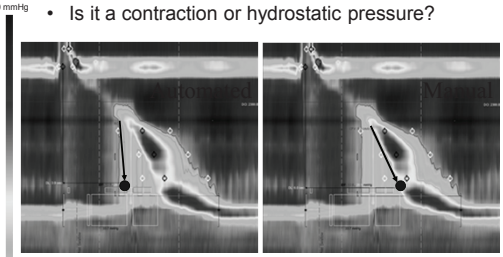
Wet	Dry
1- IRP= 14.7 mmHg	1- IRP= 20.1 mmHg
2- DL= 5.8 s	2- DL= 1.8 s
3- DCI= 1525 mmHg.s.cm	3- DCI= 578 mmHg.s.cm

3- Esophageal Isobaric Pressure

(esophageal pressurization)

200 mmHg

- Is it a contraction or hydrostatic pressure?



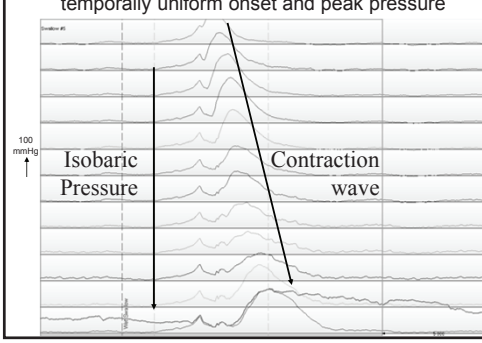
20

10 mmHg

Automated	Manual
1- IRP= 33.7 mmHg	1- IRP= 33.7 mmHg
2- DL= 3.9 s	2- DL= 6 s
3- DCI= 2389 mmHg.s.cm	3- DCI= 2389 mmHg.s.cm

Isobaric Pressure in Tracing

- Appears like a series of parallel lines with temporally uniform onset and peak pressure



Isobaric Pressure in Topography

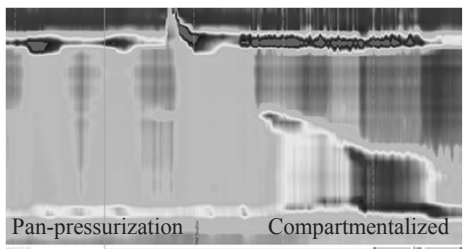
200 mmHg

20

10 mmHg

Hydrostatic Intrabolus Pressure

- *Pan-pressurization*
- *Compartmentalized pressurization*



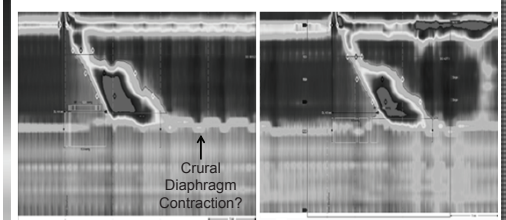
4- Pressure Artifact

200 mmHg

20

10 mmHg

- Is there hiatal hernia?
- Is there outflow obstruction?



1- IRP= 15.9 mmHg
2- DL= 4.5 s
3- DCI= 5610 mmHg.s.cm

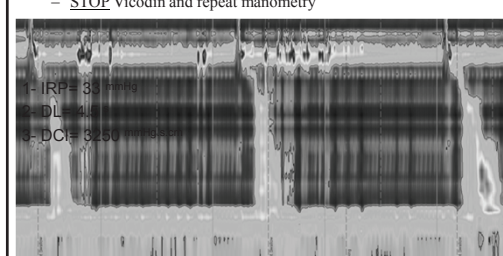
1- IRP= 9 mmHg
2- DL= 4.8 s
3- DCI= 4277 mmHg.s.cm

Case 1: BV

- 68 year female
- Atypical chest pain
- Solid and liquid dysphagia
- PMH: GERD for decades, chronic pain
- S/p Nissen fundoplication
- Vicodin as needed for back pain
- Referred by GI after 1 year of negative workup:
  - Negative cardiac catheterization
  - Negative EGD
  - Multiple balloon dilations to 20 mm
  - Multiple Botox injections

Outflow Obstruction

- Meets manometric criteria for Type III achalasia
- Recommendation:
  - STOP Vicodin and repeat manometry



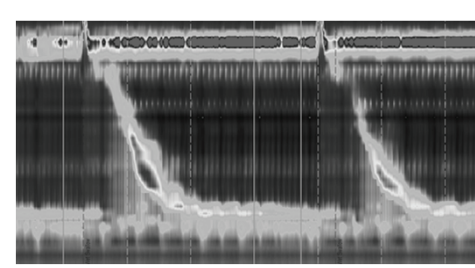
-10 mmHg 20 200 mmHg

One year later

- Patient broke her contract with pain management provider, and obtained opioid analgesics from another source
- Changed her PCP
- Off all opioids for several months
- Persistent chest pain and epigastric pain
- Dysphagia and impaired solid intake
- Patient is seeking Heller myotomy in surgery

Opioid-Induced Major Esophageal Motor Disorder

- Diagnosis of achalasia in patients who are chronically on opioid analgesics may be unreliable

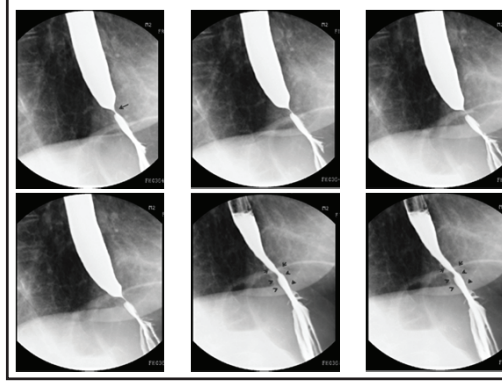


-10 mmHg 20 200 mmHg

Case 2: LT

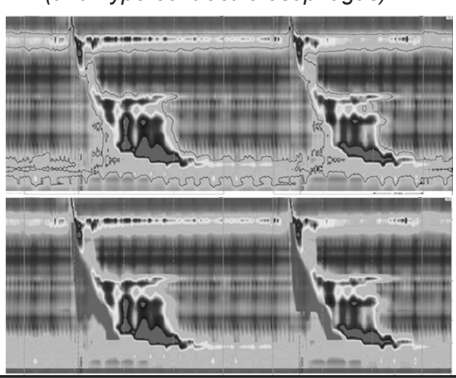
- 59 year female
- Nausea with fullness after eating
- Solid dysphagia
- PMH: GERD, Hernia and Barrett's esophagus
- Referred by surgery for preoperative evaluation and consideration of a fundoplication:
  - EGD
    - Diaphragmatic hernia
    - Barrett's esophagus
  - Normal gastric emptying
- "Refractory GERD"

Esophageal Retention

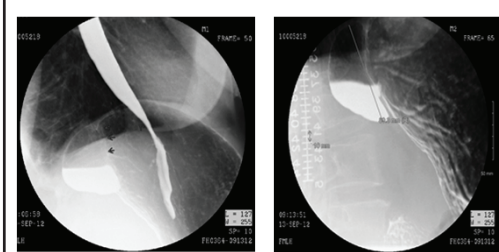


Esophageal Outflow Obstruction

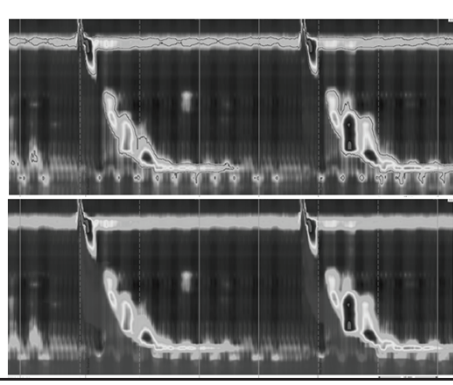
(and hypercontractile esophagus)



Gastric Diverticulum



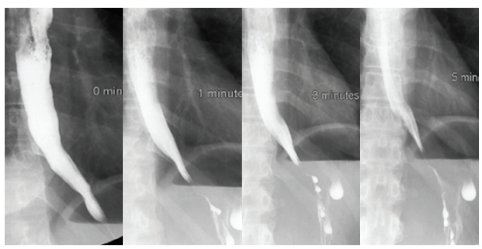
Postoperative Esophageal Motility



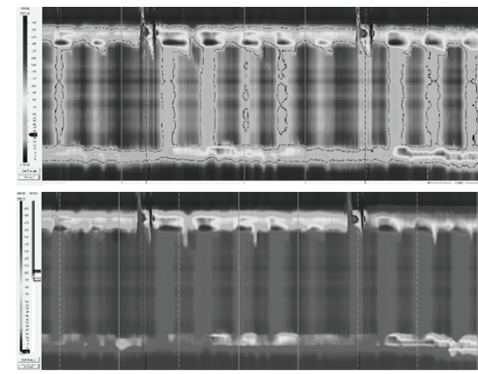
Case 3: KA

- 43 year female
- Atypical chest pain, burning and tightness
- Solid and liquid dysphagia with 25 lbs weight loss
- Throat pain and choking while drinking
- Constipation and bloating
- PMH: GERD x 6 years, Asthma, Anxiety
- FH: CAD brother at age 40
- Referred by GI after 2 years of negative workup:
  - Negative H. pylori
  - Negative EGD/Colonoscopy x 2
  - Negative RUQ US
  - GB ejection fraction normal
  - Esophagram rules out achalasia

Esophagram



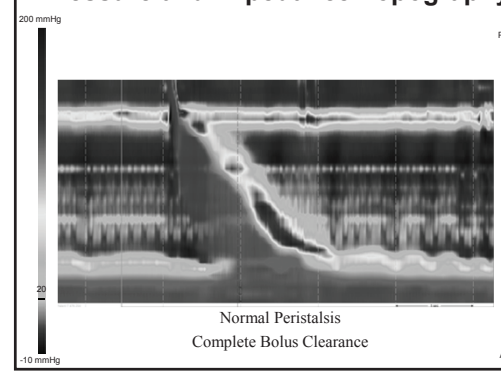
Achalasia



Minor
Esophageal Motor Disorders

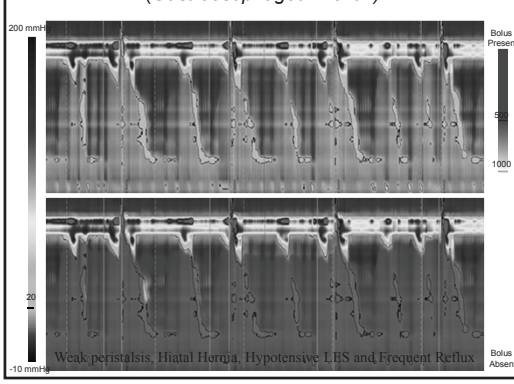
1) Ineffective esophageal motility
2) Fragmented peristalsis

Combined Esophageal Pressure and Impedance Topography



Normal Peristalsis
Complete Bolus Clearance

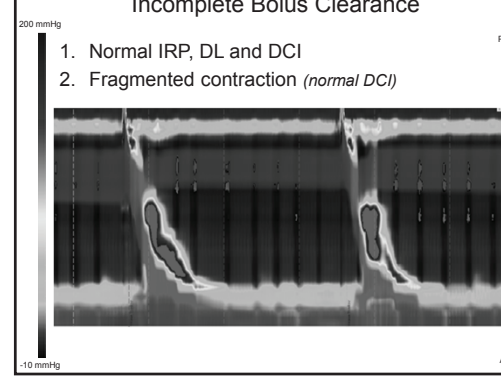
Ineffective Esophageal Motility
(*Gastroesophageal Reflux)*



Weak peristalsis, Hiatal Hernia, Hypotensive LES and Frequent Reflux

Fragmented Peristalsis
Incomplete Bolus Clearance

1. Normal IRP, DL and DCI
2. Fragmented contraction *(normal DCI)*



Medical Management of Fecal Incontinence in 10 minutes

Adil E. Bharucha, M.B.B.S., M.D.
Professor of Medicine,
Division of Gastroenterology and Hepatology
Mayo Clinic, Rochester, MN

ANMS Course 2016

Take a Careful History

Inquire About	To Identify	What next?
Bowel disturbances (bowel diary)	• Constipation or diarrhea	• Manage appropriately
When did FI begin	• After cholecystectomy • After anal surgery	• Bile acid malabsorption • Anal inury/weakness
When does FI occur	• Meal-related • Passive • During activity or after bowel movement	• ? ↑ gastrocolonic response • ? Anal weakness • ? Evacuation disorder
Consistency	• Small pellets	• ? Slow colon transit, anal weakness, evacuation disorder → cotton plugs, fiber, biofeedback therapy
	• Loose stools	• Diarrhea
Volume of leakage	• Small	• ? evacuation disorder, ↓ rectal capacity, anal weakness
	• Large volume	• Diarrhea
Diet - caffeine, sugars [“ose” or ol”]	• Significant (>10gm daily of sugars)	• Discontinue for 2 months

Overall Approach

Identify risk factors and pathophysiological mechanism(s)

History

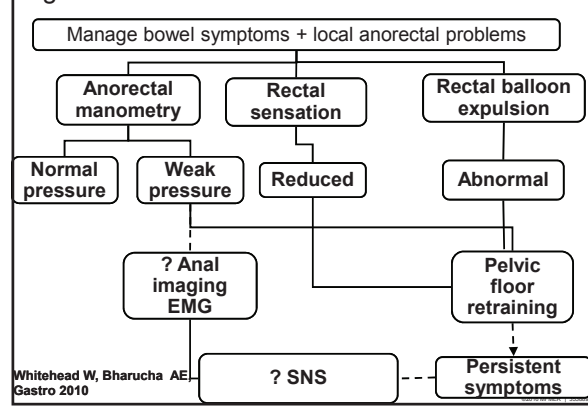
Digital rectal exam

Anorectal manometry + rectal sensation

↓

Treat appropriately

Algorithm



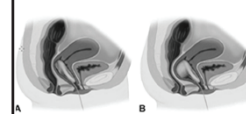
Whitehead W, Bharucha AE Gastro 2010

Evidence-Based Summary – Etiology, Mechanisms, and Management

- Diarrhea and rectal urgency - strongest risk factors for FI [1]
  - Others – cholecystectomy, smoking, rectocele…
  - Obstetric anal injury causes peripartum FI, but not a significant risk factor for FI in older women[1]
- Bowel disturbances + anorectal disturbances = FI [2,3]
- Limited evidence that antidiarrheal agents (e.g., loperamide, bile-salt binding resins) are effective in patients with diarrhea and FI [4,5]
  - 25-30% benefit from conservative therapy (sans biofeedback)
  - No studies in constipated patients with FI
  - Clonidine – not better than placebo in all comers but may be better in patients with diarrhea and FI [6]
- Biofeedback therapy is better than Kegel’s exercises in patients who do not respond to conservative therapy [7]

[1]Bharucha AE Gastro 2010, [2]Gut 2005; [3]Sun Gut 1992; [4]Bharucha Gastro 2014; [5]Wald AJG 2015; [6]Bharucha AE CGH 2014; [7]Heymen S. DCR 2009.

New anal outlet barrier devices – only tested in uncontrolled studies



- Vaginal bowel control device
  - 200 consented → 61 treated → 79% had ≥ 50% reduction in FI at 4 weeks
  - QOL improved - per protocol assessment
  - Minor adverse events - 23% Discontinuation rate not reported
  - Antidiarrheal medications permitted – data not provided

- Renew™ inserts
  - 97 initial → 73 completed → 62% (51-71%) had ≥ 50% reduction at 4 weeks
  - Antidiarrheal medications and enemas could be modified during the study
  - 78% of completers – very/extremely satisfied
  - No serious adverse events

Take Home Messages

- Take a careful history
- Take a careful history
- Take a careful history
- Take a careful history
- Take a careful history
- Do a meticulous digital rectal exam
- Cognitive medicine and simple measures are safe……and often effective

Shortcuts lead to shortcomings

Nausea, vomiting, rumination and regurgitation – how to sort them out and what is the management?

ANMS 11th Postgraduate Course

Arjan Bredenoord
Academic Medical Center Amsterdam
the Netherlands

Question: what is the diagnosis?

A: vomiting
B: GERD
C: rumination syndrome
D: don't know, more information required

Learning objectives

- Know how to use history to distinguish vomiting from regurgitation and rumination
- Know how to differentiate between regurgitation and rumination using esophageal physiology tests
- Know how to manage vomiting, regurgitation and rumination

Question: what is the diagnosis?

A: vomiting
B: GERD
C: rumination syndrome
D: don't know, more information required

Case

- Mrs J, female, 21 yrs old
- "throwing up food after eating", mostly after meals
- Some heartburn, disappeared with PPI
- PPI did not affect "throwing up food"

Differentiate vomiting vs rumination and regurgitation

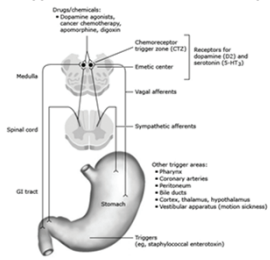
History !

– Vomiting
  - With effort, ejection of the stomach contents
  - Involves forceful contractions of the abdominal accessory muscles
  - Large volumes
  - Often nausea, retching
– Regurgitation and rumination
  - Effortless reflux of undigested contents
  - In small amounts
  - Often swallowed again

What is vomiting?

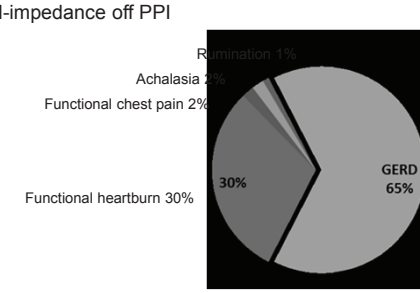
- Vomiting is a reflex, allows to get rid of ingested toxins
- Emetic center in Nucleus Tractus Solitarius, receives input from humoral factors and afferent nerves and stimulates motor nuclei that start vomitingreflex:
  - LES and stomach relaxation
  - Retrograde contractions of proximal small bowel and antrum
  - Abdominal muscle contraction

Trigger areas for nausea and vomiting



Patients with refractory reflux symptoms often do not have GERD

- 106 patients with refractory reflux symptoms
- HRM + pH-impedance off PPI



Herregods et al. Neurogastroenterol Motil 2015

Approach to nausea and vomiting

Differential diagnosis
- Medication / toxic
- Infectious
- Obstruction
- Inflammation of GI tract
- CNS
- Endocrinologic / metabolic
- Functional
- Behavioural

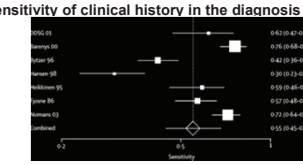
History
- Acute, chronic, recurrent
- Medication / drug / nicotine use
- Eating disorders -> bulimia
- Pregnancy
- Abdominal pain -> organic
- Abdominal distension -> obstruction
- Vomiting of foods eaten hours earlier -> gastric obstruction / emptying problem
- Vertigo, nystagmys -> vestibular
- Headache, other neurologic signs

History most important, additional testing usually not required

AGA medical position statement: Nausea and vomiting. Gastroenterology 2003

Diagnosis of GORD: value of symptoms

Sensitivity of clinical history in the diagnosis of oesophagitis



Sens = 55%

Predictive value for GERD of individual symptoms

Symptom	Sensitivity*	Specificity*	LR Positive	Probability of GERD†
Heartburn dominant	38%	89%	3.45	54%
Acid regurgitation dominant	6%	95%	1.20	29%
Heartburn present	73%	53%	1.55	34%
Acid regurgitation present	66%	58%	1.57	34%
Opinion of experienced gastroenterologist	78%	60%	1.95	39%

Moayyedi et al. Am J Gastro 1999

Regurgitation

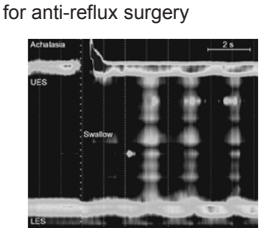
Effortless reflux of undigested contents

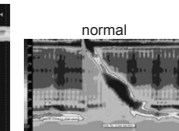
-> gastric contents: GERD

-> esophageal contents: achalasia, esophageal motor disorders, stenosis

Erroneous diagnosis of GORD in achalasia

Three patients with heartburn, regurgitation, chest pain referred for anti-reflux surgery

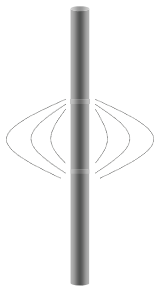




Achalasia can be mistaken for GERD

Kessing et al. Clin Gastroenterol Hepatol 2013

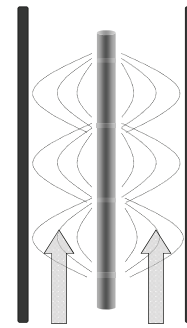
Electrical impedance monitoring



- Voltage difference between 2 electrodes
- Electrical current between electrodes
- Measurement of the resistance (impedance) of the medium between electrodes

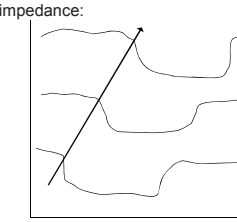
Silny J Gastrointest Motil 1991

Electrical impedance monitoring



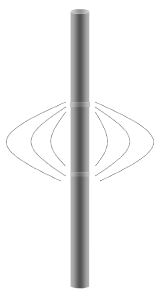
fluid:

impedance:



time

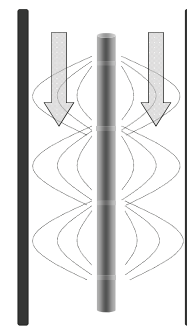
Electrical impedance monitoring



- (ions-containing) fluids are well-conductive: low impedance
- Air is non-conductive: high impedance

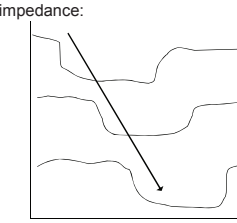
Silny J Gastrointest Motil 1991

Electrical impedance monitoring



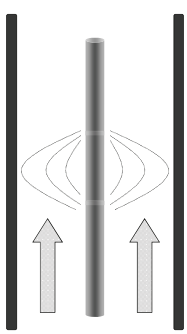
fluid:

impedance:

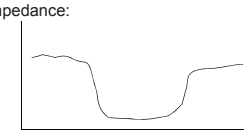


time

Electrical impedance monitoring



impedance:



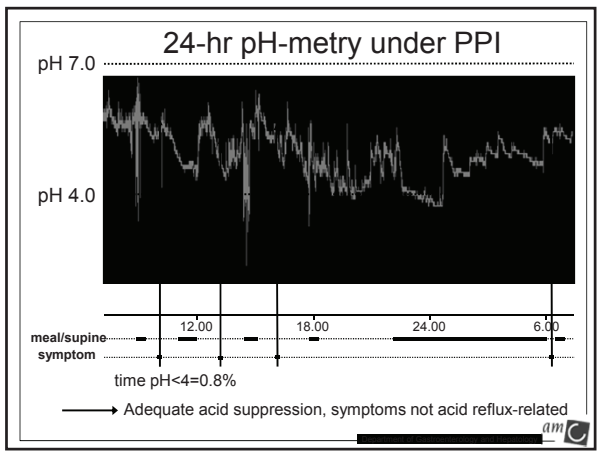
time

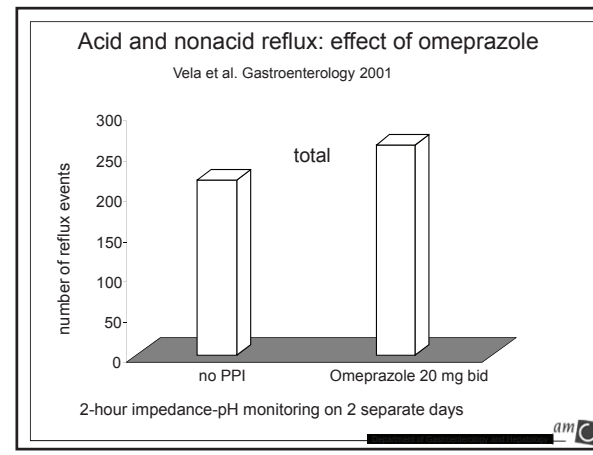
fluid

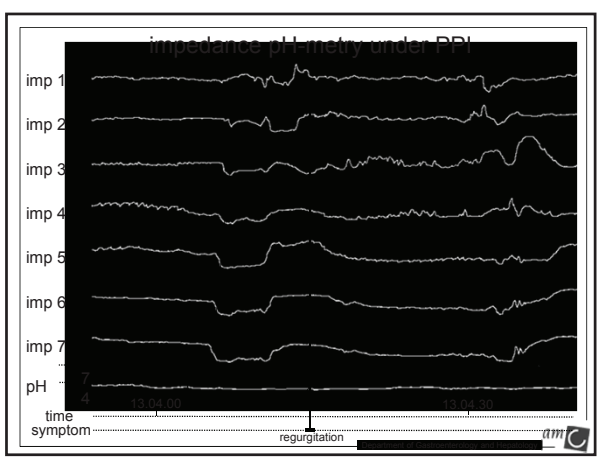
Silny J Gastrointest Motil 1991

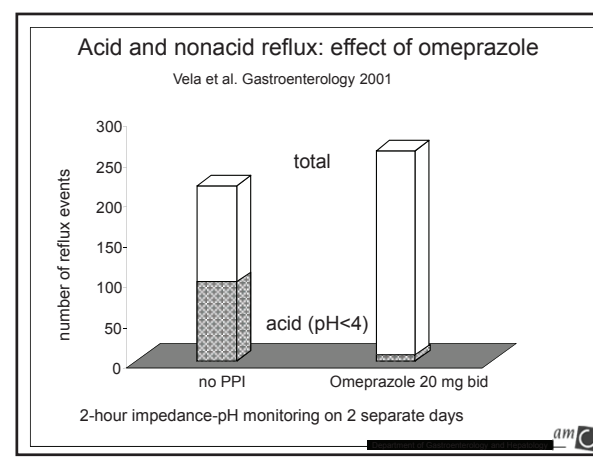
Case

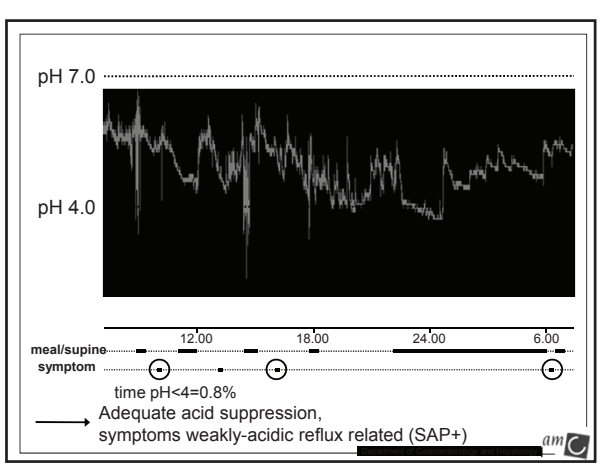
- Mr H, male, 28 yrs old
- Daily heartburn and regurgitation
- Consults GP
- Therapy: PPI
- Symptoms reduced, not disappeared
- Referral to gastroenterologist
  - 24-hr pH-metry while under PPI

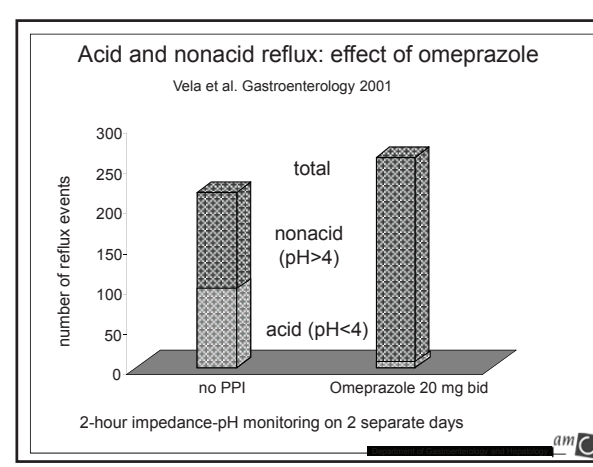

24-hr pH-metry under PPI
pH 7.0
pH 4.0
12.00
18.00
24.00
6.00
meal/supine
symptom
time pH<4=0.8%
Adequate acid suppression, symptoms not acid reflux-related


Acid and nonacid reflux: effect of omeprazole
Vela et al. Gastroenterology 2001
number of reflux events
300
250
200
150
100
50
0
total
no PPI
Omeprazole 20 mg bid
2-hour impedance-pH monitoring on 2 separate days


impedance pH-metry under PPI
imp 1
imp 2
imp 3
imp 4
imp 5
imp 6
imp 7
pH
7
4
13.04.00
13.04.30
time
symptom
regurgitation

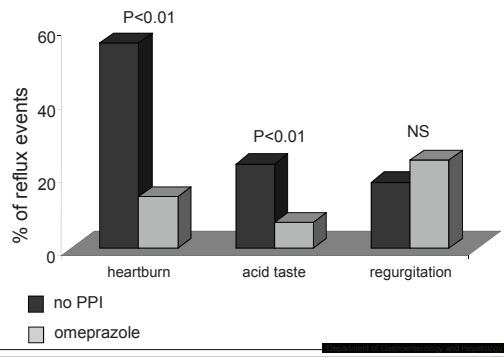

Acid and nonacid reflux: effect of omeprazole
Vela et al. Gastroenterology 2001
number of reflux events
300
250
200
150
100
50
0
total
acid (pH<4)
no PPI
Omeprazole 20 mg bid
2-hour impedance-pH monitoring on 2 separate days


pH 7.0
pH 4.0
12.00
18.00
24.00
6.00
meal/supine
symptom
time pH<4=0.8%
Adequate acid suppression,
symptoms weakly-acidic reflux related (SAP+)


Acid and nonacid reflux: effect of omeprazole
Vela et al. Gastroenterology 2001
number of reflux events
300
250
200
150
100
50
0
total
nonacid
(pH>4)
acid (pH<4)
no PPI
Omeprazole 20 mg bid
2-hour impedance-pH monitoring on 2 separate days

Acid and nonacid reflux: effect of omeprazole

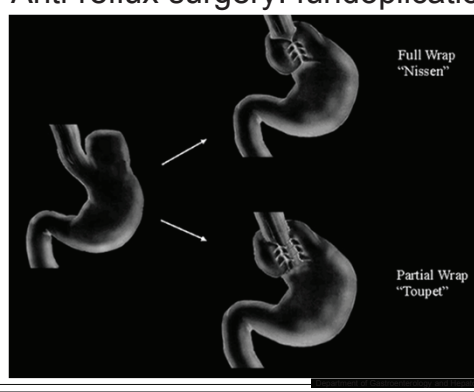
Vela et al. Gastroenterology 2001



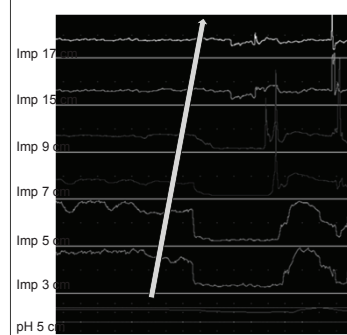
Summary: regurgitation

- Effortless reflux of esophageal or gastric contents
- Confirm diagnosis of GERD with impedance-pH monitoring
- Regurgitation responds poorly to PPI
- In case of severe complaints consider surgery

Anti-reflux surgery: fundoplication



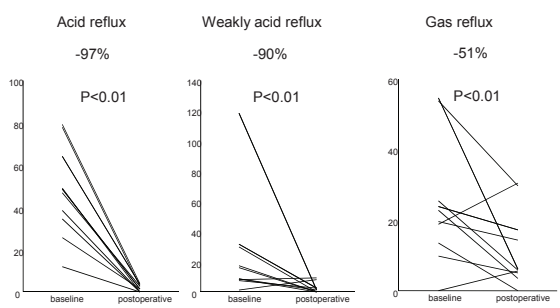
Question: measurement after meal



What do you see?
A. Rumination
B. Reflux / regurgitation
C. Vomiting
D. Could be all

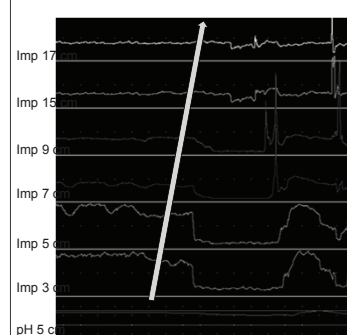
Effect of fundoplication on reflux episodes

24-uurs pH-impedantie measurements



Bredenoord et al Gut 2008

Question: measurement after meal



What do you see?
A. Rumination
B. Reflux / regurgitation
C. Vomiting
D. Could be all

Rumination syndrome

- Behavioral disorder resulting in recurrent regurgitation of undigested food, not preceded by retching
- Disorder often confused with GERD
- Typically during and immediatly after meals, stops when regurgitate becomes acidic
- Diagnosis was always based on clinical history and observations

Cause of rumination

- Case study of 46 patients with rumination
- Rumination behavior is triggered by another symptom: dyspepsia, reflux, dysphagia
- Rumination stops after removal of triggering symptoms, e.g. reflux-rumination after fundoplication
- Impedance-pH manometry showed classic rumination in 76%, but some seem to ruminate after supra-gastric belches or during reflux episodes

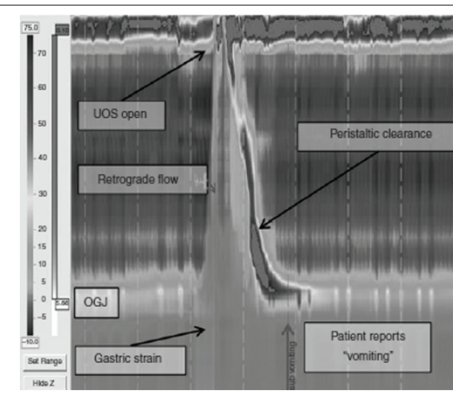
Tucker et al. APT 2013

Characteristics of patients with rumination

- 147 pts (age 5-20 yrs) in 25-yrs in Mayo Clinic, 68% female
- Duration between onset and diagnosis was 2.2 years
- 73% missed school/work, 46% hospitalized
- 11% previously underwent surgery for rumination!
- 17% psychiatric comorbidity
- Number of diagnostic tests (besides esophageal function testing) was median 3, range 0-8

Rare but severe disorder, too much testing and too long diagnostic delay – diagnosis is made clinically

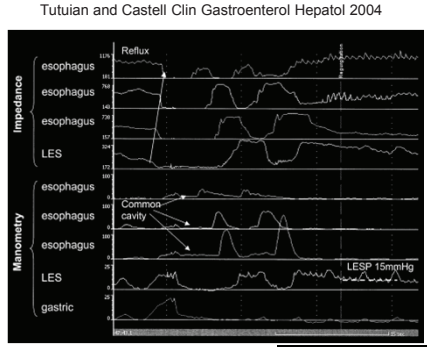
Chial et al. Pediatrics 2003



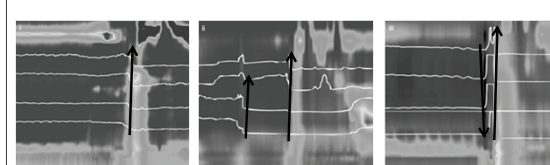
Tucker et al. APT2013

Rumination documented by using combined multichannel intraluminal impedance and manometry

Tutuian and Castell Clin Gastroenterol Hepatol 2004



3 different rumination mechanisms

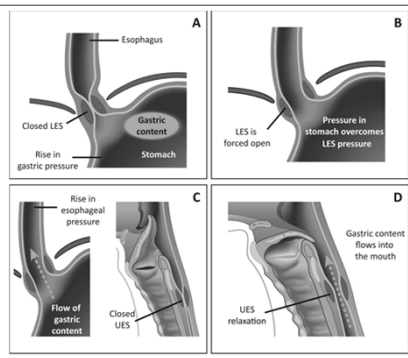


Primary rumination

Rumination following regular reflux episode - Secundary rumination

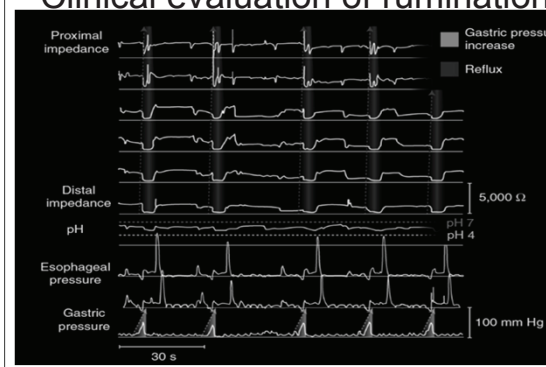
Rumination induced by SGB

Kessing et al. Am J Gastroenterology 2014

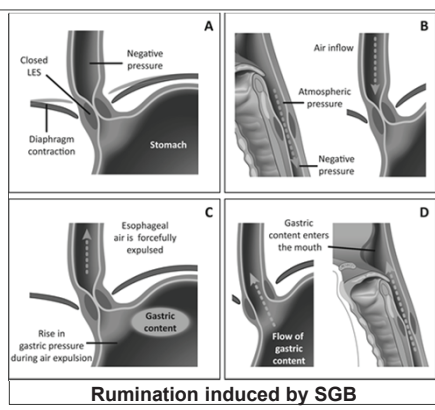


Primary rumination

Clinical evaluation of rumination

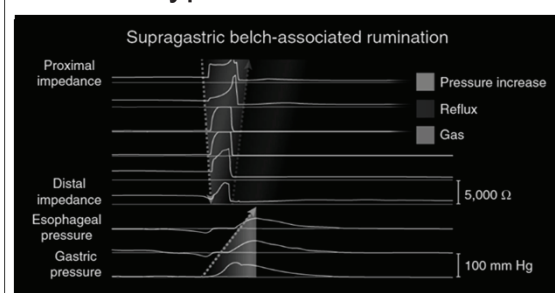


Kessing et al. Am J Gastroenterology 2014



Rumination induced by SGB

3 types of rumination



Kessing et al. Am J Gastroenterology 2014

Clinical evaluation of rumination

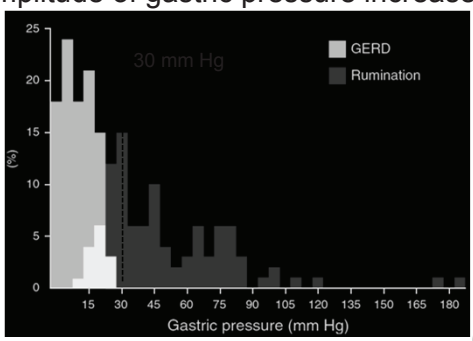
- Combined pH-impedance pressure measurements
  - At least one pressure sensor in the stomach
- Duration:
  - Measurement period should include at least one meal
  - Patient need to have symptoms during measurement
  - 24 hours not required, unless GERD in differential diagnosis

Rumination

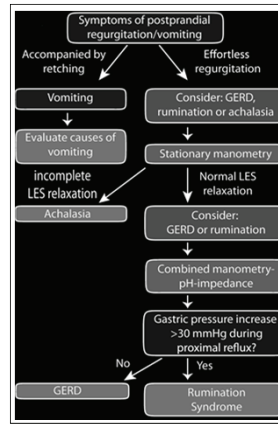
Often confused with refractory GERD

	GERD	Rumination
Effect PPI	Symptoms ↓	Symptoms ↑
Onset symptoms	1-2 hrs after meal	Directly after meal

Comparison rumination with GERD: amplitude of gastric pressure increase?



Approach to postprandial regurgitation



Kessing et al. J Clin Gastroenterol 2013

Diagnosis of rumination

- Primary criteria on pH-impedance manometry
  - Proximal reflux episodes
  - Simultaneous gastric pressure increase > 30 mmHg
- Supportive criteria
  - Repetitive events
  - Events during periods symptoms indicated by patient
- Ask patient to eat food that triggers symptoms

Conclusions

- Vomiting is distinguished from rumination and regurgitation by careful history taking
- Regurgitation? Perform HRM and impedance-pH monitoring to confirm GERD and rule out achalasia and other motility disorders
- Suspected rumination? Combine impedance monitoring with manometry

Treatment of rumination

- Response to unpleasant sensation, so treat this first (e.g. dyspepsia)
- Rumination is a learned habit, but patients are unaware of performing
  -> creat consciousness
- Diaphragmatic breathing during and after meals

Chitkara et al. Am J Gastroenterol 2006

Masqueraders of IBS-D - the latest on celiac disease, non-celiac wheat intolerance, microscopic colitis, IBD, bile acid diarrhea, and diverticular disease

Brooks D. Cash, MD
FACP, FACG, FASGE, AGAF
Professor of Medicine
University of South Alabama
Mobile, AL

Rome IV Diagnostic Criteria for Irritable Bowel Syndrome

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

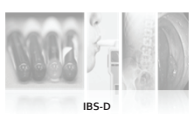
1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

"The diagnosis of IBS should be made based on the following 4 key features: clinical history; physical examination; minimal laboratory tests; and, when clinically indicated, a colonoscopy or other appropriate tests."

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Lacy B, et al. Gastroenterology 2016;150:1393-1407.

Diagnostic Testing for Patients with Suspected IBS without Alarm Features



All IBS Subtypes
CBC
Age-appropriate CRC screening

IBS-D	IBS-M	IBS-C
CRP or fecal calprotectin	CRP or fecal calprotectin	If severe or medically refractory, refer for physiologic testing
IgA TtG ± quantitative IgA	IgA TtG ± quantitative IgA	
When colonoscopy performed, obtain random biopsies	Stool diary	
SeHCAT, fecal bile acids, or serum C_4 where available	Consider abdominal plain film to assess for fecal loading	

*__Alarm features__ include age ≥50 years old, blood in stools, nocturnal symptoms, unintentional weight loss, change in symptoms, recent antibiotic use, and family history of organic GI disease.
CBC, complete blood count; CRC, colorectal screening; CRP, C-reactive protein; SeHCAT, selenium homocholic acid taurine; TtG, tissue transglutaminase.

Chey WD, et al. *JAMA*. 2015;313(9):949-958.

Diagnostic Challenges in IBS

- Symptoms vary between individuals, difficult to quantify
- Lack of biological markers
- Clinician and patient apprehension about:
  - i. Organic disease mimicking IBS
  - ii. Accepting a diagnosis lacking a diagnostic gold standard
  - iii. Unproductive/misleading diagnostic testing to exclude organic conditions

Remains a diagnosis of exclusion for many leading to greater anxiety, costs, unnecessary procedures, and misdirected treatments[2,3]

1.Spiegel B et al. *Am J Gastroenterol.* 2010;105(4):848-858. 2. Longstreth GF, Yao JF. *Gastroenterology.* 2004;126(7);1665-1673. 3. Longstreth GF, et al. *Clin Gastroenterol Hepatol.* 2005;3(4):397-400. 4. Drossman D, et al. *Gastroenterology* 2002;123:2108-2131

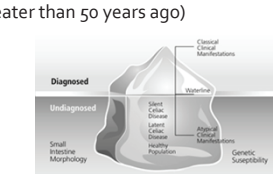
Rome IV Diagnostic Recommendations: Read the Fine Print

- CBC, CRP, or fecal calprotectin
- Routine thyroid tests (if clinically warranted)
- Celiac tests in patients with IBS-D and IBS-M (who fail empiric therapy)
- Stool analysis (culture, O&P) may be useful with diarrhea
- Colonoscopy in patients 50 years and older in the absence of warning signs (45 years in African Americans), based on national recommendations.
  - For the presence of alarm symptoms or signs, a family history of colorectal cancer and persistent diarrhea that has failed empiric therapy
  - Biopsies of different segments of the colon may be required in patients with chronic diarrhea to rule out microscopic colitis.
- Bile acid malabsorption testing in patients with IBS-D (who fail empiric therapy)
- Breath tests to rule out carbohydrate malabsorption in patients with IBS-D (and persistent symptoms)

Lacy B, et al. Gastroenterology 2016;150:1393-1407.

Celiac Disease

- "Atypical is typical:" 50% of newly diagnosed celiac patients present with atypical symptoms (extra GI+GI 15x more common than GI symptoms alone)
- Prevalence: ~1:100 in most genetically susceptible populations, NHANES: 0.71%
- Less than 10-15% cases actually diagnosed
- Increasing prevalence (4 to 5-fold greater than 50 years ago)
- Diagnostic delay ≈ 11 years

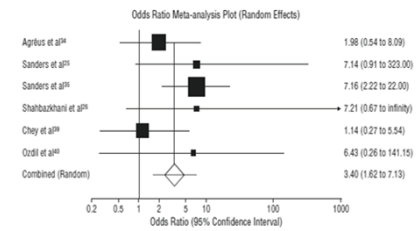


Celiac Disease and IBS

- General Practice Research Database (UK)
  - Celiac patients 3X more likely to have a prior diagnosis of IBS, even for 10 years previously
- 38% of celiac patients have IBS symptoms even on GFD
  - More likely if non-adherent with GFD
- Should you test patients with IBS symptoms for celiac disease?

Card et al. Scand J Gastroenterol 2013;48:801-7; Sainsbury et al. Clin Gastroenterol Hepatol 2013;11:359-65

IBS and Celiac Disease (Biopsy Proven): Meta-analysis

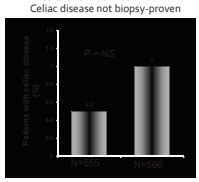


Prevalence of biopsy-proved celiac disease in cases meeting diagnostic criteria for IBS was more than 4-fold that in controls without IBS; Prevalence 4%

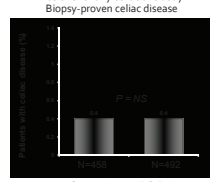
Ford, et al. Arch Intern Med 2009:169:651

IBS and Celiac Disease: US Data

Case-control study
IBS patients (physician diagnosis)
Positive for both TtG and EMA
Celiac disease not biopsy-proven



Prospective study
Non-constipated IBS patients (Rome II)
Positive for any celiac antibody
Biopsy-proven celiac disease



Prospective study: 7.3% IBS and 4.8% controls had at least 1 abnormal gluten-directed serology (most often IgG AGA)

Saito-Loftus Y, et al. *Am J Gastroenterol.* 2008;103(suppl 1):S472. Abstract 1208; Cash BD, et al. *Gastroenterol.* 2011;141:1187.

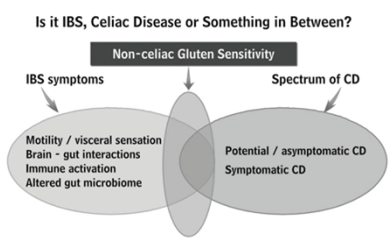
Cost-effectiveness of Testing for Celiac Disease in IBS

- Decision-analytic model of celiac testing vs. empiric IBS therapy
- Testing: incremental $11K for one additional symptomatic improvement
  - ICER greater than $50,000 when the prevalence of CD <1%
  - Testing for CD dominant when the prevalence of CD >8%
- Current data equivocal regarding value of screening for CD in patients with IBS symptoms (US data unsupportive)
  - Patient expectations (and satisfaction) and defensive practice will continue to drive frequent and low-yield diagnostic testing for CD

ICER = incremental cost-effectiveness ratio

Spiegel, et al. Gastroenterol 2004;126:1721; Ladabaum et al, *Aliment Pharmacol Ther* 2004;19:1199

Non-celiac wheat intolerance



Adapted from Verdu EF, et al. Am J Gastroenterol 2009; 1587:94

Non-Celiac Gluten/Wheat Sensitivity (NCWS)

- Defined by negative immunoallergy tests to wheat, negative celiac serology, normal duodenal histopathology, and resolution of symptoms on GFD/WFD
  - Prevalence estimates vary from 0.55% (NHANES) to 30%; true prevalence unknown
  - More common in females and young/middle aged adults
- Classic presentation: IBS-like symptoms, "foggy head", headache, fatigue, joint/muscle pain
- Evidence to support role of innate immune system

Sapone A, et al. BMC Med 2012;10:13; Cooper, BT, et al, Gastroenterology, 1980;79; 801.; Massari, S, et al, Intl Arch Allergy Immunol, 2011;155;389; Sabatino, et al, Ann Intern Med, 2012;156, 309; Catassi C, et al. Nutrients 2013;5:3839-3853

Brooks D. Cash, MD – Masqueraders of IBS-D – the latest on celiac disease, non-celiac wheat intolerance, microscopic colitis, IBD, bile acid diarrhea, and diverticular disease

Wheat: Gluten and Beyond

- Modern wheat: 7-22% protein; mostly gluten
  - 3 groups of gliadins with 50+ epitopes: immunomodulatory, cytotoxic, and gut-permeating activity
- Other constituents of wheat may affect GI tract:
  - Wheat germ agglutinin: stimulates release of inflammatory cytokines
  - α-amylase/trypsin inhibitors: elicit pro-inflammatory cytokines
  - Starches (fructans/galactans): fermentation leads to SCFA accumulation (see FODMAP diet)

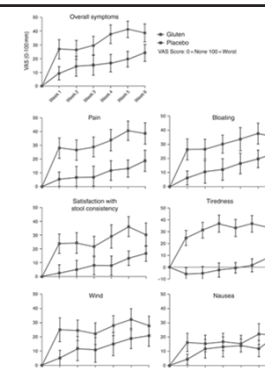
Trocone R, et al. J Intern Med 2011;269:582-90; Haas H, et al. Eur J Immunol 1999;29:918-27; Junker Y, et al. J Exp Med 2012;209:2395-2408.

Gluten Restriction in NCWS

- 34 IBS patients (- CD) controlled on GFD randomized to gluten (16 gm/D) or placebo
- 68% given gluten reported inadequate control of symptoms vs 40% with placebo (p<.001)

No changes in:
- Fecal lactoferrin
- Celiac antibodies
- C-reactive protein
- Intestinal permeability

No effect based on HLA DQ2/DQ8



Biesiekierski et al. Am J Gastroenterology 2011; 106:508-14

Gluten and wheat clearly cause IBS-like symptoms Maybe, maybe not…

- Placebo-controlled, cross-over, re-challenge study (n=37) with NCGS and IBS (Rome III)
  - 2 week run-in with GFD/low FODMAP diet allocated to:
    - High gluten; Low gluten; Control (whey protein)
  - All patients improved during GFD/low FODMAP run-in and worsened with both gluten and control diets
    - Gluten-specific effects in only 8%
- Corroccio et al.: 276 IBS patients responded to GFD
  - 2 groups: Wheat sensitivity or Multiple food sensitivities (atopy model)
  - Observed increased duodenal and colonic eosinophils/activated basophils
- Bottom line: Many potential reasons for improved symptoms beyond gluten avoidance; NCWS/GS likely exists; prevalence remains unknown

Biesiekierski et al, Gastroenterology 2013;145:320-8. Corrroccio A, et al. Am J Gastroenterol 2012;107:1898-1906.

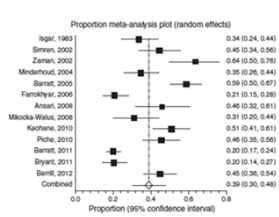
Microscopic colitis

- 466 non-C IBS underwent colonoscopy and random biopsy[1]
  - 1.5% (7/466) with microscopic colitis; 6/7 women, all IBS-D; 3 CC/4LC; mean age 49
  - 2.3% in IBS patients > 45 years
- Two recent meta-analyses (2016) with conflicting results
  - Kamp et al: 33.4% MC patients fit IBS criteria; 8.3% MC in IBD-D patients[2]
    - Conclusion: OR of MC in IBS of 0.68 makes value of colonoscopy and biopsy debatable
  - Guagnozzi et al: 40% MC patients fit IBS criteria; 9.8% MC in IBS-D patients[3]
    - Conclusion: "ruling out a diagnosis of MC by means of colonoscopy and adequate mucosal biopsies should always be considered, especially in patients with IBS-D subtype"
- von Armin et al: Fecal calprotectin may be a marker for MC (small study)
- Pragmatic conclusion: low yield if looking for MC, but reasonable to biopsy if performing colonoscopy since most MC responds well to treatment

1. Chey WD, et al. Am J Gastroenterol 2010;105: 859-65. 2. Kamp EJCA, et al. Clin Gastroenterol Hep 2016;14:659-68. 3. Guagnozzi D, et al. Aliment Pharmacol Ther 2016; von Armin U, et al. Clin Exp Gastro 2016;9:97-103.

Inflamatory Bowel Disease

- Significant overlap between IBS and IBD
  - High stakes for misdiagnosis of IBD
- Pimentel et al: 7.7 year prodrome in patients with Crohn's before formal diagnosis (1.2 years with UC)
  - 25% Crohn's/21% UC had IBS symptoms
  - 6.9 years after removal of IBS symptoms
- Halpin et al: Meta-analysis of 13 studies; 1703 IBD patients
  - Prevalence of IBS symptoms: 40% (OR: 4.9)
  - More common with active IBD but still present in IBD in remission
  - CD>UC (46% vice 36%), even in remission

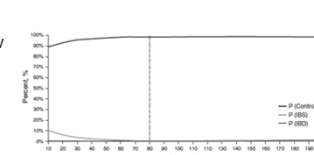


Pimental M, et al. Am J Gastroenterol 2000;95:3458-62.Halpin SJ, Ford AC. Am J Gastroenterol 2012;107:1474-82.

Differentiating IBS and IBD

- Alarm features
- Sigmoidoscopy, colonoscopy
- Stool: lactoferrin, calprotectin
- Serum: ESR, CRP, TNF-alpha[1]

- Menees et al: Systematic review of 12 studies[2]
  - ESR: poor discriminatory power between IBS and IBD

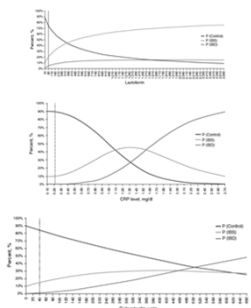


1. Vivinus-Nebot M, et al. Gut 2014; 63:744-52. 2. Menees SB, et al. Am J Gastroenterol 2015;110:444-54.

Brooks D. Cash, MD – Masqueraders of IBS-D – the latest on celiac disease, non-celiac wheat intolerance, microscopic colitis, IBD, bile acid diarrhea, and diverticular disease

Differentiating IBS and IBD

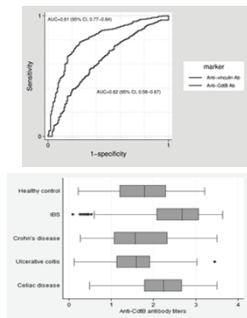
- Fecal lactoferrin: poor discriminatory power between IBS and IBD
- Serum CRP: high NPV for IBD
  - Negative test goes against IBD; IBS suggested by "exclusion"
- Fecal calprotectin: high NPV for IBS
  - Negative test goes against IBD; IBS suggested by "exclusion"



Menees SB, et al. Am J Gastroenterol 2015;110:444-54.

Anti-CdtB/anti-vinculin

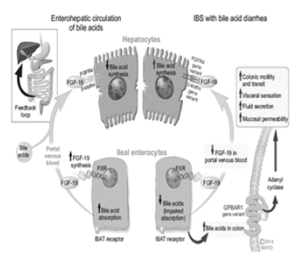
- Cytolethal distending toxin B (CdtB) exposure
  - production of anti-vinculin antibodies leads to neuronal degradation and altered motility leading to dysbiosis and IBS symptoms
- Validated via well-characterized IBS-D population (n=2375) vs controls, celiac, IBD patients
  - Good discrimination between IBS-D and comparator groups
    - Positive test consistent with IBS-D (does not exclude IBD)



Pimentel M, et al. PLoS One 2015;10(5):e0126438.

Bile acid diarrhea

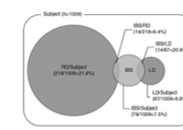
- Prevalence estimated 25-50% IBS-D
- Colonic bile acids
  - Stimulate entero-endocrine cells, accelerate colonic transit
  - Activate visceral sensation and fluid secretion (via intracellular cAMP, increased mucosal permeability, chloride ion secretion)
- Empiric therapy (diagnostic tests pending)
  - Bile acid sequestrants/binders
  - FXR agonists (obeticholic acid, GW4064) in development



Camilleri M. *Gut Liver.* 2015;9:332-339.

Diverticular disease (DD)

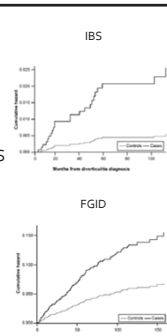
- 70% of individuals ≥ age 80 in US
  - ¼ experience inflammatory/infectious complication
  - Chronic gastrointestinal symptoms with and without peri-diverticular inflammatory changes (SCAD and SUDD)
    - Demonstration of altered motility, visceral hypersensitivity, altered intestinal microbiota
- Evidence suggests linkage between diverticulosis and IBS symptoms
  - Jung: 17% frequent lower abdominal pain; 29% altered bowel habits
  - Simpson: 2x as many (71%) post-diverticulitis patients have recurrent abdominal pain
  - Yamada: OR 8.8 for IBS-D; 8.2 for IBS-M; left-sided association only



Strate LL, et al. Am J Gastroenterol 2012;107:1486-93.; Jung H, et al. Am J Gastroenterol 2010;105:652-61. Yamada E, et al. Am J Gastroenterol 2014;109:1900-05.

Diverticular disease

- Cohen: Retrospective case-control evaluating incidence of post-diverticulitis-IBS (PDV-IBS) in 326 cases and matched controls over 9 year period[1]
  - Adjusted HR 4.7 (95% CI: 1.6-14.0) for development of IBS
  - 2.4 (95% CI: 1.6-3.6) for development of other functional GI disorder
- Cuomo: Prolonged abdominal pain (>24 hours) supports DD
- Tursi: 72 patients with prolonged (>24 hours) pain and DD; 42 with SUDD, 30 met IBS criteria[2]
  - Fecal calprotectin elevated in 64.3% SUDD patients and none of IBS patients (p<0.0001)



1. Cohen E, et al. Clin Gastroenterol Hepatol 2013;11:1614-19. 2. Tursi A, et al. Int J Colorectal Dis 2009;24:49-55.

Diverticular disease

- Unanswered questions
  - Is it helpful to biopsy around diverticuli in IBS patients?
  - What are the effects of treatment of macro or microscopic peri-diverticular inflammation in IBS patients?
    - Treat like SUDD or SCAD with fiber; antibiotics; mesalamine; corticosteroids; probiotics?
    - Previous treatment studies in unselected IBS patients unimpressive/negative
    - Best evidence for "symptom" improvement with antibiotics and probiotics when inflammation present

Conclusions

- Consideration of IBS masqueraders is part of any diagnostic evaluation of IBS
  - Level 1 evidence for specific diagnostic testing for these conditions in IBS patients without alarm features is low yield
  - Testing to exclude these masqueraders does not appear to be cost effective
- Positive diagnostics to "rule in" IBS show promise to be cost saving
- Future investigations evaluating programmatic application of combination of clinical criteria, biomarkers, and/or psychological markers are needed

FODMAPs & IBS: An Update

William D. Chey, MD
Nostrant Professor of Medicine & Nutrition Sciences
Director – GI Nutrition Program
University of Michigan

University of Michigan Health System

THE WALL STREET JOURNAL.

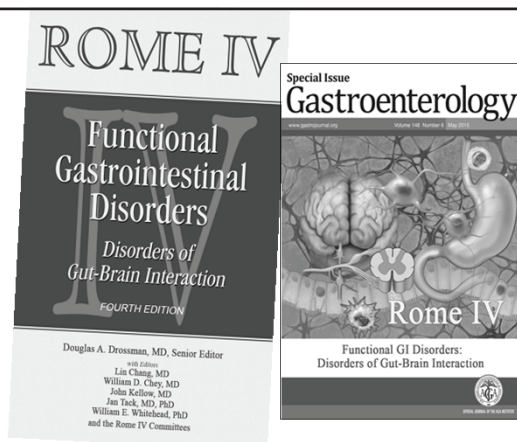
Home World U.S. Politics Economy Business Tech Markets Opinion Arts Life Real Estate

LIFE | HEALTH | HEALTH & WELLNESS

More Options to Treat Irritable Bowel Syndrome

Dietitians and gastroenterologists point to new drugs and the spread of the low-Fodmap diet to battle IBS

A dietary approach to easing that burden has gained steam in the U.S. as physicians like Dr. Chey listen to patients who would rather avoid taking a prescription drug, he says. The University of Michigan, University of Chicago and Stanford University are among the academic medical centers that have embraced the low Fodmap diet as an option for patients. Some have hired dietitians specializing in gastrointestinal disorders to help guide patients. Peter Loftus, May 2, 2016



IBS: Rome IV Criteria*

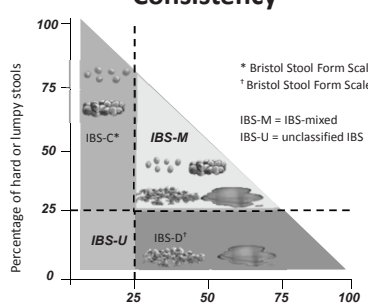
Recurrent abdominal pain ~~or discomfort~~ at least ~~3 days/month~~ 1 day per week associated with two or more of the following:

- ~~Improvement with~~ Related to defecation
- Onset associated with a change in the frequency of stool
- Onset associated with a change in the form of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

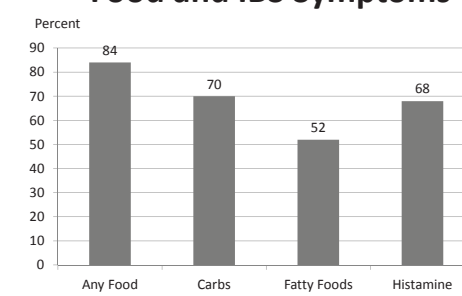
Fermin Mearin et al. *Gastroenterology*. May 2016

IBS Subtypes Are Based on Stool Consistency



Adapted from Longstreth GF, et al. Gastroenterology. 2006;130:1480-1491

Food and IBS Symptoms



197 IBS pts (Rome III)
Symptom severity correlates with number of food sensitivities
No impact of IBS subgroup

Bohn et al. Am J Gastroenterol 2013;108:634

What are FODMAPs?

- **Fermentable oligo-, di-, monosaccharides and polyols**
- **Fruits with fructose exceeding glucose**
  - **Apples, pears, watermelon**
- **Fructan containing vegetables**
  - **Onions, leeks, asparagus, artichokes**
- **Wheat based products**
  - **Bread, pasta, cereal, cake, biscuits**
- **Sorbitol and lactose containing foods**
- **Raffinose containing foods**
  - **Legumes, lentils, cabbage, brussels sprouts**

Eswaran & Chey, GI Cl North Am 2011;40:141
Shepherd, et al, Clin Gastro Hepatol 2008;6:765
Gibson & Shepherd. J Gastro Hepatol 2010;25:252

Do IBS Patients Alter Their Diets?

- 58 IBS-D & 73 Healthy Controls completed 3-7 day food diaries
  - •No differences in age, gender or total caloric intake
  - •BMI higher in IBS cohort (28.6 vs 26.1, p = 0.001)
  - •Similar total lipid, carbohydrate, & protein intake

Table 3. Average daily FODMAP intake

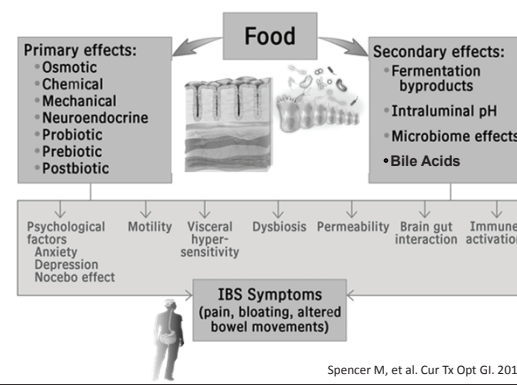
FODMAPs	IBS	Controls	p value*
Fructose (g)	18.8	19.1	0.231
Lactose (g)	9.1	10.1	0.029
Total polyols (g)	0.6	1.4	<0.001
mannitol (g)	0.2	0.3	0.004
sorbitol (g)	0.2	0.4	<0.001
xylitol (g)	0.01	0.03	0.013**
erythritol (g)	0.05	0.3	0.813
inositol (g)	0.1	0.1	0.096
maltitol (g)	0.0	0.1	0.868
pinitol (g)	0.01	0.02	0.785

*adjusted for age, gender, BMI, and total caloric intake
** not significant by ANOVA analysis

Spencer M et al. DDW 15

Why Would Food Cause IBS Symptoms?

Food and GI Symptoms

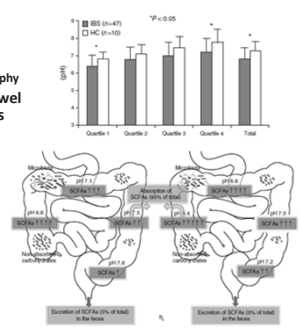


Spencer M, et al. Cur Tx Opt GI. 2014

Colonic Fermentation is altered in IBS

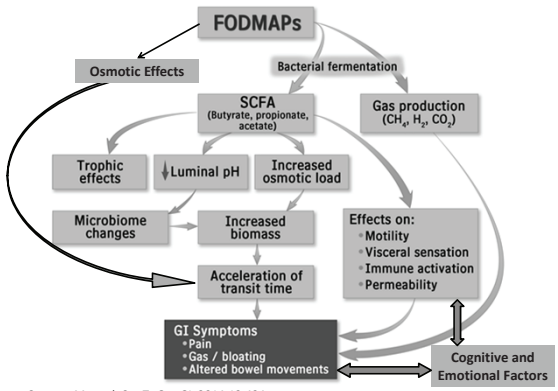
- **114 IBS pts & 33 HCs**
  - **pH & transit by Smartpill**
  - **SCFAs by gas chromatography**
- **Colonic but not small bowel pH lower in IBS pts v. HCs**
- **SCFA levels lower in IBS-C v. IBS-D, M, HCs**
- **Colonic pH correlated with transit and IBS symptom severity**
- **SCFA negatively correlated with transit**

Take Home Point: Colonic fermentation may be altered in IBS



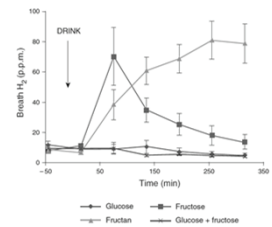
Ringel-Kulka et al. Am J Gastroenterol 2015;110:1339

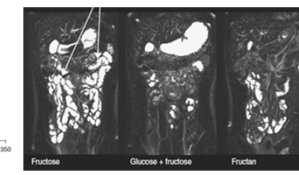
Low FODMAP Diet for IBS: What is the Evidence?



Spencer M, et al. Cur Tx Opt GI. 2014;12:424

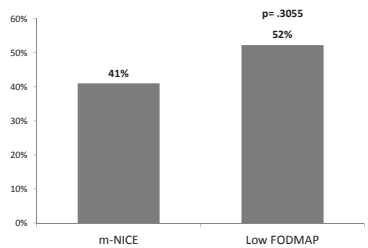
FODMAPs exert osmotic and fermentation related effects which trigger symptoms in IBS





Murray et al. Am J Gastroeterol 2014;109:110

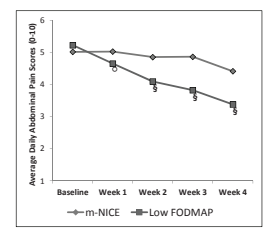
Low FODMAP vs. mNICE Diets for IBS-D: Adequate Relief



"In the last week, have you had adequate relief of your GI symptoms?"
Proportion of patients that answered "Yes" for ≥50% of weeks 3 and 4

Eswaran, Chey et al. DDW 2016

Weekly Abdominal Pain & Bloating Scores

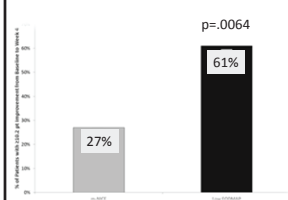


* = p ≤.05
+ = p ≤.01
# = p ≤.001
§ = p ≤.0001

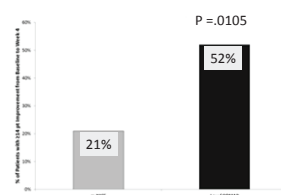
P values refer to the change WITHIN group comparing to baseline score

Eswaran, Chey et al. DDW 2016

Effects on IBS-QOL



Minimally important response (MIR) = 10



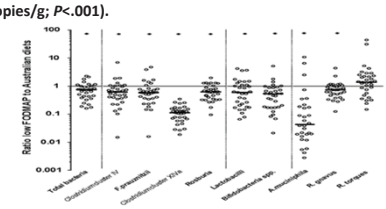
Meaningful clinical response (MCR) = 14

Drossman et al, AJG, 2007

Eswaran, Chey et al. DDW 2016

FODMAP Effects on the Microbiome

- **Low FODMAP diet led to higher fecal pH (7.37 vs. 7.16; *P*=.001).**
- **LFD and Australian diets led to similar SCFA levels**
- **LFD associated with increased microbial diversity and reduced total bacterial abundance (9.63 [9.53-9.73] vs. 9.83 [9.72-9.93] $\log_{10}$ copies/g; *P*<.001).**

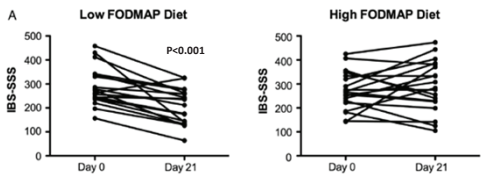


- **"The functional significance and health implications of such changes might lead to caution about reducing FODMAP intake in the longer term,"**

Halmost et al. Gut 2015;64:93-100

Low FODMAP vs. High FODMAP diet: An RCT from Canada

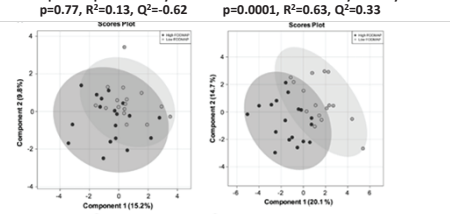
- LFD (N=19) vs. HFD (N=18) x 3 weeks
  - Primary endpoint: IBS-SSS
  - Stool Microbiome Analysis
  - Urinary Metabolomics Analysis
- Primary Endpoint:



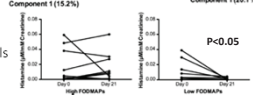
McIntosh et al. Gut 2016, online early

Low FODMAP vs. High FODMAP diet: Effects on the Metabolome

- Principal component analysis of urine metabolome on day 0 & day 21
  p=0.77, R^2=0.13, Q^2=-0.62 p=0.0001, R^2=0.63, Q^2=0.33



Urine Histamine Levels



McIntosh et al. Gut 2016, online early

FODMAP Microbiome Biomarkers and Response to the Low-FODMAP Diet

- 33 children with IBS completed the study
- Less abdominal pain occurred during the low FODMAP diet vs. typical US childhood diet
- Responders were enriched at baseline in taxa with known *greater saccharolytic metabolic capacity*
  - e.g. Bacteroides, Ruminococcaceae, Faecalibacterium prausnitzii
- Responders also enriched at baseline for *3 Kyoto Encyclopedia of Genes and Genomes orthologues*
  - two relate to carbohydrate metabolism

Chumpitazi et al. Aliment Pharmacol Ther 2015; 42: 418–427

Key Points about the Low FODMAP Diet

Teaching is ideally provided with the assistance of a trained dietician.
In the absence of a dietician, appropriately vetted books, web-based resources & mobile apps can help patients to implement the Low FODMAP diet in a medically responsible manner. A one page handout is NOT sufficient to implement the diet.
A 2-4 week trial is usually sufficient to gauge clinical response.
Bloating and abdominal pain are the most likely symptoms to respond. Diarrhea is more likely to improve than constipation.
The full Low FODMAP diet is NOT intended to last a lifetime. Responders should be instructed to implement a stepwise reintroduction of foods containing individual FODMAPs to identify triggers and allow diversification of their diet.
The Low FODMAP diet is NOT intended for persons who do not experience gastrointestinal symptoms

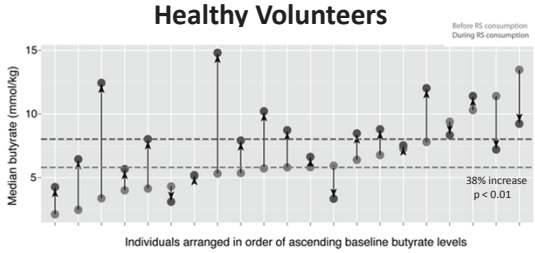
Chey. Am J Gastroenterol 2016;111:366

Moving Beyond Elimination: Functional Foods

- "A foodstuff that provides a health benefit beyond basic nutrition, demonstrating specific health or medical benefits, including the prevention and treatment of disease" (Food & Agricultural Organization, United Nations)
- **Can be categorized as:**
  - Conventional foods that contain bioactive components
  - Foods enriched or fortified with bioactive food compounds
  - Synthesized food ingredients such as ***indigestible oligosaccharides*** that provide a health benefit, or serve as precursors to compounds that provide a health benefit

Crowe KM, J Acad Nutr Diet 2013;113:1096
http://www.fao.org/docrep/004/y2775e/y2775e08.htm

Resistant Starch increases butyrate in Healthy Volunteers



Dynamics of both starch-degrading and butyrogenic bacteria explain much of the observed variation

The future: supplementation rather than elimination?

Summary

- ***Food can affect GI function and sensation resulting in GI symptoms such as abdominal pain, cramping, bloating, urgency and diarrhea***
- ***Emerging evidence supports a primary role of diet in the treatment of patients with IBS***
  - ***More than half of will improve with diet changes***
  - ***Diet appears at least as effective as medications***
- ***Registered dieticians should play a prominent role in the care of patients with GI disorders***
- ***Diet will soon move from reactive (elimination) to proactive/preventive (supplementation)***

MICHIGAN BOWEL CONTROL PROGRAM
UNIVERSITY OF MICHIGAN HEALTH SYSTEM
877.462.6935

Digestive Diseases Center for Nutrition & Behavior

Functional Bowel Disorders Clinic
888-229-7408

Texas Children's Hospital
BCM Baylor College of Medicine

Challenging Problems and New Techniques – What do when everything fails?

GI Motility and Neurogastroenterology in Clinical Practice

Presenter: Bruno Chumpitazi, M.D., M.P.H.
Discussants: Manu Sood, M.D.
Ajay Kaul, M.D.

Case #1

- 10 yo Caucasian M with significant developmental delay presents with h/o frequent ED visits and admissions for "dehydration" x 6 months
- Intermittent bouts of regurgitation of liquids/solids within minutes of ingestion x several days - not associated with retching or other symptoms
- Remaining history and physical examination are unremarkable

Case #1: Workup Discussion

- Endoscopy
- Gastric emptying scintigraphy/ Imaging
- Esophageal manometry
- Antroduodenal manometry
- Other

Case #1: Treatment Discussion

- Diaphragmatic breathing
- Proton pump inhibitor and/or Baclofen
- Psychological/ Behavioral
- Comprehensive rumination program
- Surgery

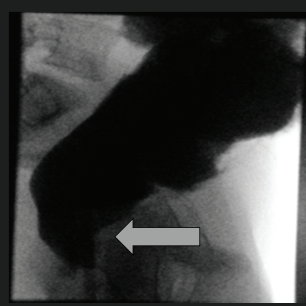
Case #2

- 6 yo F with Mowat Wilson syndrome and Hirschsprung's s/p Soave pull-through and s/p cecostomy presents for a second opinion for abdominal distention and constipation.
- Recent workup: ganglion cells on rectal biopsy
- Flushes do not evacuate well: abdominal distention and requires rectal tube evacuation.

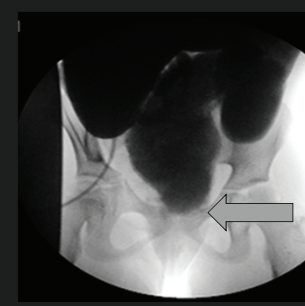
Case #2: Workup Discussion

- Laboratory
- Anorectal manometry/ repeat rectal biopsies
- Colonic manometry (low vs. high resolution)
- Barium enema (retrograde)
- Antegrade contrast enema

Case #2: Retrograde Enema



Case #2: Antegrade Enema



Case #2 Treatment

- Panelist Discussion

Case #3

- 2 yo Caucasian M - third opinion for abdominal distention and feeding intolerance since birth
- Thriving but hospitalized every 3 months with abdominal distention and bilious emesis x 5-7 days. Distention worsens throughout the day – better after sleeping/ defecation.
- Minimal improvement with prokinetics/ aggressive bowel regimen.

Case #3

- Requires urinary catheterization
- Father with similar issues beginning in young adulthood and is s/p several surgical procedures
- Genetics whole exome sequencing confirmation of ACTG2 variant: familial visceral myopathy
- Parents want to know how to help in order to minimize progression

Case #3: Workup Discussion

- Laboratory
- Imaging
- Manometry
- pH/impedance
- Other

Case #3 Treatment Discussion

- Nutritional interventions
- Prokinetics
- Surgical procedures
- Other

Case #4

- 13 yo overweight Hispanic F presents for third opinion with medically refractory constipation x 2 years
- BM frequency: 1x/week on regimen of 4 laxatives: Miralax, Magnesium citrate, Docusate, Bisacodyl
- She has had several admissions for inpatient colonic cleanouts over the past 6 months

Case #4

- Anorectal manometry with normal: RAIR; sphincter pressure; squeeze; and defecation dynamics. Elevated sensation threshold
- Colonic manometry (low resolution): HAPC over initial 60 cm but lack of distal HAPC propagation in the distal 45 cm of the colon
- Previous recommendation: Cecostomy with sigmoid resection. Family demanding high resolution colonic manometry study.

Case #4

- Laboratory
- Transit evaluation
- Manometry
- KUB/ Bowel regimen protocol
- Other

Case #4 Treatment Discussion

- Panelists

Case #5

- 15 yo Caucasian F with presents with progressive dysphagia
- Comprehensive evaluation notable for esophageal manometry identifying Type II esophageal achalasia
- Family requests referral for Per Oral Esophageal Myotomy (POEM)

Case #5: Treatment Discussion

- POEM
- Medications
- Balloon Dilation
- Heller myotomy
- BoTox

Select References

- Chen WF et al. "Long-term outcomes of peroral endoscopic myotomy of achalasia in pediatric patients: a prospective, single-center study." *Gastrointest Endosc* 2015; 81:91-100.
- Dickie BH et al. "The problematic Soave cuff in Hirschsprung disease: manifestations and treatment." *J Pediatr Surg* 2014; 49:77-80.
- Green AD et al. "Severe pediatric rumination syndrome: successful interdisciplinary inpatient management." *J Pediatr Gastroenterol Nutr* 2011; 52:414-8.
- Koppen IJ et al. "Surgical decision-making in the management of children with intractable functional constipation: What are we doing and are we doing it right?" *J Pediatr Surg* 2016 Jun 6 [Epub]
- Matera I et al. "Variants of the ACTG2 gene correlate with degree of severity and presence of megacystis in chronic intestinal pseudo-obstruction" *Eur J Hum Genet* 2016; 24:1211-5.
- Saleh CM et al. "Utilization of esophageal function testing for the diagnosis of the rumination syndrome and belching disorders" *Gastrointest Endosc Clin N Am* 2014; 24(4):633-42.

CASE PRESENTATIONS

Joseph M Croffie MD
Riley Children's Hospital
Indiana University School of Medicine

CASE 1

- 12-year-old previously healthy until 3 weeks prior to presentation when she began experiencing abdominal pain, nausea and vomiting
- 10 days prior to presentation woke up with progressively worsening epigastric pain, exacerbated by eating or drinking, that took her to ER
- In ER; CBC, CMP, Amylase, lipase, UA and CT abdomen and pelvis normal
- Treated with GI cocktail without benefit
- Discharged on Dilaudid and Phenergan and instructed to f/u with primary doctor

CASE 1

- A day after ER visit, goes to primary doctor's office with no relieve in symptoms.
- Primary doctor orders RUQ abdominal ultrasound and HIDA scan: normal. Prescribed Prilosec and Ultram.
- 48 hours later, returned to ER with persistent symptoms of epigastric pain and vomiting. She is prescribed Sucralfate and referred to GI.
- 48 hours later, seen in GI Clinic. Reports no abdominal pain but has significantly decreased appetite due to nausea, early satiety, intermittent non-bilious, non-bloody emesis. Has lost 16 pounds. Denies dysphagia or odynophagia but tolerates liquids more than solids. Denies diarrhea, constipation, hematochezia. Has not been to school.

CASE 1

- Past medical history: Significant for asthma and seasonal allergies.
- Past surgical history: Significant for Bilateral PE tubes at 1 year of age, tonsillectomy, and adenoidectomy at 3 years of age.
- Social history: Lives with mother, a GI nurse, step-father, a police officer, and 10-year-old sister. No recent travel.
- Family History: Significant for gastric cancer in biological father at age 30 treated with chemo. Brother has IBS. Negative for peptic ulcer disease, celiac disease, IBD, Hepatobiliary disease.

CASE 1

Physical examination:

Significant for mild epigastric tenderness o/w normal
Weight: 62.5 Kg (90%tile) BMI: 23.6 (90%tile)

Question to discussants: Based on these findings what should one consider in the differential diagnosis?

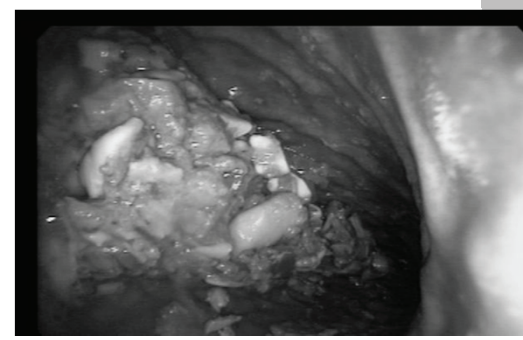
CASE 1

Differential Diagnosis

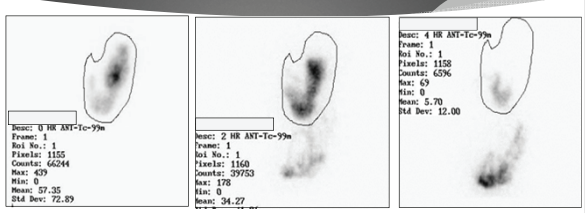
- Esophagitis
- Gastritis
- Duodenitis
- Peptic ulcer disease
- Anatomic abnormality of UGI tract
- Gastroparesis
- Functional dyspepsia

CASE 1

- UGI with small bowel follow-through: Normal
- Endoscopy: Large amount of retained food in the stomach. Otherwise normal endoscopy with normal biopsies of esophagus, and duodenum. Mild chronic inactive gastritis on stomach biopsies. No H. Pylori.



4-hr Gastric Emptying Test: New International Standard



T=0 after test meal

After 2 hours
Normal: ≤60% retention

After 4 hours
Normal: ≤10% retention

CASE 1

4 hour gastric emptying test with standard eggs and toast:

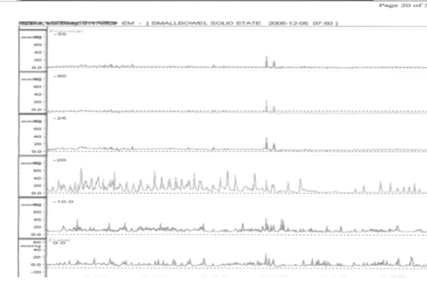
- 87% retained at 90 minutes
- 78% retained at 120 minutes
- 67% retained at 180 minutes
- 45% retained at 240 minutes

Question for discussants: Based on these findings, what is your diagnosis and why?

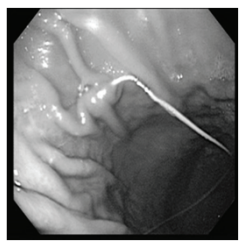
CASE 1

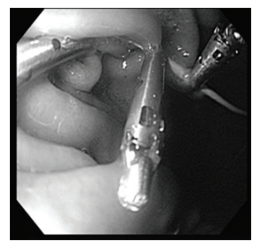
- Patient responds to EES initially but after several weeks is no longer responding.
- Switched to Domperidone but discontinued after 4 weeks due to no response.
- Treated with Cisapride under limited access protocol. No significant response.

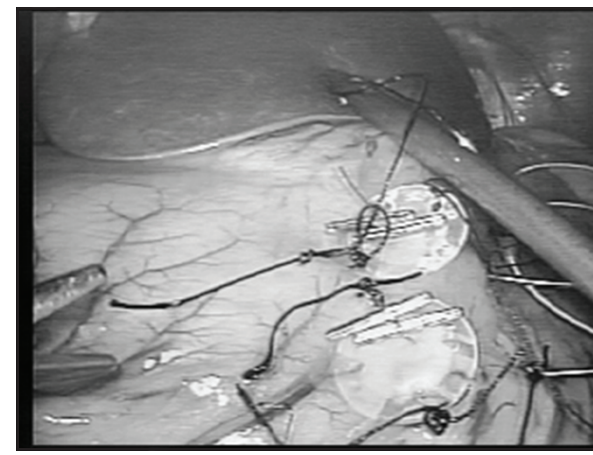
CASE 1. AD Motility test: Post Prandial



Endoscopic Transnasal Temporary GES







CASE 2

- 16-year-old boy referred to GI motility clinic by his primary Gastroenterologist.
- Has 5 year history of epigastric abdominal pain, nausea, post-prandial fullness, early satiety, bloating, frequent "burping", occasional vomiting (including old food). Denies diarrhea, constipation, bloody stools, weight loss.
- Symptoms not relieved by avoidance of fatty foods, "acidic " foods, and Lactose. Treatment with a PPI not helpful.
- Tests done to date include CBC, CMP, T4, TSH, amylase, lipase, celiac disease serology, H. Pylori breath test, UGI barium study, abdominal ultrasound, CT of abdomen all normal.
- EGD and esophageal pH probe: normal.
- Gastric emptying test: Incomplete as patient vomited test meal
- HIDA scan: Slightly delayed gallbladder ejection fraction (25% NI=35%). Cholecystectomy relieved symptoms for 2 weeks only.

CASE 2

- Past medical history: Significant for surgery on a broken arm and the previously mentioned cholecystectomy; otherwise negative for any significant medical problems.
- Family history: Significant for high cholesterol and high blood pressure in both parents, and chronic liver disease in paternal grandfather who was an alcoholic.
- Social history: Lives with both parents and 2 siblings. He is in 10th grade. School performance has declined because he has missed a lot of school.
- Current medication is Amitriptyline 10mg q hs: not helping.

CASE 2

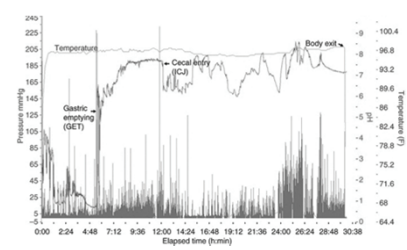
Physical Examination:

Complete examination including abdominal and rectal examinations: normal

Weight: 96.3 Kg (98%tile)

BMI: 28.9 (96%tile)

CASE 2



CASE 2

Smart pill reveals gastric emptying time of 5.5 hours (normal is < 5 hours). Small bowel and colon transit times normal.

Question to discussants: Does this patient have the same disease as previous patient?

Discussion

- Gastroparesis (GP) is defined as a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction of the stomach.(1)
- Functional dyspepsia is defined as a condition that significantly impacts the usual activities of a patient and is characterized by one or more of the symptoms of postprandial fullness, early satiety, epigastric pain or burning, unexplained after routine evaluation. Two subtypes are identified: Postprandial distress syndrome and Epigastric pain syndrome(2)
- (1) Wo and Parkman: Practical Gastroenterology. December 2006
- (2) Stanghellini et al. Rome IV. Gastroenterology May 2016

Symptoms of Gastroparesis vs Dyspepsia

Gastroparesis
- Nausea
- Vomiting
- Early satiety
- Postprandial fullness
- Epigastric pain/ discomfort
- Symptoms worse with food
- Weight loss

Dyspepsia
- Postprandial fullness
- Epigastric pain/discomfort
- Early satiety
- Bloating
- Belching
- Nausea
- Vomiting
- Symptoms worse with food

Delayed Gastric Emptying in Functional Dyspepsia

- Occurs in 30% of adult patients with functional dyspepsia (3) and up to 47% of children with dyspepsia(4)

(3) Lacy, B: Am J Gastroenterology 107(11) 2012

(4) Hyams et al: Rome IV. Gastroenterology May 2016

Discussion

- Question to discussants: Are they two distinct entities or two sides of the same coin?

Conclusion and Take Home

- There is significant overlap between symptoms of functional dyspepsia and Gastroparesis
- Excluding Diabetic Gastroparesis, both disorders are idiopathic and may be post infectious
- Finding delayed gastric emptying ≠ gastroparesis. Should it?

Dietary Therapies for Upper FGID

Bethany Doerfler MS, RD, LDN
Clinical Research Dietitian
Division of Gastroenterology and Hepatology, Northwestern University

Northwestern Medicine

On Our Plate Today…

- Dietary Therapies for GER
  - Comparing Conventional vs. Updated dietary advice
  - Weight loss tool box for MDs
- Gastroparesis
  - Do patients really need to avoid fruits and vegetables?
- Functional Nausea

Northwestern Medicine

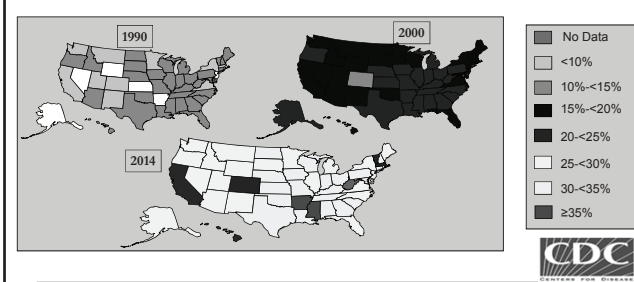
Diet Therapy for GERD: Conventional Wisdom

ACG Guidelines:
- ✓ Weight loss
- ✓ HOB elevation
- ✓ Cessation of eating 2-3 hours before bed
- ✓ Smoking cessation
- ✓ Routine and global elimination of foods is not recommended

Katz PO et al. Am J Gastroenterol 2013;108:308-328

Northwestern Medicine

Should Lifestyle Be First Line Therapy in GER?



CDC website, Mokdad AH. JAMA 1999;282:161 , 2001;286:10, 2003;289:

Northwestern Medicine

Weight Loss and Reduction in Gastroesophageal Reflux. A Prospective Population-Based Cohort Study: The HUNT Study

Eivind Ness-Jensen, MD[1,2], Anna Lindam, MSc[3], Jesper Lagergren, MD, PhD[3,4] and Kristian Hveem, MD, PhD[1]

OBJECTIVES: **High body mass index (BMI) is an established risk factor of gastroesophageal reflux symptoms (GERS). The aim of this study was to clarify if weight loss reduces GERS.**

METHODS: **The study was part of the Nord-Trøndelag health study (the HUNT study), a prospective population-based cohort study conducted in Nord-Trøndelag County, Norway. All residents of the county from 20 years of age were invited. In 1995–1997 (HUNT 2) and 2006–2009 (HUNT 3), 58,869 and 44,997 individuals, respectively, responded to a questionnaire on heartburn and acid regurgitation. Among these, 29,610 individuals (61% response rate) participated at both times and were included in the present study. The association between weight loss and reduction of GERS was calculated using logistic regression. The analyses were stratified by antireflux medication and the results adjusted for sex, age, cigarette smoking, alcohol consumption, education, and physical exercise.**

RESULTS: **Weight loss was dose-dependently associated with a reduction of GERS and an increased treatment success with antireflux medication. Among individuals with >3.5 units decrease in BMI, the adjusted odds ratio (OR) of loss of any (minor or severe) GERS was 1.98 (95% confidence interval (CI) 1.45–2.72) when using no or less than weekly antireflux medication, and 3.95 (95% CI 2.03–7.65) when using at least weekly antireflux medication. The corresponding ORs of loss of severe GERS was 0.90 (95% CI 0.32–2.55) and 3.11 (95% CI 1.13–8.58).**

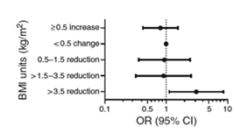
CONCLUSIONS: **Weight loss was dose-dependently associated with both a reduction of GERS and an increased treatment success with antireflux medication in the general population.**

Am J Gastroenterol 2013; 108:376–382; doi:10.1038/ajg.2012.466; published online 29 January 2013

Northwestern Medicine

HUNT Study

Weight Loss Improves GER symptoms prospectively



- Weight loss improved GER symptoms in dose dependent manner
- 3.5 unit Drop in BMI associated with most improvement
- Mean BMI = (27)
- 3.5 unit drop = 10-12% body weight drop
- Weekly medication users saw greatest improvement as BMI dropped
- Weight loss enhanced effects medication

Ness-Jensen E. Am J Gastroenterol 2013;108:376-82

Northwestern Medicine

Epic Best Practice Advisory for GERD: *Pilot Study*

- BPA triggers for overweight (BMI > 30) patients with ICD code of GERD
- When Accepted – 2 referral orders are automatically added to unsigned orders and information is included in patient's After Visit Summary

Northwestern Medicine

Weight Management Protocol: Key Points

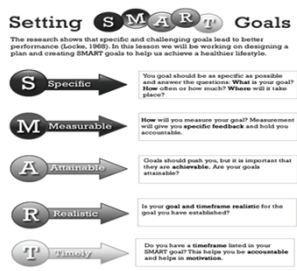
- Health Educators (Health Learning Center): provide RD designed weight loss meal plans, tips, snack ideas and behavior change strategies
- They conduct regular check-ins with the patient over 6 months and monitor their symptoms and weight
- Results:
  - 92% with weight loss
  - 65% with reduction in GerdQ (Validated GERD symptom questionnaire)
  - Greater weight loss and % excess body weight loss in enrolled patients

Northwestern Medicine

AWM: Behavior Therapy

Strategies for Behavior therapy

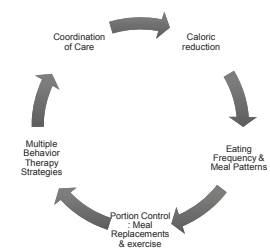
- Motivational Interviewing
  - Significantly enhances adherence to program recommendations
- Goal Setting
  - SMART goals
- Problem Solving



Northwestern Medicine

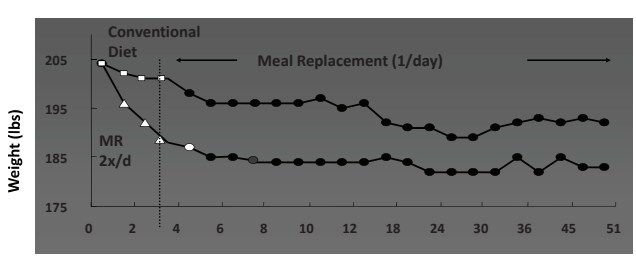
Weight Loss Tool Box

Nutrition Intervention



Northwestern Medicine

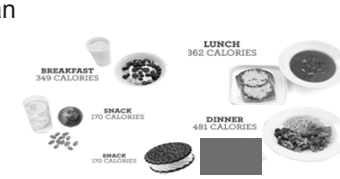
Effect of Meal Replacement Plan on Body Weight



Am J Clin Nutr 1999;69:198, Obesity Res 2000;8:399

Northwestern Medicine

Structured Meal Plan



1200 calorie day
Breakfast: 250
Lunch:300
Snack 150
Dinner: 400
Snack: 100

1500 calorie day
Breakfast: 350
Lunch: 400
Snack: 150
Dinner: 450
Snack: 150

Northwestern Medicine

Structured Meal Plans

UNLIMITED Vegetable	Fruit	Protein	Whole Grain/ Starchy Veggies
Green beans sauté	Pear (1 medium)	Chicken breast (3 oz)	Instant brown rice (3/4 cup, cooked)
Fresh tomato slices and green beans	Strawberries (1 cup)	Baked Tofu or tempeh, diced (3 oz)	Whole wheat pasta (3/4 cup cooked)
Spinach salad	Pineapple (1 cup juice removed)	Turkey meatloaf (3 oz)	Baked sweet potato (small; size of soap bar)
Spinach salad	Peach (1 medium)	Three bean salad (¼ cup)	Whole wheat couscous (3/4 cup)
Romaine lettuce, and tomatoes & raw veggies	Plums (2 small)	Turkey breast (3 oz) Hummus (2 Tbsp.)	Whole grain bun (1 small)
Tomato slices, romaine lettuce, and pickle slices	Orange (1 medium or 2 "cutie" mandarins)	Lean ground beef/turkey patty (3 oz)	Whole wheat pita (1)
Sautéed spinach and mushrooms	Banana (½ of medium),	Eggs (2) scrambled	Whole grain tortilla (1)

Northwestern Medicine

Gastroparesis

Northwestern Medicine

Complex Symptoms of Gastroparesis

Instigating factors
- Trauma/Vagal Nerve Damage
- Neuropathy
- Post infectious

Exacerbating and perpetuating factors
- Eating Disorders
- Anxiety & Depression
- Dietary Variability

Nausea
Vomiting
Bloating
GERD
Bezoars
SIBO

Nausea
Character difference DG vs. IG
96% GP report nausea
DG= somatic distress
GI distress
Total nausea

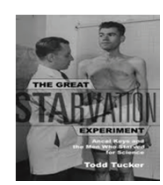
Nutritional Status
- High risk
- 305 GP assessed
- 64% calorie deficient
- Weight inversely related to higher symptom scores
- Nutritional Support may be indicated

Jaffe & Parkman, J Clin Gastroenterol 2011, 45;317-21; Parkman et al. Gastroenterology 2011;141:486-98

Northwestern Medicine

How does Malnutrition Complicate Gastroparesis?

- Delayed GI motility
- Changes in brush border activity
- Months to re-feed



Kalm & Semba. J Nutr 135:1347-1352, 2005

Northwestern Medicine

Screen for Malnutrition: Subjective Global Assessment

Normal < 5% UBW lost
No change in dietary intake
No history of nausea, vomiting, diarrhea

Moderate 5-10% of UBW in past 6 months
Abnormal dietary intake for 1 month
Nausea, vomiting, diarrhea

Severe Malnutrition >10% UBW <6 month
Inadequate intake >1 month
Nausea, vomiting , diarrhea > 1 month

Parrish CR. Practical Gastroenterology. August 2005, 29-66

Northwestern Medicine

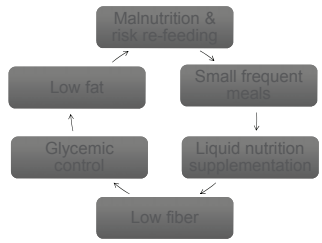
Bloggers with GP recommend avoiding:

Reality: Bezoars rare occur most often in post-GI surgery

- Erzumlu K. W J Gastroenterol. 2005 Mar 28;11(12):1813-7; Kement M. World J Gastroenterol. 2012 March 7; 18(9): 960-964

Northwestern Medicine

Dietary Therapy for Gastroparesis



Camilleri M. Gastroenterology 131(2):2006: 640-658; Keld R. J Hum Nutr Diet, 24: 421-430; Olausson EA. Diabetes Research and Clinical Practice 80:231-237, Gastroenterology 2011 Jan;140(1):101-15

Northwestern Medicine

Q: What is Small Frequent Meal?
A: 3 Meals & 3 Snacks

Meals	Cream of Wheat (1/2 cup) Egg (1 scrambled) Added Margarine Ripe Fruit Milk or Kefir	Pureed Butternut Squash Soup 6 crackers, 1-2 oz cheese	3-4 oz Baked Fish Medium Baked Potato Cooked Carrots Milk or Kefir
Snacks	Ripe Banana 1-2 tbsp Creamy Peanut Butter	½ Sandwich ½ cup ripe or canned fruit	Fruit Smoothie: Mango & Greek Yogurt with Protein Powder

Northwestern Medicine

Summary

GERD
- Global limitation of acidic foods not necessary
- Weight loss
- Technique driven weight loss aides patients

Gastroparesis & Nausea
- Glycemic control
- Utilize texture modifications
- 5-6 small meals
- Avoid excessive weight loss
- Assess and treat malnutrition

Northwestern Medicine

Ronnie Fass, MD − Functional esophageal disorders – How to incorporate Rome IV into my clinical practice?

Talk not provided

MAYO CLINIC

Irritable bowel syndrome and evidence-based therapeutic approach

Madhu Grover, M.D.

11th Postgraduate Course
Gastrointestinal Motility & Neurogastroenterology in Clinical Practice
August 25, 2016, San Francisco, CA, USA

Objectives

- Approach towards management of constipation predominant (IBS-C), and diarrhea predominant (IBS-D)
- Focus on pharmacological therapies
  - Established (with evidence)
  - New and emerging
- Not covering
  - Dietary interventions
  - Probiotics and microbiota associated therapies
  - Psychological treatments

FDA endpoints for IBS treatment trials

- IBS-C
  - Abdominal pain: ≥30% ↓ in weekly average of past 24 hour worst abdominal pain compared with baseline and
  - Stool frequency: ≥1 ↑ in complete spontaneous bowel movement/week compared with baseline
- IBS-D
  - Abdominal pain: ≥30% ↓ in weekly average of past 24 hour worst abdominal pain compared with baseline and
  - Stool frequency: ≥50% ↓ in the number of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline

  OR daily responder (30% ↓ pain and Type 5 for all bowel movements or no bowel movement that day)

➢ Responder: If they met responder criteria for atleast 50% of the days or weeks studied

Clinical scenario

34 yr female presents with bilateral crampy lower abdominal pain, nausea and bloating. She gets a bowel movement once in 4 days with the help of MiraLAX®. She takes Citrucel and stool softener twice a day. The pain gets better with bowel movement but starts building up quickly. The bloating almost never improves and appears to be her most bothersome symptom. She doesn't get an urge to defecate routinely but after MiraLAX, she gets cramps and is able to pass stool within 3-4 minutes without excessive straining. The stool is lumpy (Bristol Type 2). She denies any weight loss or gastrointestinal bleeding.

Physical examination reveals a soft and non-tender abdomen. Rectal examination reveals good resting tone and squeeze. She is able to expel your examining finger on 2/2 attempts at simulated defecation.

➢ Diagnosis: IBS-C

Rome IV: New definition for IBS

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with ≥2 or more of the following:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

➢ IBS-C: >25% of bowel movements with Bristol stool form types 1 or 2 and <25% with Bristol stool form types 6 or 7

Osmotic laxatives

- Broad categories
  - Poorly absorbed mono and di saccharides: Lactulose, mannitol, sorbitol, glycerin suppositories
  - Saline laxatives: Magnesium (citrate, sulphate, hydroxide)
  - Polyethylene glycol
- Lactulose: 3 RCTs
  - Improves stool frequency and consistency
  - Adverse effects: nausea, vomiting, bloating, flatulence, cramps

Polyethylene glycol (PEG)

- Overall: No evidence that PEG formulations alleviate pain or provide overall symptom relief in IBS
- FDA approved for occasional constipation; not extensively studied in IBS-C
  - RCT of PEG vs PEG+Tegaserod (n=27)[1]: Improved stool frequency but not pain
  - RCT in IBS-C with rectal hypersensitivity (n=42)[2]: Improved consistency but no effects on stool frequency or pain
  - RCT of PEG with electrolytes (n=68)[3]: ↑ mean spontaneous bowel movements at 4 weeks; no effects on abdominal pain compared with placebo

1. Khoshoo V, Aliment Pharmacol Ther 2006; 23: 191-6
2. Awad RA , Colorectal Dis 2010; 12: 1131-8
3. Chapman RW, Am J Gastroenterol 2013; 108: 1508-15

Stimulant laxatives

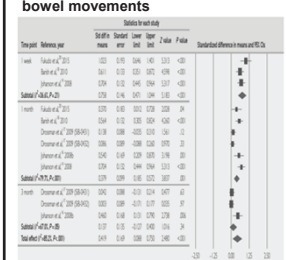
- Anthraquinones (sennosides), Bisacodyl, Castor oil
- 4 trials (none placebo controlled)
- No difference between stimulant laxative and control (usually laxative) on stool consistency or frequency
- One study showed osmotic laxative (lactulose) was superior to “irritant laxative”
- Insufficient evidence to make a recommendation regarding efficacy

Type 2 Chloride channel activator: Lubiprostone (Amitiza®)

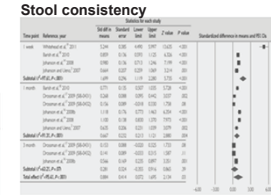
- Secretagogue: stimulates intestinal Cl^- secretion
- FDA approval
  - IBS-C: 8 mcg BID (adult women)
  - CIC: 24 mcg BID
  - Opioid induced constipation in chronic non-cancer pain: 24 mcg BID

Lubiprostone

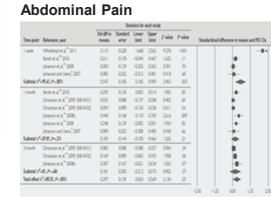
Weekly frequency of spontaneous bowel movements



Stool consistency

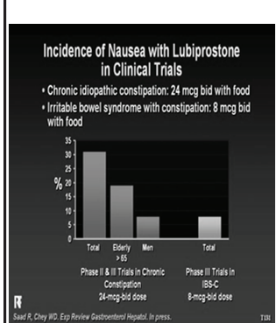


Abdominal Pain



Li F, Mayo Clin Proc. 2016 Apr;91(4):456-68.

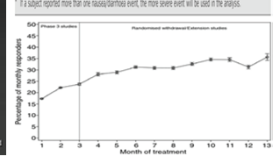
Lubiprostone: practical considerations



Long term (36 week) open label follow-up after IBS-C phase 3 trials (8 mcg BID dose)

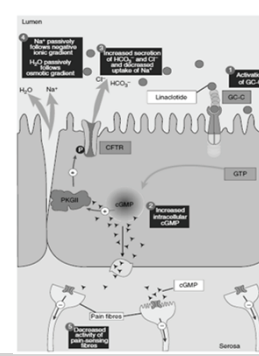
	Diarrhoea				Nausea			
Severity*	P/L (N = 179)	L/P/L (N = 80)	L/L (N = 261)	Total (N = 520)	P/L (N = 179)	L/P/L (N = 80)	L/L (N = 261)	Total (N = 520)
Mild	3 (1.7)	1 (1.3)	9 (3.4)	13 (2.5)	2 (1.1)	1 (1.3)	12 (4.6)	15 (2.9)
Moderate	8 (4.5)	3 (3.8)	6 (2.3)	17 (3.3)	7 (3.9)	2 (2.5)	8 (3.1)	17 (3.3)
Severe	2 (1.1)	1 (1.3)	1 (0.4)	4 (0.8)	0 (0)	1 (1.3)	0 (0)	1 (0.2)

* If a subject reported more than one nausea/diarrhoea event, the more severe event will be used in the analysis.



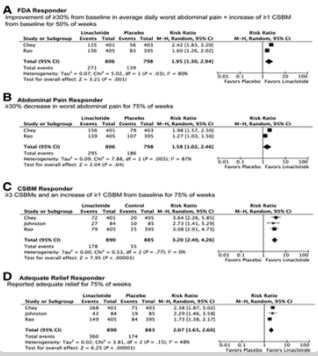
Chey WD, Aliment Pharmacol Ther. 2012 Mar;35(5):587-99

Guanylate cyclase C agonists



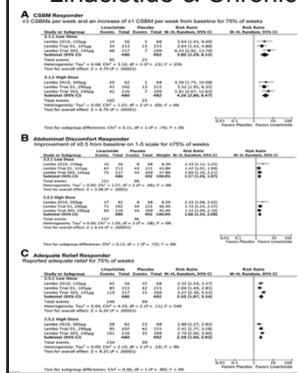
- Linaclotide
  - Elevates cGMP, phosphorylates CFTR, stimulates Cl^-, $HCO3^-$ secretion and inhibits Na^+ absorption
  - Inhibits visceral nociceptors
- 290 µg: EMA (moderate-to-severe IBS-C); FDA (IBS-C) 145 µg: FDA (chronic constipation)
- Plecanatide
  - Effective in phase 2b (n=946)

Linaclotide & IBS-C



Outcome	RR	NNT
FDA responder	1.9 (1.3-2.9)	7
CSBM responder	3.2 (2.4-4.3)	8
Abdominal pain responder	1.6 (1.0-2.5)	8
Combined CSBM & pain responder	3.1 (1.8-5.5)	12
Adequate relief responder	2.1 (1.6-2.6)	5

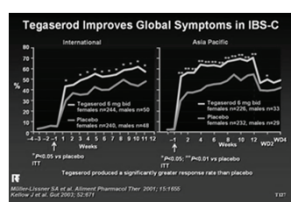
Linaclotide & Chronic constipation



Outcome	Dose (µg)	RR	NNT
CSBM responder	145	3.8 (2.0-6.5)	7
	290	4.3 (2.8-6.5)	7
Abdominal pain responder	145	1.6 (1.3-2.0)	9
	290	1.7 (1.3-2.1)	8
Bloating responder	145	2.0 (1.4-2.7)	7
	290	1.9 (1.5-2.4)	7
Constipation severity responder	145	2.1 (1.7-2.5)	5
	290	2.1 (1.7-2.6)	5
Adequate relief responder	145	2.5 (1.9-3.3)	4
	290	2.4 (1.9-2.9)	4

5 HT4 agonists

- Stimulate motility & secretion
  - Receptor also in the heart
- Old: Cisapride, Renzapride, Tegaserod
- New: Prucalopride, Mosapride, Velusetrag, Naronapride, YKP10811
- Tegaserod
  - Approved for women with IBS-C; men and women (<65 years) with chronic constipation
  - Withdrawn 2008
  - Emergency IND access only



Prucalopride

- >150 fold greater sensitivity for 5 HT4 receptors; greater intrinsic activity and specificity for intestinal receptor
- Available in Canada & Europe

	≥3 CSBM)/wk	↑ >1 CSBM/wk over baseline	Δ CSBM from baseline	Δ SBM from baseline
Camilleri, 2008	2.5 (1.7,3.7)	1.8 (1.4, 2.3)	-	-
Coremans, 2003	1.9 (0.8, 4.9)	1.2 (0.7, 1.8)	-	-
Ke, 2012	3.2 (2.2, 4.8)	2.1 (1.7, 2.6)	1.3 (1.0, 1.6)	2.3 (1.9, 2.7)
Mueller-Lissner, 2010	1.7 (1.0, 2.8)	1.7 (1.2, 2.4)	1.2 (0.6, 1.7)	1.1 (0.3, 1.9)
Piessevaux, 2015	1.2 (0.8, 1.8)	1.1 (0.9, 1.4)	0.4 (0.1, 0.8)	-
Quigley, 2009	2.0 (1.3, 2.9)	1.6 (1.3, 2.1)	0.7 (0.3, 1.1)	1.8 (1.2, 2.4)
Tack, 2009	2.2 (1.5, 3.4)	2.0 (1.5, 2.6)	-	-
Emmanuel, 2002	0.9 (0.7, 1.2)	-	-	2.5 (1.3, 3.7)
Yiannakou, 2015	2.1 (1.5, 3.1)	1.2 (1.0, 1.5)	-	-
Overall	**1.8 (1.4, 2.4)**	**1.5 (1.3, 1.8)**	**0.9 (0.7, 1.1)**	**2.0 (1.7, 2.3)**

Bile acid modulation

- Increasing bile acid delivery to the colon results in secretory diarrhea by increasing permeability, activating adenylate cyclase and increasing colonic motility
- Elobixibat (A3309)
  - Partially and highly selective inhibition of ileal bile acid transporter; Minimal systemic absorption
  - Phase Ia dose-ranging trial (n=30, chronic constipation): accelerated colonic transit
  - Phase IIa (n=36, females with chronic constipation): accelerated colonic transit, improved stool consistency, and straining
  - Phase IIb (n=190): Increased weekly spontaneous bowel movements, improved stool consistency, and straining
    - Side effects: abdominal cramps

Summary of treatments for IBS-C

- Strategies for constipation without proven effectiveness for pain in IBS-C
  - Osmotic laxatives (PEG)
- For overall symptom relief (constipation & pain)
  - Secretagogues (Lubiprostone, Linaclotide)
  - 5HT4 agonist (Prucalopride)- Not FDA approved
- Emerging therapies
  - Bile acid pathway modulators (Elobixibat)

Clinical scenario

46 yr female presents with a 5 year history of intermittent post-prandial crampy abdominal pain with urgency and 3-4 loose bowel movements a day which started after an episode of foodborne illness. She has undergone a cholecystectomy, hysterectomy, and a laparoscopy. Upon further questioning, she reports "stress" over divorce of her daughter. She has lost her job as a secretary and is unable to go out with her grandchildren and friends due to concerns for "flare-ups". She has lost 10 lbs of weight.

A recent EGD and colonoscopy with biopsies, CT-enterography and a stool collection for fat have been negative. She notices that Imodium helps with the diarrhea but she "reserves it" for social occasions and travel.

Physical examination reveals an anxious appearing female with generalized guarding during abdominal examination that eases up with distraction.

➢ Diagnosis: IBS-D

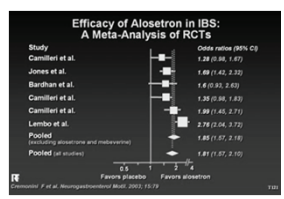
Loperamide

- 3 RCT of low/intermediate quality in IBS-D
- Decreased stool frequency and improved stool consistency. No effects on abdominal pain and global IBS symptoms
- Usually 1st line for functional diarrhea. Not sufficient for global symptoms of IBS.

Hovdenak N. Scand J Gastroenterol 1987 ; 130 : 81-4
Lavo B. Scand J Gastroenterol 1987 ; 130 : 77-80

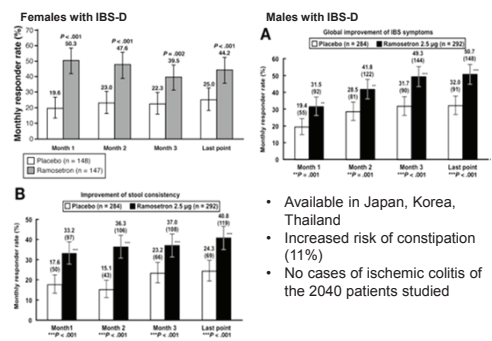
5 HT3 antagonists

- Decrease motility & secretion; visceral analgesia
- Alosetron
  - Women with severe IBS-D
- Available under restricted access program for women with
  - IBS symptoms ≥ 6 months
  - No GI anatomic or biochemical abnormality
  - No response to conventional therapy
  - Severe IBS (diarrhea & ≥1 of):
    - Frequent, severe abdominal pain/discomfort
    - Frequent bowel urgency or fecal incontinence
    - Disability or restriction of daily activities due to IBS



[1]Cole JA et al. Am J Gastro. 2004;99:466
[2]Singh S et al. Gastroenterology. 2004;(1):A349
[3]Chang L et al. Am J Gastro 2006;101:1059

Ramosetron



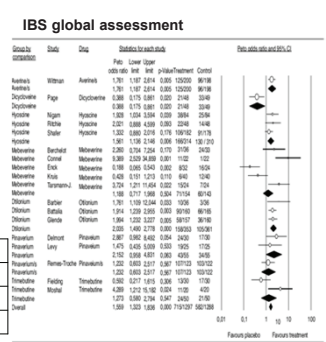
- Available in Japan, Korea, Thailand
- Increased risk of constipation (11%)
- No cases of ischemic colitis of the 2040 patients studied

Fukudo S, Clin Gastroenterol Hepatol. 2014 Jun;12(6):953-9
Fukudo S, Gastroenterol. 2016 Feb;150(2):358-66

Antispasmodics

- Smooth muscle relaxation
  - Direct effect: mebeverine, pinaverium
  - Anticholinergic: dicyclomine, hyoscyamine
- Poor trials designs, heterogeneity, small sample sizes
- Side effects: dry mouth constipation, urinary retention, visual disturbances
- Usually well tolerated

Drug	NNT
Otilonium	5
Hyoscine bromide	3
Dicyclomine hydrochloride	4



Martínez-Vázquez MA, Rev Gastroenterol Mex. 2012 ;77(2):82-90

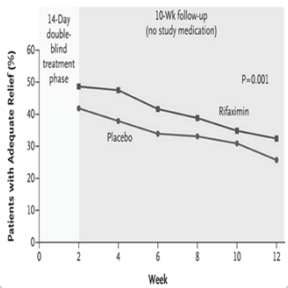
Peppermint oil

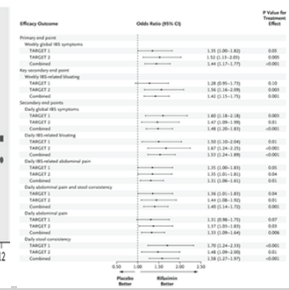
- Smooth muscle relaxation; may have effects on visceral hypersensitivity
- 5 RCTs
  - Overall, statistically significant effect in favor of peppermint oil compared with placebo; NNT=3
  - Enteric-coated preparations; 187-225 mg TID
  - No increased risk of adverse effects

Ford AC, Am J Gastroenterol 2014; 109:S2-S26

Rifaximin

- Recently FDA approved for management of IBS-D
  - 550 mg TID for 14 days.
  - For recurrence: Retreat (14 days); up to two times





Pimentel M et al. N Engl J Med 2011;364:22-32.

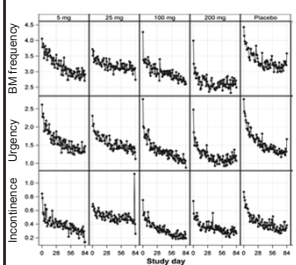
Rifaximin: practical considerations

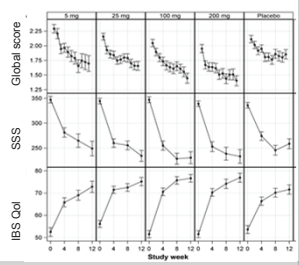
Adverse event	Patients, n (%)		
	All rifaximin (pooled) (n = 1103)	Rifaximin 550 mg (pooled) (n = 1008)	Placebo (n = 839)
Any AE	579 (52.5)	529 (52.5)	436 (52.6)
Specific AE in ≥2% of patients*			
Headache	59 (5.3)	55 (5.5)	51 (6.1)
UTI	50 (4.5)	45 (4.5)	47 (5.7)
Nausea	48 (4.4)	41 (4.1)	31 (3.7)
Abdominal pain	41 (3.7)	40 (4.0)	39 (4.7)
Diarrhoea	37 (3.4)	35 (3.5)	26 (3.1)
UTI	37 (3.4)	32 (3.2)	18 (2.2)
Nasopharyngitis	26 (2.4)	26 (2.6)	39 (4.7)
Sinusitis	24 (2.2)	23 (2.3)	23 (2.8)
Vomiting	22 (2.0)	20 (2.0)	12 (1.4)
Back pain	22 (2.0)	20 (2.0)	19 (2.3)
AE severity†			
Mild	268 (24.3)	244 (24.2)	169 (20.4)
Moderate	246 (22.3)	225 (22.3)	214 (25.8)
Severe	63 (5.7)	58 (5.8)	53 (6.4)
Drug-related AEs	134 (12.1)	124 (12.3)	89 (10.7)
Serious AEs			
Any serious AE	16 (1.5)	15 (1.5)	18 (2.2)
Drug-related serious AEs	1 (0.1)	1 (0.1)	2 (0.2)
Deaths	0	0	0
AEs resulting in study discontinuation			
Any AE	22 (2.0)	19 (1.9)	14 (1.7)
Drug-related AE	9 (0.8)	9 (0.9)	7 (0.8)

- Mechanisms of action unclear and under investigated
  - Proposed mechanism: treatment of small intestinal bacterial overgrowth (SIBO)
  - Prevalence and pathophysiological significance of SIBO in IBS is unclear
  - Potential long-term consequences of antibiotic use
- Meta-analysis: Improvement in bloating and global IBS systems and not bowel function
- Hypersensitivity reaction: exfoliative dermatitis, angioneurotic edema, and anaphylaxis
- Pregnancy: Category C

Eluxadoline (Viberzi®)

- Recently FDA approved for management of IBS-D
- **μ-receptor agonist**: ↓ abdominal pain & motility
  δ-receptor antagonist: prevents excessive motility inhibition & provides analgesia without inducing tolerance





Dove LS, Gastroenterol. 2013 Aug;145(2):329-38.

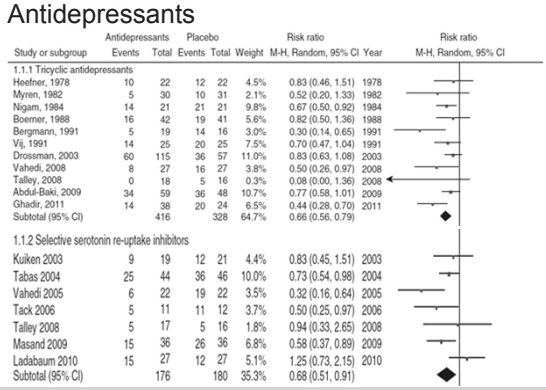
Eluxadoline: practical considerations

	5 mg (n = 105)	25 mg (n = 170)	100 mg (n = 165)	200 mg (n = 172)	Placebo (n = 159)
At least 1 TEAE	46 (44)	86 (51)	73 (44)	90 (52)	78 (49)
Nausea	6 (6)	11 (6)	9 (5)	18 (10)	7 (4)
Headache	3 (3)	12 (7)	5 (3)	7 (4)	6 (4)
Nasopharyngitis	4 (4)	8 (5)	7 (4)	6 (4)	6 (4)
Abdominal pain	3 (3)	6 (4)	4 (2)	13 (8)	3 (2)
Dizziness	4 (4)	4 (2)	5 (3)	11 (6)	4 (3)
Vomiting	1 (1)	7 (4)	7 (4)	12 (7)	1 (1)
Constipation	2 (2)	5 (3)	10 (6)	6 (3)	4 (3)

- 3 serious adverse events of pancreatitis: 2 (200 mg, within 1st 2 doses), 1 (25 mg, after 18 days of BID dosing). All resolved rapidly without sequelae
- Recommended dose: 100 mg BID; 75 mg BID in following-no gallbladder, unable to tolerate 100 mg, receiving OATP1B1 inhibitors, hepatic impairment
- Discontinue if severe constipation for >4 days; Not to take 2 doses at once
- Contraindications: known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction, alcoholism, history of pancreatitis, structural diseases of the pancreas, severe hepatic impairment (Child-Pugh Class C)

Dove LS, Gastroenterol. 2013 Aug;145(2):329-38.

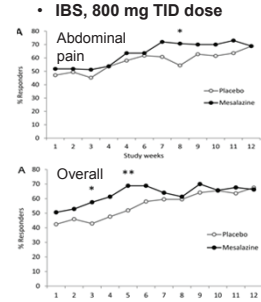
Antidepressants



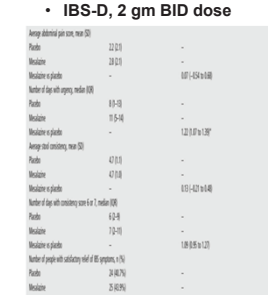
Ford AC, Am J Gastroenterol 2014; 109:1350–1365

Mesalazine

- To target "low-grade inflammation" seen in IBS
- **IBS, 800 mg TID dose**



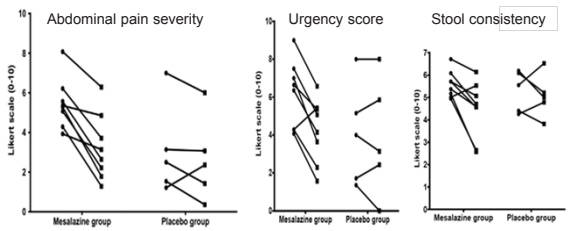
- **IBS-D, 2 gm BID dose**



Barbara G, et al. Gut 2016;65:82–90.
Lam C, et al. Gut 2016;65:91–99.

Mesalazine

- **Subgroup analysis PI-IBS**



Bile acid sequestrants

- 25-30% with IBS-D have evidence of bile acid malabsorption[1]
- Cholestyramine 4 g TID
  - Poorly tolerated: taste & stickiness to teeth
- Colesevelam:
  - Unblinded trial (n=12, IBS-D with increased bile acid excretion)[2]: Improved Bristol stool form, no effects on weekly stool frequency
  - Placebo controlled (n=24, Overall IBS-D)[3]: No significant effects on overall transit and clinical symptoms
  - Off-label use: 1-3 tablets BID (625 mg tablet)

Summary of treatments for IBS-D

- Strategies for constipation without proven effectiveness for pain in IBS-D
  - Loperamide
- For overall symptom relief (diarrhea & pain)
  - Non absorbable antibiotics (Rifaximin)
  - μ opioid agonist (Eluxadoline)
  - Antispasmodics (Otilonium)
  - ? Peppermint oil
- Emerging therapies
  - 5 HT4 antagonists (Ramosetron)
  - Bile acid sequesterants (Colesevelam)

Thank You

Gastric Function Abnormalities—Using the New Rome IV Criteria to Manage Your Patients

William L. Hasler, MD
Professor, Division of Gastroenterology
University of Michigan Health System
Ann Arbor, MI

Rome IV Gastroduodenal Disorders

- Functional dyspepsia (FD):
  - ≥1 of: bothersome postprandial fullness, early satiation, epigastric pain or burning
  - No evidence of structural disease
  - Postprandial distress syndrome (PDS): bothersome *postprandial* fullness and/or early satiation ≥3 days/wk
  - Epigastric pain syndrome (EPS): bothersome epigastric pain and/or burning ≥ 1 day/wk, may/may not be postprandial
  - Vomiting warrants consideration of another disorder; sx relieved by BM or flatus passage not part of FD; GERD may coexist
- Rationale for changes:
  - Emphasized postprandial relation of symptoms for PDS
  - Emphasized that vomiting warrants search for another diagnosis
  - Changes in frequency

Stanghellini et al., Gastro 2016

Rome IV Gastroduodenal Disorders

- Cyclic vomiting syndrome (CVS):
  - ≥3 discrete episodes in past yr, ≥2 episodes in past 6 mo with at least 1 wk between episodes
  - Absence of vomiting between episodes, but milder symptoms may be present
  - Supportive: may have personal or family hx of migraines
- Cannabinoid hyperemesis syndrome (CHS):
  - Stereotypical episodic vomiting resembling CVS
  - Presentation after prolonged cannabis use
  - Relief with sustained cessation of cannabis use
  - Supportive: may be associated with pathologic bathing
- Rationale for changes:
  - Acknowledge that some CVS patients have interepisodic symptoms
  - CHS identified as separate entity because of different pathophysiology, dassociated phenomena (bathing), and treatment

Stanghellini et al., Gastro 2016

Cannabis Use in FV vs. CVS

- Background: Chronic extensive cannabis use associated with cyclic vomiting and pathologic bathing behavior; resolves with cessation of cannabis use
- Methods: Record review of 62 FV and 82 CVS patients
- Results:
  - Younger age (OR 0.7, 0.5-0.9), male sex (OR 0.4, 0.2-0.9) associated with CVS
  - Cannabinoid use (OR 2.9, 1.2-7.2) associated with CVS
  - No differences in BMI, tobacco use, GE

Allen et al., Gut 2004
Choung et al., NGM 2012

New Rome IV Categorization of Nausea and Vomiting

ROME III	*ROME IV*
Chronic Idiopathic Nausea: ▪ Bothersome nausea several times weekly ▪ Not usually associated with vomiting ▪ Absence of organic or metabolic disease	Chronic Nausea Vomiting Syndrome (CNVS): ▪ Bothersome nausea at least 1 day/week and/or 1 or more vomiting episodes/week ▪ Absence of eating disorder, self-induced vomiting, rumination, regurgitation ▪ No organic, systemic, or metabolic cause of symptoms
Functional Vomiting: ▪ At least 1 vomiting episode/week ▪ Absence of eating disorder, self-induced vomiting, rumination, psychiatric disease ▪ No CNS or metabolic cause of symptoms	

- Rationale for changes:
  - Paucity of data suggesting differential diagnostic approach with similar management

Stanghellini et al., Gastro 2016

Methods of Assessing GI Functions

Function Measured	Method	Therapeutic Target
Gastric emptying	Gastric scintigraphy Wireless motility capsule Gastric emptying breath test Ultrasound MRI	Gastrokinetic
Gastric accommodation	Satiety testing MRI SPECT Barostat	Fundic relaxant
Extragastric transit	Wireless motility capsule Video capsule endoscopy SB and colon scintigraphy SB barium radiography Lactulose breath testing Radioopaque markers	Extragastric prokinetic
Gastric and extragastric contractility	Antroduodenal manometry Wireless motility capsule EndoFLIP	Prokinetic, pyloric therapies
Gastric myoelectric activity	Electrogastrography (EGG)	?

Rationale for Measuring Gastric Emptying

PURE PROKINETIC

- Erythromycin (and other macrolides)
- Pyloric botulinum toxin

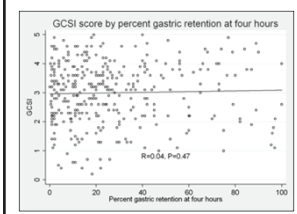
COMBINED PROKINETIC AND ANTIEMETIC

- Metoclopramide
- Domperidone

NO PROKINETIC EFFECT

- Antidepressants
- Most antiemetics

Symptom Relation to Delayed Gastric Emptying



Method	Mean Nausea Score (0-5)	
	Delayed	Normal
Solid scintigraphy	3.4	3.5
Liquid scintigraphy	3.2	3.1
Wireless motility capsule	2.9	3.1

Pasricha et al., CGH 2011
Pasricha et al., DDW 2015
Hasler et al., DDW 2016

Functional Gastroduodenal Disorders Overlap With Gastroparesis

	Gastric Emptying Delay		
Rome III Diagnosis	Mild (10-20%)	Mod (20-35%)	Severe (>35%)
Functional dyspepsia	84.3%	81.8%	72.7%
Postprandial distress syndrome	87.0%	92.4%	95.6%
Chronic idiopathic nausea	35.2%	42.4%	25.0%
Functional vomiting	36.1%	34.9%	45.6%

Parkman et al., Gastro 2011

Relation of Symptom Benefits of Prokinetics to Gastric Emptying Acceleration

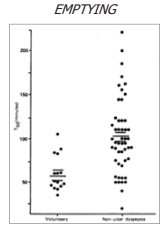
- Methods:
  - Medline search of controlled gastropareis prokinetic trials (metoclopramide-6, domperidone-6, cisapride-14, levosulpiride-3, erythromycin-3, botulinum toxin-2)
- Results:
  - Most drugs improved symptoms and emptying
  - No study reported correlation between symptoms and emptying
  - Meta-regression correlation analysis showed no relationship
- Caveat-1: 4/6 drugs studied had combined action as prokinetic and central antiemetic
- Caveat-2: Emptying measures very crude; lack of effect on emptying does not exclude role for motor stimulation

Janssen et al., AJG 2013

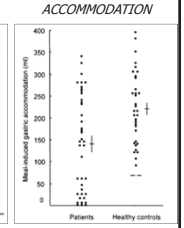
Demonstration of Dysmotility in Functional Dyspepsia

- Prevalence of delayed gastric emptying 24-59% of patients
- Rapid gastric emptying at 1 hr observed in 41% of patients
- Impaired gastric fundic accommodation in up to 40% of patients
- Impaired accommodation associated with redistribution of food to the distal stomach

DELAYED EMPTYING

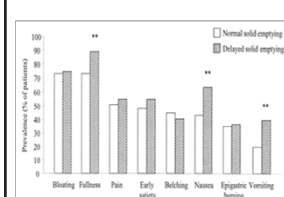


BLUNTED ACCOMMODATION

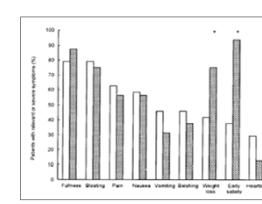


Waldron et al., Gut 1991
Delgado-Aros et al., Gastro 2004
Tack et al., Gastro 1998

Symptom Prevalence in Functional Dyspepsia in Relation to Gastric Emptying and Accommodation



- 392 functional dyspepsia patients undergoing GEBT



- 40 functional dyspepsia patients undergoing barostat

Tack et al., Gastro 1998
Sarnelli et al., AJG 2003

Relation of Symptoms to Gastric Emptying in Functional Dyspepsia

Study	N	Prevalence of Delayed Gastric Emptying	Correlation
Wegener 1989	43	30	None
Jian 1989	28	59	None
Talley 1989	32	30	None
Waldron 1991	50	42	None
Klauser 1993	69	35	None
Scott 1993	75	28	None
Stanghellini 1997	343	34	Associated with postprandial fullness, vomiting
Perri 1998	304	33	Associated with postprandial fullness, nausea, vomiting
Talley 2001	551	24	None
Sarnelli 2003	392	23	Associated with postprandial fullness, nausea, vomiting
Talley 2006	864	34	Associated with postprandial fullness, nausea

Stanghellini, Tack, Gut 2014

Therapies Targeting Dysmotility in Functional Dyspepsia

- Prokinetics show relative risk reduction of 33% vs. placebo with NNT of 6.
- Results driven by cisapride and domperidone studies, ?publication bias.
- In 34 gastroparesis trials, no correlation of symptom benefits of prokinetics with emptying acceleration.
- Acotiamide (blocks M_1 and M_2 autoreceptors/inhibits cholinesterase, enhances accommodation and stimulates emptying) improved overall symptoms vs. placebo in 892 patients over 4 weeks
- Buspirone (5-HT_{1A} agonist, relaxes fundus/improves meal tolerance) reduced overall symptoms and pain in RCT in functional dyspepsia.

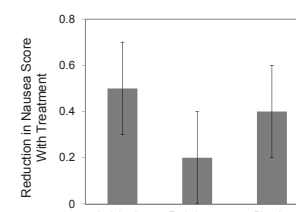
Stanghellini et al., Gastro 2016
Janssen et al., AJG 2013

Neuromodulatory Agents for Functional Gastroduodenal Disorders

Drug(s)	Mechanisms of Action	Proposed Clinical Utility
Tricyclics (amitriptyline, nortriptyline, desipramine)	Norepinephrine reuptake inhibition with variable serotonin (and dopamine) reuptake inhibition	Cyclic vomiting syndrome Functional vomiting Nausea and vomiting with diabetes ?Gastroparesis
Mirtazapine	"Indirect" CNS 5-HT_{1A} agonism, 5-HT_2 antagonism, 5-HT_{2C} inverse agonism, 5-HT_3 antagonism, α_2 antagonism, H_1 inverse agonism	Hyperemesis gravidarum Postoperative nausea and vomiting Chemotherapy-induced nausea and vomiting ?Gastroparesis ?Functional gastroduodenal disease
Olanzapine	5-HT_2 inverse agonism, 5-HT_3 antagonism, M_1 antagonism, M_3 antagonism, D_2 antagonism, H_1 inverse agonism	Chemotherapy-induced nausea and vomiting
Gabapentin	Interacts with voltage sensitive Ca^{++} channels	Postoperative nausea and vomiting ?Functional gastroduodenal disease

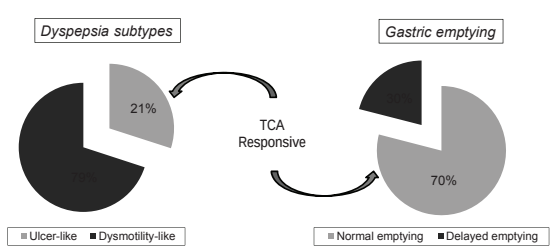
Controlled Tricyclic Trial in Functional Dyspepsia

- 292 functional dyspeptics treated with amitriptyline 50 mg/d, escitalipram 10 mg/d, or placebo x 10 wk
- Adequate response to amitripyline (53%), escitalopram (38%), placebo (40%)(P=0.05)



Talley et al., Gastro 2015

Controlled Tricyclic Trial in Functional Dyspepsia—Subgroup Analysis

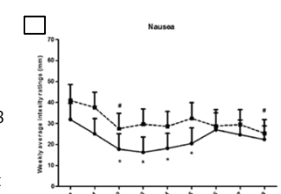


- Patients with dysmotility-like dyspepsia and delayed gastric emptying less likely to respond to TCA

Talley et al., Gastro 2015
Hasler, Koch, Gastro 2015

Controlled Mirtazapine Trial in Functional Dyspepsia

- 34 functional dyspeptics with >10% weight loss treated with mirtazapine 15 mg/d vs. placebo x 8 weeks
- Mirtazapine reduced dyspepsia scores at 4 wk (P=0.003) and 8 wk (P=0.02); placebo had no effect
- Mirtazapine produced ~4 kg wt gain over 8 wk; placebo produced no change



Tack et al., CGH 2016

Antiemetics for CNVS

Drug class	Examples	Published data
H_1 antagonists	Dimenhydrinate, meclizine, promethazine	None
M_1 antagonists	Transdermal scopolamine	None
D_2 antagonists	Thiethyperazine, prochlorperazine	1 case report (thiethylperazine)
5-HT_3 antagonists	Ondansetron, granisetron	1 case report of intraperitoneal ondansetron in diabetics Case series of 36 pts with transdermal granisetron (50% response rate)
NK_1 antagonists	Aprepitant, rolapitant	2 case reports
CB_1 agonists	Dronabinol	None
Benzodiazepines	Lorazepam	None
Corticosteroids	Dexamethasone	3 patients (abstract)

Simmons and Parkman, DDS 2014

Treatment Options for CVS

TREAT ACUTE ATTACKS

- Antiemetics:
  - 5-HT_3 antagonists
- Anti-migraine treatments:
  - Triptans
- Benzodiazepines

PREVENT FUTURE ATTACKS

- Tricyclic antidepressants
- Anti-epileptics:
  - Topiramate
  - Zonisamide
  - Levetiracetam
  - Valproate
- Anti-migraine treatments:
  - Beta blockers
  - Cyproheptadine
- Mitochondrial stabilizers:
  - L-carnitine
  - Co-enzyme Q10

Summary

- New Rome IV criteria include modifications for previously defined entities (FD, CVS) and 2 new diagnoses (CNVS, CHS).
- Dysmotility likely is prevalent in these conditions, but its impact on management is uncertain.
- Treatment is largely based on symptoms.
- Further research is needed.

ANMS – 11th Postgraduate Course on Gastrointestinal Motility & Neurogastroenterology in Clinical Practice
August 25, 2016

Surgical Management of Fecal Incontinence

Andreas M Kaiser, MD FACS FASCRS
Professor of Clinical Surgery

Division of Colorectal Surgery
Keck School of Medicine of USC

USC University of Southern California

Keck School of Medicine of USC

Disclosures

- Consultant Olympus
- GI Health Foundation
- McGraw-Hill
- Uptodate

Keck School of Medicine of USC

Prevalence of fecal incontinence

- International population-based studies: 0.004 - 18%
- US telephone survey: 2.2%. 30% >65 years old, 63% female
- Switzerland:
  - 4.4% in the community
  - 5.6% for general outpatients
  - 15.9% for urogynecology patients

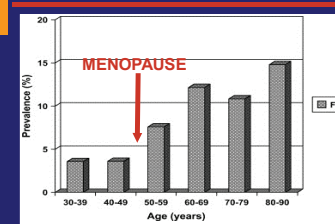
2 - 10%

- US: 18.4% in outpatients
  - daily in 2.7%
  - weekly in 4.5%
  - monthly or less in 7.1%
- Incontinence disproportionately affects individuals with severe physical and mental disabilities (46-47%)

Selected references:
R Nelson JAMA 1995; DL Faltin Int Urogynecol J Pelvic Floor Dysfunct 2001; JF Johanson Am J Gastroenterol 1996
MJ Borrie CMAJ 1992, R Nelson DCR 1998
Ditah I et al. Am J Gastroenterol. 2012

Keck School of Medicine of USC

Prevalence related to age



from:
JL Melville *Am J OB/GYN* 2006

Population-based, age-stratified postal survey of 6000 women aged 30 to 90 years enrolled in a large HMO, 64% response rate

Selected references:
JL Melville – Am J OB/GYN 2006

Keck School of Medicine of USC

Impact of fecal incontinence

- Development of secondary medical morbidities:
  - e.g., skin maceration
  - urinary tract infections
  - decubitus ulcers, etc.
  - depression
- Major reason for admission to nursing home care.

Selected references:
M Kamm BMJ 1998
SR Brown Cochrane 2009.

Keck School of Medicine of USC

Impact of fecal incontinence

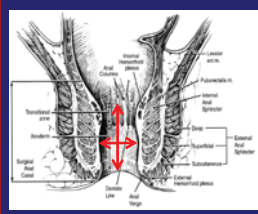
- Substantial direct and indirect financial expenses to:
  - patients (e.g. diapers, clothes, loss of productivity)
  - employers (days off)
  - insurances (health care cost, unemployment, etc).
- Impact on quality of life
  - self-esteem, embarrassment, shame, depression
  - need to organize life around easy access to bathroom
  - avoidance of enjoyable activities, etc).

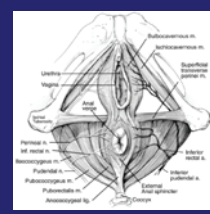
Selected references:
M Kamm BMJ 1998
SR Brown Cochrane 2009. Xu X et al. DCR 2012

Keck School of Medicine of USC

Normal continence mechanism

- Anal sphincter complex + innervation:





Selected references:
AM Kaiser Surg Clin N Am 2002

Keck School of Medicine of USC

Definition - caveat

- Fecal control is not just equivalent to normal sphincter muscles
- Other factors are equally important (see next slide)
- Fecal incontinence
  ≠ diagnosis but symptom
  = common final pathway symptom of multiple independent etiologies.
- Measurement of FI not objective.

Selected references:
NICE guidelines 2007
Rao SSC. Gastroenterology, 2004.

Keck School of Medicine of USC

Clinical Subtypes of Fecal Incontinence

- Passive incontinence:
  - Unaware of stool or gas passage
  - Associated with IAS dysfunction
- Urge incontinence:
  - Release of feces despite awareness and attempted retention
  - 88% associated with EAS dysfunction
- Fecal "seepage"
  - Presence of small amount of fecal material on undergarments
  - Due to impaired rectal sensation

Selected references:
Rao SSC et al. Am J Gastroenterol. 2004
Rao SSC et al. Gastroenterology. 2004.

Keck School of Medicine of USC

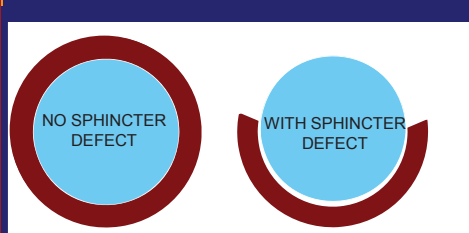
Acquired fecal incontinence

- **Vaginal delivery**: = most common sphincter injury
  - Occult sphincter defects (up to 35% of primiparous women)
    - detected by ultrasonography even after normal vaginal delivery; associated incontinence rate ranging from 13-23%
  - 29.7% of sphincter defects immediately symptomatic; probability of long-term fecal incontinence 58–82.8%
- **Anorectal surgery or trauma**:
  - Hemorrhoidectomy
  - Fistulotomy
  - Lateral internal sphincterotomy
  - Anal dilation
  - Sphincter-sparing colorectal resections (loss of reservoir and stretching of the sphincter

Selected references:
J Garcia-Aguilar DCR 1996, DC Nyam DCR 1999, IM MacIntyre Lancet 1972, MG Read BJS 1982, IJ Lindsey DCR 2004

Keck School of Medicine of USC

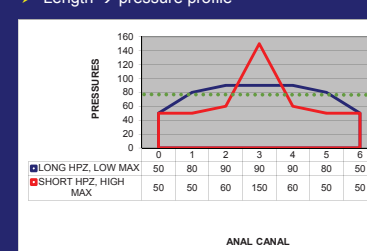
Incontinence: Effect of sphincter defect on contraction efficiency



Keck School of Medicine of USC

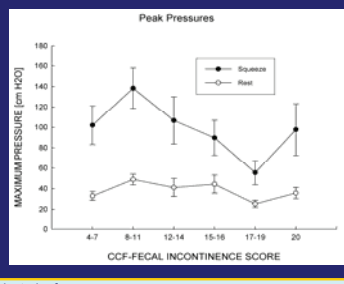
Sphincter function - Hypothesis

- Morphological integrity → circumferential
- Absolute strength
- Length → pressure profile



Keck School of Medicine of USC

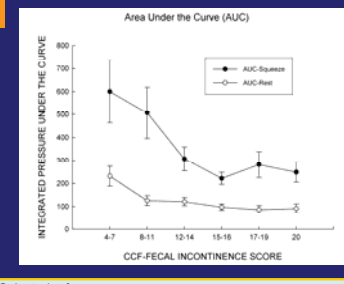
Maximal pressure vs. AUPC (area under the pressure curve



Selected references:
JW Nunoo-Mensah, D Klaristenfeld, AM Kaiser, 2006

Keck School of Medicine of USC

Maximal pressure vs. AUPC (area under the pressure curve



Selected references:
JW Nunoo-Mensah, D Klaristenfeld, AM Kaiser, 2006

Keck School of Medicine of USC

Mathematical model of fecal control

μ = viscosity
L = anal canal length
P = anal pressure
C = compliance
V = rectal volume
α = anal canal diameter

$$\frac{\mu \cdot k \cdot L^2}{2 \cdot a} > P_{rectum}$$

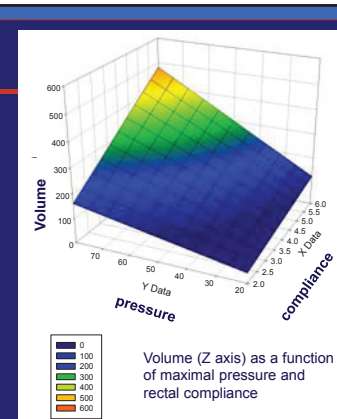
$$\frac{C \cdot \mu \cdot L \cdot P_{\max}}{a} > V_{rectum}$$

Fecal control = Balanced interaction between:
- anal sphincter complex ("plug"): pressure, length, diameter
- stool consistency
- rectal reservoir function

(… + neurological function)

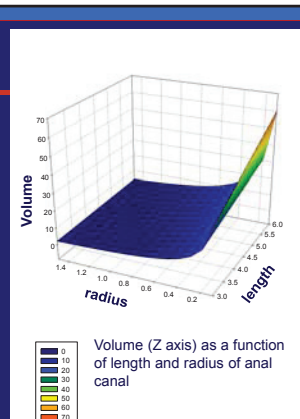
Selected references:
AM Kaiser and S Israelit, 2006

Keck School of Medicine of USC



Volume (Z axis) as a function of maximal pressure and rectal compliance

Keck School of Medicine of USC



Volume (Z axis) as a function of length and radius of anal canal

Keck School of Medicine of USC

Scoring systems

- CCFIS, FISI, FIQL
- Lack of physiological index of fecal incontinence
- → scoring systems based on patients' subjective reports of symptoms: eg Cleveland Clinic Florida Index:
  - frequency of incontinence
  - type of incontinence
  - extent of lifestyle changes
  - need to wear a pad

Problem: coping behavior not standardized!!

Selected references:
JM Jorge and SD Wexner DCR 1993
CJ Vaizey, Gut 1999

Keck School of Medicine of USC

"Wexner" score / CCF incontinence score

Type of incontinence	Frequency				
	Never	Rarely (<1/mo)	Sometimes (< 1/wk but ≥1/mo)	Usually (< 1/d but ≥1/wk)	Always (≥1/day)
Solid	0	1	2	3	4
Liquid	0	1	2	3	4
Gas	0	1	2	3	4
Wears pad	0	1	2	3	4
Lifestyle alteration	0	1	2	3	4

DAYS WEEKS MONTHS

4 3 2 1

Keck School of Medicine of USC

Treatment approaches

- Nihilism
- Conservative
- Physical therapy/biofeedback
- Surgery

Keck School of Medicine of USC

Goals of Surgical Treatment

- Correction of morphological deformities, problems:
  - prolapse, cloaca, fistula, keyhole deformity, tumor, etc
- Repair of isolated sphincter defect
- Improve existing sphincter function
  - SNS, PTNS
  - SECCA
  - Injectables (collagen, beads, dextranomer, etc).
  - (Implantation of Thiersch)
- Replace sphincter:
  - Implantation of ABS, magnetic ring
  - Graciloplasty
- Reduce fecal load
  - MACE
- Divert:
  - Colostomy

Keck School of Medicine of USC

ASCRS Task Force "New Technologies for FI"

In order to keep pace with rapidly advancing technology, the Executive Council of the American Society of Colon and Rectal Surgeons (ASCRS) convened a task force composed of Society chairpersons and key members of the Standards of Practice, New Technology, and Socioeconomic Committees.

This systematic review sought to assess the currently available evidence for various new techniques in order to provide a rational basis for practitioners, healthcare workers, and patients who desire information about the value and perspective of these new treatment tools.

Current status: new technologies for the treatment of patients with fecal incontinence

Andreas M. Kaiser · Guy R. Orangio · Massarat Zutshi · Suraj Alva · Tracy L. Hull · Peter W. Marcello · David A. Margolin · Janice F. Rafferty · W. Donald Buie · Steven D. Wexner

Selected references:

ASCRS Task Force, Surg Endosc 2014

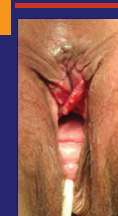
Keck School of Medicine of USC

Surgery: Improving sphincter function

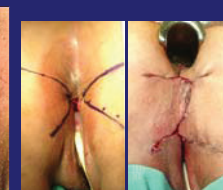
1. Correction of deformities
2. Surgical elimination of underlying causes:
   - eg rectal prolapse
   - rectovaginal fistula
3. Overlapping sphincter repair
4. Others:
   - SECCA procedure
   - Injection of beads, implantation of Thiersch
   - Sacral nerve stimulation

Keck School of Medicine of USC

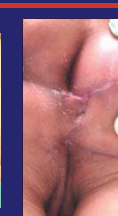
Cloaca-like deformity post obstetrical injury



PREOP



INTRA-OP SPINCTEROPLASTY + X-FLAPS



4 WEEKS

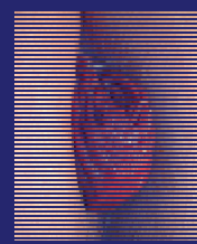
Selected references:

AM Kaiser DCR 2007; AM Kaiser Colorect Dis 2008

Keck School of Medicine of USC

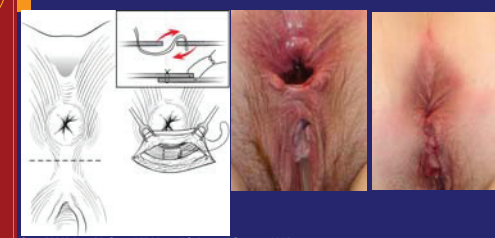
Correction of underlying problems

- "Correct prolapse first"
- Physiology testing unreliable as long as "shoe in the door"
- Possibility of sphincter recovery



Keck School of Medicine of USC

Overlapping sphincteroplasty



from AM Kaiser, McGraw-Hill Manual Colorectal Surgery 2008

Selected references:
S Maslekar JACS 2007

Keck School of Medicine of USC

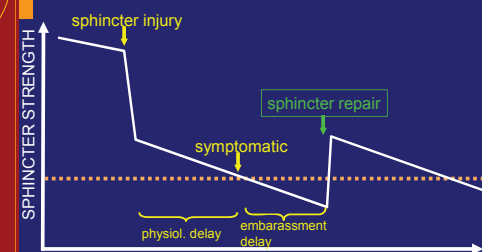
Sphincteroplasty - outcomes

- Short-term:
  - 75-86% improvement
  - Urgency frequently persisting
- Long-term results:
  - after 5 years: 20-50% still continent
- Questions:
  - Impact of pudendal neuropathy
  - Combination with PT
  - Combinatin with sacral nerve stimulation?

Selected references:
S Maslekar JACS 2007; A Bravo Gutierez DCR 2004; Al Halverson DCR 2003; AJ Malouf Lancet 2000

Keck School of Medicine of USC

Sphincteroplasty – mechanism of poor outcomes



Selected references:
AM Kaiser – ASCRS Core subjects 2009

Keck School of Medicine of USC

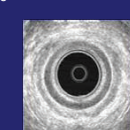
Alternative surgical strategies?

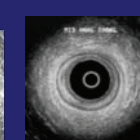
?

Keck School of Medicine of USC

RFA/Injectables: Patient selection

- Mild to moderate incontinence (CCFIS 1-14):
  - Passive incontinence
- IAS dysfunction
  - morphologically intact but functionally weak IAS
  - structurally damaged IAS
- Primarily reduced resting tone.

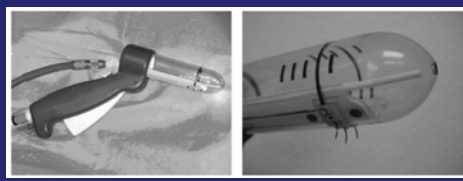

Normal IAS


Atrophic IAS

- Injectables NOT indicated for:

Keck School of Medicine of USC

Radiofrequency Administration (SECCA)



- Thermo-controlled delivery of radiofrequency energy (465 kHz) to the anal canal → thermal lesions in the muscle while preserving the mucosal integrity.
- Increase the outlet resistance, possibly improve sensation: scarring and sphincter remodeling ??
- FDA approval in 2002

Keck School of Medicine of USC

Radiofrequency Administration (SECCA)

Author	Year	n	FI severity score* (range or SD)		Functional success rate (%)	
			Before	After	Complete continence	>50 % improvement
Takahashi et al. [24]	2002	10	13.5 (11–16)	5 (4–7)	NA	80 (8/10)
Efron et al. [27]	2003	50	14.6 ± 3.4	11.1 ± 4.9	0	0 (0/50)
Takahashi et al. [25]	2003	10	13.8	7.3	NA	80 (8/10)
Felt-Bersma et al. [28]	2007	11	18.8/24 (Vaizey score)	11.5/24 (Vaizey score)	NA	NA
Lefebure et al. [29]	2008	15	14.1 ± −4.5	12.3 ± 4.6	0	13 (2/15)
Takahashi-Monroy et al. [26]	2008	19 (10 + 9)	14.4	8.3		84 (16/19)
Kim et al. [30]	2009	8	35.1/61 (FISI)	25.6/61 (FISI)	0	37.5 (3/8)
Ruiz et al. [31]	2010	16/24	15.6 ± 3.2	12.9 ± 4.6	0	12.5 (2/16)
Abbas et al. [32]	2012	27	16 (8–20)	10.9	0	22

Selected references:
ASCRS Task Force, Surg Endosc 2014
Efron et al DCR 2003

Keck School of Medicine of USC

Radiofrequency Administration (SECCA)

- 6 prospective patient series (published in 8 reports), and one retrospective series:
  - Small case numbers: median 15 (range 8-50)
  - Follow-up: overall short with 6-12 months; only one series with 3 different time points had >12 months follow-up.
  - Largest cohort: prospective multicenter trial in the USA with 50 patients (2003).

Selected references:
ASCRS Task Force, Surg Endosc 2014
Efron et al DCR 2003

Keck School of Medicine of USC

Radiofrequency Administration (SECCA)

Author	Year	n	FI severity score* (range or SD)		Functional success rate (%)	
			Before	After	Complete continence	>50 % improvement
Takahashi et al. [24]	2002	10	13.5 (11–16)	5 (4–7)	NA	80 (8/10)
Efron et al. [27]	2003	50	14.6 ± 3.4	11.1 ± 4.9	0	0 (0/50)
Takahashi et al. [25]	2003	10	13.8	7.3	NA	80 (8/10)
Felt-Bersma et al. [28]	2007	11	18.8/24 (Vaizey score)	11.5/24 (Vaizey score)	NA	NA
Lefebure et al. [29]	2008	15	14.1 ± −4.5	12.3 ± 4.6	0	13 (2/15)
Takahashi-Monroy et al. [26]	2008	19 (10 + 9)	14.4	8.3		84 (16/19)
Kim et al. [30]	2009	8	35.1/61 (FISI)	25.6/61 (FISI)	0	37.5 (3/8)
Ruiz et al. [31]	2010	16/24	15.6 ± 3.2	12.9 ± 4.6	0	12.5 (2/16)
Abbas et al. [32]	2012	27	16 (8–20)	10.9	0	22

Selected references:
ASCRS Task Force, Surg Endosc 2014
Efron et al DCR 2003

Keck School of Medicine of USC

Radiofrequency Administration (SECCA)

Selected references:
Takahashi-Monroy T et al, DCR 2008

Keck School of Medicine of USC

Radiofrequency Administration (SECCA)

- Statistically significant but clinically irrelevant improvement for mild fecal incontinence:
  - CCFIS from 14.6 to 11.1 @ 6 months
  - 0% complete continence
  - 0-37.5% (up to 84% ??) improvement of >50%
- Complications: pain, ulcerations, and bleeding.
- Durability: only in minority of patients
- ASCRS Task Force rec: Based on moderate quality evidence, the overall risks of the procedure are low, while the efficacy in improving symptoms of fecal incontinence is low to intermediate (GRADE Recommendation: 2B)

Selected references:
Efron JE et al, DCR 2003; Abbas MA et al, DCR 2012
ASCRS Task Force, Surg Endosc 2014

Keck School of Medicine of USC

Injectables

- Carbon beads
- Teflon beads
- Silicon biomaterial (PTQ)
- Collagen
- Autologous fat

Conventional injectables

- Non-animal stabilized hyaluronic acid/dextranomer (NASHA/Dx)
- Gatekeeper
- Stem cells

Selected references:
ASCRS Task Force, Surg Endosc 2014

Keck School of Medicine of USC

Injectable bulking agents

- Conventional:
  - Hydroxyl apatite
  - Carbon beads
  - Teflon beads
  - Collagen
- FDA approval:
  - for urinary
  - not for fecal

Selected references:
ASCRS Task Force, Surg Endosc 2014

Author	Year	n	FI severity score* (range)		Functional success rate (%)	
			Before	After	Complete continence	>50 % improvement
Kumar et al. [9]	1998	17	NA	NA	NA	NA
Davis et al. [10]	2003	18	11.89	8.07	NA	NA
Tjandra et al. [11]	2004	82	14.5 (10-20)	5 (2-13)	0	>50
			14.5 (11-20)	8 (2-12)	0	>40
Stojkovic et al. [12]	2006	73	10	6	5	NA
Chan and Tjandra [13]	2006	7	12 (9-14)	2 (0-5)	NA	>50
Altomare et al. [14]	2008	33	12	8[a]	0	33.3
Ganio et al. [15]	2008	10	85.6[b]	28[a]	0	80
Maeda et al. [16]	2008	5	15[c]	12	NA	NA
		5	16[c]	14	NA	NA
de la Portilla et al. [17]	2008	20	13.5	9.4	0	60
Soerensen et al. [18]	2008	35	12.7	11	0	NA
Aigner et al. [19]	2009	11	12.27	4.91	0	NA
Bartlett and Ho [20]	2009	74	10 (6.8-15)	1 (0-4.3)[d]	0	70
Tjandra et al. [21]	2009	20	11.45	3.80	NA	90
Beggs et al. [22]	2010	23	18.7	10.9	0	NA
Maslekar et al. [23]	2013	100	14	8	0	68

Injectables - Systematic review 2008

Conclusions

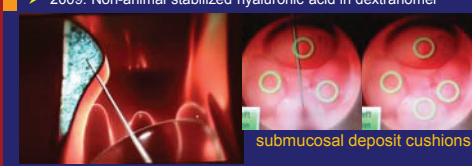
- Currently (i.e. 2008) there is little evidence for the effectiveness of injectable bulking agents in managing passive FI.
- The inability to obtain results from two further RCTs concerned the reviewers and hindered their ability to make strong recommendations.
- The identified injectable bulking agents appear to be safe with only minor complications reported.

Selected references:
Luo C et al – Colorectal Disease 2008

Keck School of Medicine of USC

Injection of NASHA/Dx (Solesta®)

- 2009: Non-animal stabilized hyaluronic acid in dextranomer



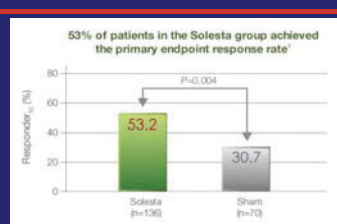
submucosal deposit cushions

- Office procedure: 4x1cc of solution injected above dentate line into submucosa (through anoscope)
- Office procedure

Selected references:
Dodi et al – DCR 2009; Graf et al – Lancet 2011

Keck School of Medicine of USC

Injection of NASHA/Dx (Solesta®)



Median number of incontinence episodes during 2 weeks in the active treatment group decreased from 15.0 (IQR 9.6–27.5) at baseline to 6.2 (2.0–15.5) at 12 months (*P*<.0001)

Selected references:
Graf et al – Lancet 2011

Keck School of Medicine of USC

NASHA/Dx injections – Literature review

- Pilot study:
  - 34 patients: average 50% reduction of FI episodes
  - DCR 2009
- Prospective randomized, sham-controlled trial:
  - 206 patients (2:1 distribution)
  - Lancet 2011
- Open label multicenter trial:
  - 115 patients
  - Gastroenterol Res Pract 2010
- PRT injection vs. biofeedback:
  - 126 patients: similar reduction in FI episodes
  - Scand J Gastroenterol 2013

SILENCE SINCE 2014/2015!

Keck School of Medicine of USC

Sacral Nerve Stimulation (SNS)

1. **Tined lead** is placed parallel to the sacral (S2, S3, or S4) nerve
2. **Implantable neurostimulator** generates mild electrical pulses that are delivered through the lead electrodes
3. **Clinician and patient programmers** are used to set the parameters of the electrical pulses

Keck School of Medicine of USC

Sacral Nerve Stimulation (SNS) - Setup

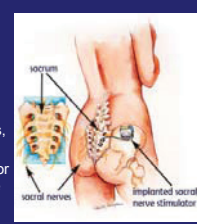
- Two outpatient surgeries:
  - 1st operation: placement of test electrode to S3
    - Moderate sedation/superficial anesthesia
    - Fluoroscopy guidance
    - Intraoperative testing of stimulation: plantar flexion of greater toe and bellow sign of pelvic floor
  - 2nd operation:
    - Succsss: → placement of definitive battery
    - Failure: → Removal of test electrode

Selected references:
ASCRS guidelines 2015

Keck School of Medicine of USC

Sacral Nerve Stimulation (SNS)

- Promising overall results: exact mechanism unknown.
- SNS more effective than optimal medical therapy:
  - >50% improvement in 90% of pts, perfect continence in 47%.
  - infection and lead displacement or continuing pain remain challenge in up to 25% of patients



Selected references:
KE Matzel DCR 2001; KE Matzel Lancet 2004;
JJ Tjandra DCR 2008; US multicenter trial, Ann Surg 2010.

Keck School of Medicine of USC

Sacral Nerve Stimulation (SNS)

Ripetti et al. [36]	2002	16/4	12.2	NA	0	100
Rasmussen et al. [37]	2004	45/37	16	6[b]	NA	86
Jarrett et al. [38]	2004	266/149	15.2	5[b]	41–75	75–100
Conaghan and Faruuk [39]	2005	5/3	NA	NA	67	100
Gourcerol et al. [40]	2007	61/33	14.4	NA	18	69
Melenhorst et al. [41]	2007	134/100	NA	NA	NA	79
Hetzer et al. [42]	2007	44/37	14	5[b]	NA	77
Dudding et al. [43]	2008	70/51	NA	NA	29	85
Munoz-Duyos et al. [44]	2008	43/29	NA	NA	48	61
Chan and Tjandra [45]	2008	60/53	16	1.2[b]	47.2	71
Vitton et al. [46]	2008	5/5	NA	NA	NA	100
Roman et al. [47]	2008	18/18	14.9	4.9[b]	NA	78
Boyle et al. [48]	2009	15/13	12	9[b]	NA	77
Altomare et al. [49]	2009	94/60	15	5[b]	18	75
Vallet et al. [50]	2010	45/32	16.1	6.9[b]	4	51
Michelsen et al. [33]	2010	167/126	16	10[b]	NA	54
Dudding et al. [51]	2010	9/8	NA	NA	33	78
Boyle et al. [52]	2011	50/40	15	8[b]	26	54
Lim et al. [53]	2011	80/53	11.5	8[b]	NA	NA
Wexner et al. [54]	2010	133/120	39[d]	30[b]	40	87
Mellgren et al. [55]	2011	133/120	39.9[d]	28[b]	40	86
Devroede et al. [56]	2012	133/120	39.9[d]	28[b]	34	87
George et al. [57]	2012	25/23	20[d]	7.5[b]	56	100
Hull et al. [60]	2013	76	38[d]	28	36	89

Sacral Nerve Stimulation (SNS) – Future?

- No anophysiology parameters predict whether the SNS is successful or not
- Placement of test electrode is the only positive predictor of success.
- Consequences of SNS success:
  - Potentially placement of test electrode WITHOUT prior anophysiology testing
  - Potentially planned combination of sphincteroplasties WITH SNS?

Selected references:
ASCRS guidelines 2015

Keck School of Medicine of USC

Sacral Nerve Stimulation (SNS)

- Non implantation rate: ~1/3 (depending on strictness of selection criteria
- Implantation:
  - → ~50% excellent
  - → ~50% insufficient response

2/3 of the patients after SNS remain insufficiently treated!

Selected references:
KE Matzel DCR 2001; KE Matzel Lancet 2004;
JJ Tjandra DCR 2008;
US multicenter trial, Ann Surg 2010, 2013

Keck School of Medicine of USC

Sphincter replacement

- Graciloplasty
  - non-stimulated
  - stimulated: dynamic graciloplasty
  - Problem: high complication (60%), lack of dynamic control

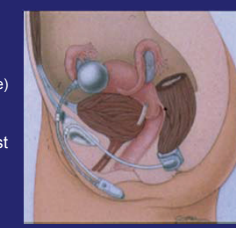


Selected references:
AM Kaiser DCR 2002; SR Brown Cochrane 2007; PEO'Brien DCR 2004; JM Devesa DCR 2002; WD Wong DCR 2002; PA Lehur DCR 2002.

Keck School of Medicine of USC

Sphincter replacement

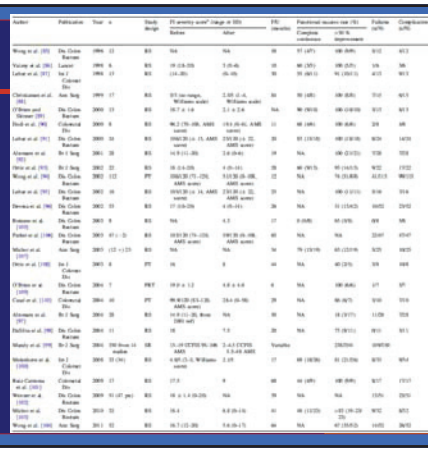
- Artificial bowel sphincter:
  - Failure due to infection/erosion
    - Initially 40% (literature) → currently <10% (USC)
  - If the ABS heals → best possible function the patients can dream of
  - Longterm: material dysfunction?



Selected references:
AM Kaiser DCR 2002; SR Brown Cochrane 2007; PEO'Brien DCR 2004; JM Devesa DCR 2002; WD Wong DCR 2002; PA Lehur DCR 2002.

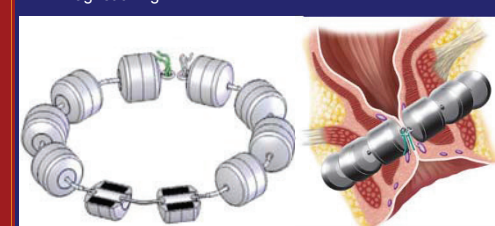
Keck School of Medicine of USC

ABS



Sphincter replacement

- Magnetic ring



Keck School of Medicine of USC

Sphincter replacement

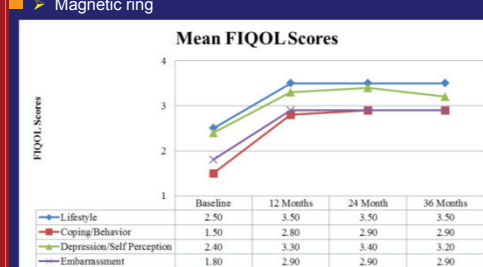
- Magnetic ring

Author	Publication	Year	n	Study design	FI severity score[a] (range or SD) Before	After	F/U (months)
Lehur et al. [111]	D is Colon Rectum	2010	14	Prospective, observational feasibility study	17 (12–19)		6 (median)
Wong et al. [112]	Dis Colon Rectum	2011	10	Case-matched comparing magnetic sphincter with artificial bowel sphincter	17 (13–19)	6	8 (median)
Wong et al. [113]	Colorectal Dis	2012	12	Non-randomized comparativeConsecutive patients failing SNS were implanted with the magnetic device and then compared with the SNS group	16.5 (11–19)	to 6 (3–15)	18 (8–30)

Keck School of Medicine of USC

Sphincter replacement

- Magnetic ring

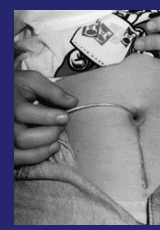


Keck School of Medicine of USC

Surgery: Reduction of stool load

Malone Antegrade Colonic Enema (MACE):

- Appendicostomy (e.g. at umbilicus) or Trap-door button:
  - Timed washout of the whole colon → eliminate stool load
  - Problem: leakage of residual colonic fluid during several hours following the irrigation



Selected references:
EW Gerharz JACS 1997
G Porter Int J Colorectal Dis 2006

Keck School of Medicine of USC

Diversion (ostomy)

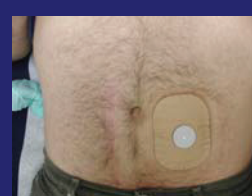
- If other therapies have failed or if comorbidities preclude more aggressive therapy:
  - fecal diversion = excellent alternative
  - colostomy does not restore continence, but control of bowel evacuation
  - permits resumption of a normal personal and social life
- Caveat:
  A bad ostomy may even be worse:
  → Emphasis to create a well-constructed stoma at an appropriate site

Selected references:
RD Madoff Gastroenterology 2004;
C Norton DCR 2005

Keck School of Medicine of USC

Colostomy training

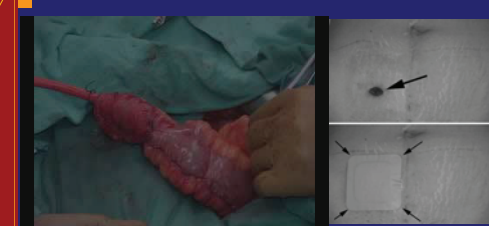
- Even a colostomy can be controlled:
  → colostomy training → timed/predictable evacuation
  → cover + filter



Selected references:
RD Madoff Gastroenterology 2004;
C Norton DCR 2005

Keck School of Medicine of USC

Continent ileostomy – T-pouch



Selected references:
AM Kaiser DCR 2002
AM Kaiser DCR 2012

Keck School of Medicine of USC

2016 Recommendations

- Severe morphological abnormality:
- Examples:
  - Cloaca-like deformity after 4th degree obstetrical injury
  - Full thickness rectal prolapse, perineal trauma, etc.
- Recommendation:
  - Correct the defect first and initiate supportive conservative measures.
  - Sphincter reconstruction may require non-stimulated muscle transfer (e.g. unilateral or bilateral graciloplasty or gluteoplasty).
  - Once the anatomy is restored, further options may be considered including on a case-by-case basis:
    - e.g. injectables, radiofrequency, SNS, or ABS

Keck School of Medicine of USC

2016 Recommendations

Sphincter defect (without previous repair), without major visible anatomical abnormality:

- Examples:
  - Fecal incontinence after vaginal delivery, post-surgical (hemorrhoidectomy, fistulotomy, sphincterotomy, etc.)
- Recommendation:
  - Consider sphincteroplasty if conservative measures failed.
  - Alternatively: SNS, radiofrequency, injectables.

Keck School of Medicine of USC

2016 Recommendations

Failed sphincter repair, without major visible anatomical abnormality:

- Minor fecal incontinence
  - (CCFIS 1–6): radiofrequency, injectables, PTNS, poss SNS.
- Moderate fecal incontinence
  - (CCFIS 7–13): SNS, radiofrequency, injectables.
  - If failed: magnetic ring, ABS.
- Severe fecal incontinence
  - (CCFIS 14–20): SNS, magnetic ring, ABS
  - rarely nonstimulated graciloplasty

Keck School of Medicine of USC

2016 Recommendations

Failed surgical interventions, failed conservative measures, or contraindications to other interventions.

- Consider trap-door button or MACE procedure
- Colostomy

Keck School of Medicine of USC

Summary

- Patients' desire to have "control" is typically very strong
- Patients' threshold to acknowledge a problem is very high
- Successful management of fecal incontinence starts with a thorough understanding of:
  - the factors contributing to the normal control
  - disease processes
  - workup and interpretation of individual results
  - tailoring of individual treatment plan
  - no "one size fits all"
- New technologies abundant but not indicated for all patients, and objective results less strong than advertised
- Silver bullet still missing

Keck School of Medicine of USC

Thank you for your attention

Andreas M. Kaiser, MD FACS FASCRS
Professor of Clinical Surgery

USC Department of Colorectal Surgery
1441 Eastlake Avenue, Suite 7418
Los Angeles, CA 90033
Ph: (323) 865-3690
Fax: (323) 865-3671

Email: akaiser@usc.edu

Keck School of Medicine of USC

Disclosures

metaMe
HEALTH AGGREGATOR

GastroGirl™
EMPOWERING OPTIMAL DIGESTIVE HEALTH

Icahn School of Medicine at Mount Sinai

How to convince a patient *without* pathologic acid that they ***do not need their PPI***

Laurie Keefer, PhD
Associate Professor of Medicine
GI Health Psychologist

Gastroesophageal Reflux Disease and PPI use

- GERD affects 20% of population
  - Success for healing esophagitis is as high as 80-90%;
  - 40% of people on PPIs experience "breakthrough" symptoms
  - 50% of people are not satisfied with symptom relief from once-daily PPI
- **Only 30% of people on PPIs actually need them!!!**

Fass R, Shapiro M, Dekel R , et al. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease: where next?. Aliment Pharmacol Ther. 2005;22:79–94. 40

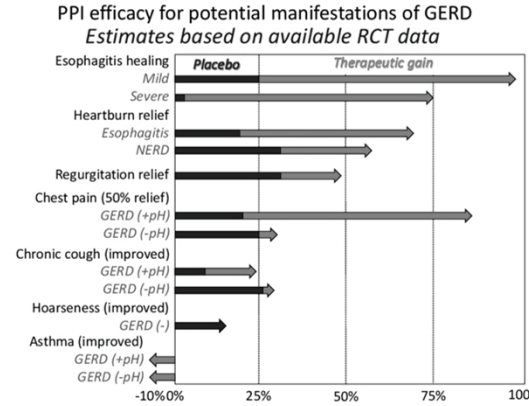


Table 1 | **Reported associations with PPI use and adverse events**

Adverse event	Odds or hazard ratio	95% CI
Hip fracture with PPI use >1 year[4]	OR 1.44	1.30–1.59
Hip fracture with long-term PPI use	OR 2.65	1.80–3.90
Community-acquired pneumonia[5]	OR 1.49	1.16–1.92
Clostridium difficile infection[6]	OR 2.10	1.20–3.50
Acute interstitial nephritis[7]	OR 5.16	2.21–12.05
Acute kidney injury in patients >18 years[8]	OR 1.72	1.27–2.32
Hypomagnesaemia[3]	OR 1.78	1.01–2.92
Myocardial infarction[9]	HR 1.16	1.09–1.24
Dementia[10]	HR 1.44	1.36–1.52

Kia, L. & Kahrilas, P. J. (2016) Risks associated with chronic PPI use — signal or noise? *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2016.44

Patients with **refractory** reflux symptoms: What do they have and how should they be managed?

Kahrilas, PJ, Keefer, L., Pandolfino JE, NGM 2015, 27, 1195-1201

- Acid Enthusiasts
  - increase dose, add more potent drug
- Technology Enthusiasts
  - Impedence testing
- **Symptom Perception Enthusiasts**
  - Emphasis on hypersensitivity, hypervigilance, and the possibility that symptoms are not reflux-based

Laurie Keefer, PhD − How to convince a patient *without* pathologic acid that they **do not need their PPI**

Mechanisms of heartburn

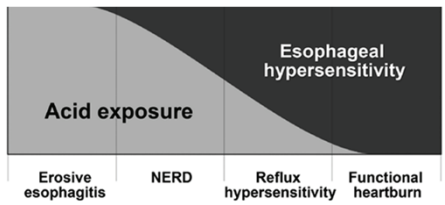


Figure 2. The interplay between esophageal hypersensitivity and acid exposure in the reflux symptom spectrum. Symptoms in erosive esophagitis are dominated by abnormal acid exposure whereas symptoms in functional heartburn are dominated by hypersensitivity. Symptoms in NERD and reflux hypersensitivity are related to a combination of both acid exposure and hypersensitivity, with a shift reflecting a more pronounced effect of acid exposure along the NERD diagnostic spectrum and a more pronounced effect of esophageal hypersensitivity along the reflux hypersensitivity diagnostic spectrum.

Pandolfino et al., Esophageal Disorders, Gastro 2016; 150: 1368-1379

Where do symptoms come from if not reflux?

- Lifestyle/Health behaviors
- Psychological comorbidity?
- **Esophageal Hypervigilance**

Esophageal Hypervigilance

- A heightened state of awareness or sensitivity **coupled with behaviors** that serve to detect future threats

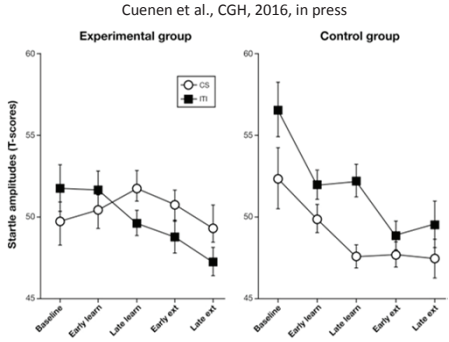
Middle aged man with GERD controlled on PPI experiences heartburn while out to dinner with wife → Man observes, continues enjoying dinner and goes on to movies. May take tums from wife's purse → Symptoms go away in a couple of hours

Esophageal Hypervigilance

Middle aged man with GERD controlled on PPI experiences heartburn while out to dinner with wife → Man observes right away, starts to analyze what he may have done to cause them, stops eating meal and cancels movie plans. Takes several tums from wife's purse and goes home to bed. → Symptoms go away in a couple of hours → Accidentally reinforced, avoids date nights → QOL Impaired

Learned Fear of Gastrointestinal Sensations in Healthy Adults

Cuenen et al., CGH, 2016, in press



Mean startle amplitudes (T scores) for the (*A*) experimental group and the (*B*) control group.

Northwestern Approach to PPI Withdrawal

Week 1: Reduce your medication by 50%
- May use over-the-counter antacid (Tums, Rolaids, Mylanta, Maalox)

Week 2: Reduce your lower dose to every other day
- May use over-the-counter antacid (Tums, Rolaids, Mylanta, Maalox)

Week 3: Stop your medications
- Should reflux symptoms return, please contact Gwen Cassidy, NP at XXX-XXX-XXXX

Alternatives to PPI

- Lifestyle recommendations
- Tricyclic antidepressants
- SSRIs
- Hypnosis

Lifestyle Intervention in Gastroesophageal Reflux Disease

E. Ness-Jensen et al., CGH, 2016: 14: 175-82

- **Weight reduction dose-dependently decreases reflux symptoms**
- **Tobacco smoking cessation reduced reflux symptoms in *normal*-weight individuals**
- Late meal (2 hours before bedtime) associated with more pH-verified supine reflux than early meal (6 hours before bedtime)
- Dietary fiber increased number of days without heartburn and reduced severity score
- Elevation of the head of the bed by a 10-inch wedge decreased the time that esophageal pH was less than 4 compared with a flat position

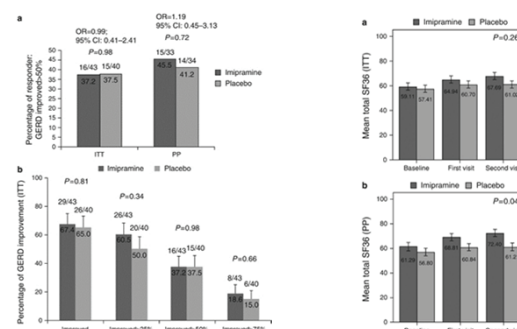
Pain Modulators for Functional Esophageal Disorders

Class of drug	Dose	Disorder	RCT	Side effects	Response
TCAs					
Imipramine	50 mg/day	NCCP	+	+/-	57%
Amitriptyline	10–20 mg/day	NCCP, globus	+	+/-	52%
SSRIs					
Sertraline	50–200 mg/day	NCCP	+	+	57%
Paroxetine	50–75 mg/day	NCCP	+	+/-	Modest
Citalopram	20 mg/day	ES	+	+/-	Significant
Trazodone					
Vs clomipramine	50/25 mg/day	NCCP	-	+	Modest
Trazodone alone	100–150 mg/day	dysmotility	+	+/-	29%–41%
SNRIs					
Venlafaxine	75 mg/day	NCCP	+	++	52%
Other					
Theophylline	200 mg twice/day	NCCP	+	+/-	58%
Gabapentin	300 mg 3 times/day	globus	+	+/-	66%

Pandolfino et al., Esophageal Disorders, Gastro 2016; 150: 1368-1379

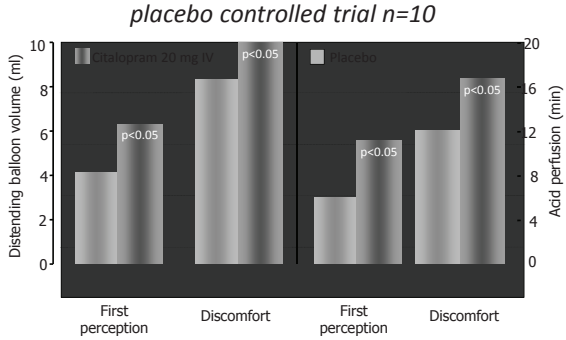
Imipramine for Treatment of Esophageal Hypersensitivity and Functional Heartburn

Limsrivilai, J. et al., AJG, 2016, 111:217-24



Improvement of esophageal hypersensitivity with acute dose of citalopram

placebo controlled trial n=10



Broekaert D et al. APT 2006;23:365

Esophageal directed hypnotherapy for functional heartburn

M. E. Riehl, J. E. Pandolfino, O. S. Palsson, L. Keefer, Diseases of the Esophagus, 2015

SF8 Physical Component		SF8 Mental Component		QUALRAD		Visceral Sensitivity Index		Heartburn Catastrophizing Scale	
Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
39.5 (8.1)	41.3 (12.6)	45.5 (13.1)	53.5 (8.9)	4.1 (.99)	5.4 (1.3)	55.6 (24.1)	64.4 (23)	20.7 (11.9)	12.8 (10.4)
t(8) = - .82, p = ns		**t(8) = -2.4, p = .05***		**t(8) = -3.4, p = .01***		**t(8) = -3.3 p = .01***		**t(8) = 2.3,p = .06**	

Mean age = 45(11), 89% F, 100% married, 44% college +, 100%White, 67% on PPI

Take Home Points

- The majority of GERD patients without documented esophagitis do not need a PPI
- Patients are reluctant to stop their PPI
  - lack of understanding of reflux phenotypes
  - mucosal healing vs. symptom perception
    - esophageal hypervigilance
- Behavioral strategies may assist with PPI withdrawal and symptom control

Northwestern Medicine

Gut directed hypnotherapy: How to customize it for your practice

Sarah Kinsinger, PhD, ABPP

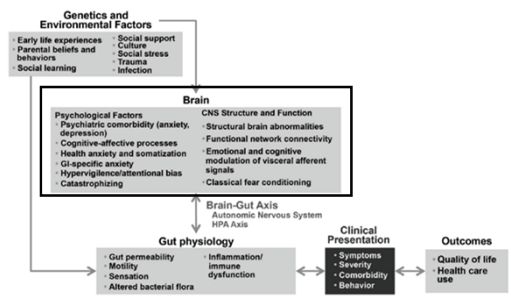
Director, GI Behavioral Medicine
Division of Gastroenterology and Hepatology
Northwestern University Feinberg School of Medicine
http://dhcbmed.nm.org

Objectives

- Review the rationale and effectiveness profile of gut-directed hypnotherapy
- Discuss the use and application of hypnosis to upper functional gastrointestinal disorders (FGIDs)
- Provide examples of hypnotic imagery and suggestions for various upper FGIDs

Northwestern Medicine

Biopsychosocial Model of Functional GI Disorders (FGIDs)



Adapted from: Oudenhove, LV et al. Biopsychosocial aspects of functional gastrointestinal disorders: How central and environmental processes contribute to the development and expression of functional gastrointestinal disorders. *Gastro.* 2016;150:1355-1367.

Northwestern Medicine

ELSEVIER

Journal of Psychosomatic Research 64 (2008) 621 – 623

Journal of Psychosomatic Research

Review article

Hypnotherapy for irritable bowel syndrome: The response of colonic and noncolonic symptoms

Peter J. Whorwell*

University of Manchester, Manchester, United Kingdom

Received 5 September 2007; received in revised form 21 January 2008; accepted 19 February 2008

Abstract

There is now good evidence that hypnotherapy benefits a substantial proportion of patients with irritable bowel syndrome and that improvement is maintained for many years. Most patients seen in secondary care with this condition also suffer from a wide range of noncolonic symptoms such as backache and lethargy, as well as a number of musculoskeletal, urological, and gynaecological problems. These features do not typically respond well to conventional medical treatment approaches, but fortunately, their intensity is often reduced by hypnosis. The mechanisms by which hypnosis mediates its benefit are not entirely clear, but there is evidence that, in addition to its psychological effects, it can modulate gastrointestinal physiology, alter the central processing of noxious stimuli, and even influence immune function.

Keywords: IBS; Symptoms; Hypnotherapy; Mechanisms

Northwestern Medicine

Medical Hypnosis

- Hypnosis has long history as a medical tool
- Dates back to 1800s
- Medical intervention before anesthesia was discovered in 1846
- Wealth of research demonstrating efficacy for chronic pain
- Commonly used with burn victims, postoperative pain/nausea, cancer-related pain, IBS, functional abdominal pain in children

Pintar, J & Lynn, SJ. *Hypnosis: A brief history.* Wiley-Blackwell: Malden, MA, 2008; Jensen & Patterson. Hypnotic approaches for chronic pain management: Clinical implications of recent research findings. *Am Psychol* 2014; 69: 167-77.

Northwestern Medicine

Gut- directed Hypnosis

- Developed as treatment for IBS by Peter Whorwell in 1980s
- 1st trial of hypnosis in refractory IBS patients demonstrated reductions in pain, bloating, and bowel habits in hypnotherapy group vs control group
- Gut- directed hypnosis protocols
  - Manchester protocol = 12 sessions
  - UNC protocol = 7 sessions

Gonsalkorale, WM. Gut-directed hypnotherapy: the Manchester approach for treatment of irritable bowel syndrome. *Int J Clin Exp Hypn* 2006; 54: 27-50; Palsoon, OS. Standardized hypnosis treatment for irritable bowel syndrome: The North Caroline protocol. *Int J Clin Exp Hypn* 2006; 54: 51-64; Whorwell, PJ, Prior, A, Faragher, EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable bowel syndrome. *Lancet* 1984; 2: 1232-4.

Northwestern Medicine

Table 2. Randomized Controlled Trials of Hypnosis Treatment for Functional Gastrointestinal Disorders.

Study:	Disorder treated:	Symptoms improved:	Sample Size:	Control groups	Outcome:
Whorwell et al., 1984[33]	IBS	G,E	30	supportive therapy + placebo pills	Hypnosis superior
Forbes et al, 2000[34]	IBS	G	52	(non-hypnotic) audiotapes	Hypnosis superior
Galovski & Blanchard, 1998[35]	IBS	G,E	11	waiting list	Hypnosis superior
Palsson et al, 2002 (Study 2)[36]	IBS	G,E	24	waiting list	Hypnosis superior
Roberts et al, 2006[37]	IBS	G,Q	81	usual medical care	Hypnosis superior
Lindfors et al., 2012 (Study 1)[38]	IBS	G,E,Q	90	supportive therapy	Hypnosis superior
Lindfors et al., 2012 (Study 2)[38]	IBS	Q	48	waiting list	no difference
Vlieger et al, 2007[39]	Pediatric abdominal pain	G	52	medical care + supportive therapy	Hypnosis superior
van Tilburg et al., 2010[40]*	Pediatric abdominal pain	G	34	usual medical care supportive therapy,	Hypnosis superior
Calvert et al, 2002[41]	Functional dyspepsia	G,E,Q	126	placebo pills,ranitidine	Hypnosis superior
Jones et al., 2006[42]	Non-cardiac chest pain	G,Q	28	supportive therapy + placebo pills	Hypnosis superior

*G=Gastrointestinal symptoms improved within group; E=Emotional symptoms improved within group; Q=Quality of life improved within group; *=Mostly or entirely self-administered treatment*

Palsson & Whitehead. Psychological treatments in functional GI disorders: A primer for the gastroenterologist. *Clin Gastroenterol Hepatol* 2013; 11: 208-216.

Northwestern Medicine

Effectiveness profile of Gut-directed hypnosis for IBS

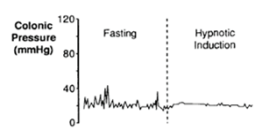
- **NNT (IBS) = 2.5** (95% CI, 1.5 to 7)
- Response rates >85% in refractory cases
- Cost effective at 1year
- Durable– continued improvement up to 3years, maintenance at 5years

Ford AC, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol, 2014,* 109:1350-65; Miller, V et al. Hypnotherapy for irritable bowel syndrome: an audit of one thousand adult patients. *Aliment Pharmacol Ther*, 2015; 41: 844-55; Palsson O. Hypnosis for gut problems. *Euro Gastro Hep Rev*, 2010;6(1):42–6

Northwestern Medicine

Possible Mechanisms of Hypnosis

- Psychological factors
- Gut motility
- Visceral sensitivity
- Central processing
- Autonomic nervous system activity
- Immune function



Klein & Spiegel. Modulation of gastric acid secretion by hypnosis. *Gastro* 1989; 96: 1383- 7; Prior, Colgan, Whorwell. Changes in rectal sensitivity after hypnotherapy in patients with irritable bowel syndrome. *Gut* 1990; 31: 896-898; Whorwell, Houghton, Taylor, & Maxton. Physiological effects of emotion: assessment via hypnosis. *Lancet* 1992; 340: 69-72;

Northwestern Medicine

Northwestern Medicine

What is Hypnosis?

What is hypnosis?

"Hypnosis uses verbal guidance and a special mental state of heightened receptivity to facilitate therapeutic psychological and physiological changes"

Palsson & Whitehead. Psychological treatments in functional GI disorders: A primer for the gastroenterologist. *Clin Gastroenterol Hepatol* 2013; 11: 208-216.

Northwestern Medicine

Northwestern Medicine

Components of Hypnosis

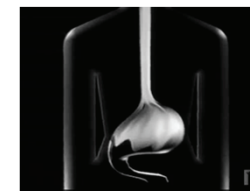
Induction	Suggestions
• Guided physical relaxation	• Metaphors
• Narrowing focus of attention	• Imagery
• Encouraging things to happen automatically	• Therapeutic verbal suggestions
• Vividly engaging the imagination	
• Facilitating dissociation	

Northwestern Medicine®

Palsson, Hypnosis treatment for Gut Problems. *Eur Gastro Hep Rev* 2010;6(1):42-46

Gut-Directed Hypnosis

Picture a wave of medication spreading down from your stomach all the way down through your intestines creating a strong protective coating…a strong protective coating that makes your intestines immune to irritation, and protects you from feeling upset inside…



Northwestern Medicine®

Palsson, Hypnosis treatment for Gut Problems. *Eur Gastro Hep Rev* 2010;6(1):42-46

IBS- Specific Suggestions

Suggestions	Examples
Regulating smooth muscle activity	"your bowels are beginning to function in all situations with a healthy, quiet, natural rhythm that is comfortable and soothing and hardly noticeable at all…"
Reduce impact of stress on GI system	"you feel inside like nothing can disturb your deep comfort…like nothing can upset you or cause you discomfort or pain…"
Reduce gut pain perception	"…sensations that used to be uncomfortable now increasingly feel just mild and soothing and do not bother you anymore."
Increase patient's sense of control over symptoms	"you can feel confident in your ability to keep strengthening your body's natural resistance to stress and discomfort…"

Northwestern Medicine®

Palsson, Hypnosis treatment for Gut Problems. *Eur Gastro Hep Rev* 2010;6(1):42-46

Northwestern Medicine®

Customizing Hypnosis for Upper FGIDs

Use of Hypnosis with Upper FGIDs

- Functional dyspepsia[1]
- Globus sensation[2]
- Heartburn[3]
- Non-cardiac chest pain[4]
- Dysphagia[5]

1. Calvert et al. Long-term improvement in functional dyspepsia using hypnotherapy. *Gastro* 2002; 123: 1778- 85.
2. Kiebles et al. Do patients with globus sensation respond to hypnotically assisted relaxation therapy? A case series report. *Dis Esophagus* 2010; 23: 545- 553.
3. Riehl et al. The feasibility and acceptability of esophageal directed hypnotherapy for functional heartburn. Dis Esophagus 2015; Advance online publication..
4. Jones et al. Treatment of non-cardiac chest pain: A controlled trial of hypnotherapy. *Gut* 2006; 55: 1403-8.
5. Riehl & Keefer. Hypnotherapy for esophageal disorders. *Am J Clin Hypn* 2015; 58:22-33

Northwestern Medicine®

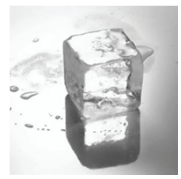
Hypnosis for Functional Dysphagia

Imagine the water winding its way through the naturally made canal, the walls of the stream allowing free flow, gentle flow… and your esophagus can function in just the same way… with a gentle flow, with natural muscular contractions, moving food and liquid gently and easily all the way to your stomach… Just easy, natural rhythms of normal digestive functioning…

Northwestern Medicine®

Hypnosis for Globus

Imagine that the sensation in your throat is like an ice cube gently hovering in the back of your throat…this ice cube can slowly melt…melting gently and steadily down your esophagus…The sensation of something stuck in your throat gently fades away, as if disintegrating right there…this sensation will become milder and milder until it is hardly noticeable at all…



Northwestern Medicine

Hypnosis for Heartburn

Out there in this garden it feels like you are completely wrapped in deep, warm, and relaxing comfort… And you can let that warm and soothing sensation spread deep inside your chest… all the way into your esophagus… filling your chest with a healthy, undisturbed feeling… You will carry this feeling of undisturbed healthy comfort in your chest from day to day. It will be with you even when you pay no attention to it…

Northwestern Medicine

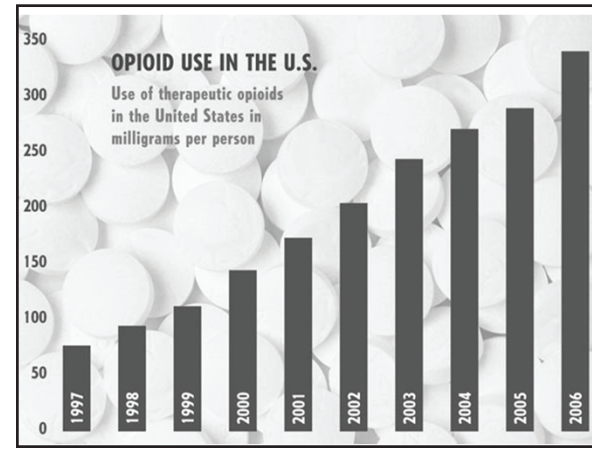
Take Home Points

- Gut-directed hypnosis is an evidence-based treatment for IBS
- Hypnosis can simultaneously target autonomic arousal, visceral anxiety, central pain amplification and maladaptive cognitions
- Hypnosis can be easily adapted to address many upper FGIDs and demonstrates promise as an effective treatment option

Northwestern Medicine

Opioid Induced Constipation

Anthony Lembo, M.D.
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA

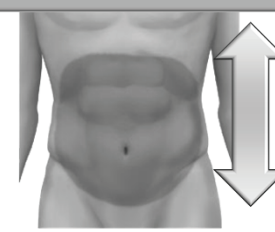


Opioid effects / Adverse reactions

- CNS dysfunction
  - Light-headedness, dizziness, sedation, euphoria, dysphoria
  - Increased intracranial pressure, miosis, myoclonus
- Respiratory: depression
- Cutaneous: pruritus
- Circulatory depression: hypotension
- GI dysfunction

The Spectrum of Opioid-induced Bowel Dysfunction

Opioids Affect the Entire GI Tract[1,2]



- **Reflux/heartburn**
- **Abdominal cramping**
- **Abdominal spasms**
- **Bloating**
- **Decreased appetite**
- **Nausea/vomiting**
- **Hard and dry stools**
- **Painful/incomplete defecation**
- **Constipation**

1. Thomas JR et al. *J Palliat Med*. 2008;11(suppl 1):S1-S19.
2. Kurz A et al. *Drugs*. 2003;63:649-671.

Rome IV Criteria for Opioid Induced Constipation*

New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy that must
include 2 or more of the following:

a. Straining during more than one-fourth (25%) of defecations
b. Lumpy or hard stools (BSFS 1−2) more than one-fourth (25%) of defecations
c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations
d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
e. Manual maneuvers to facilitate more than one-fourth (25%) of defecations (eg, digital evacuation, support of the pelvic floor)
f. Fewer than three spontaneous bowel movements per week

Loose stools are rarely present without the use of laxatives

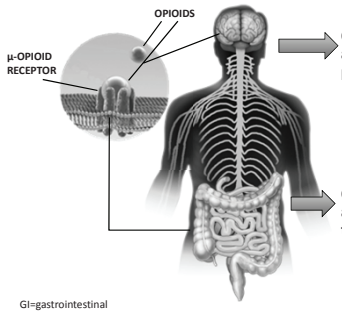
1. Lacy B et al. Bowel Disorders, Gastroenterology 2016; 150 (6) 1393-1407

Opioid-induced Constipation

- Reported in 95% of patients with cancer pain and up to 80% of patients with nonmalignant pain[1,2]
- Tolerance to OIC rarely develops[2,3]
- Prevalence of constipation increased with duration of opioid treatment in patients with chronic, non-cancer pain[4]

1. Robinson CB et al. *Clin J Oncol Nurs*. 2000;4:79-84.
2. Bell TJ et al. *Pain Med*. 2009;10:35-42.
3. Panchal SJ et al. *Int J Clin Pract*. 2007;61:1181-1187.
4. Tuteja AK et al. *Neurogastroenterol Motil*. 2010;22:424-430.

Pathophysiology of OIC



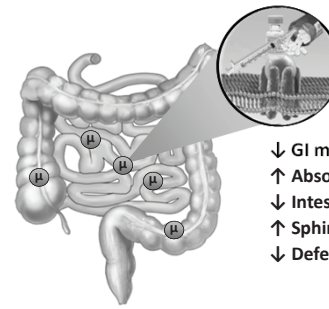
Opioids primarily exert analgesic effects via central μ-opioid receptors[1]

OIC is largely mediated by opioid actions on μ-opioid receptors in the GI tract[1-3]

GI=gastrointestinal

1. Thomas JR et al. *J Palliat Med*. 2008;11(suppl 1):S1-S19.
2. Diego L. *Expert Opin Investig Drugs*. 2011;8:1047-1056.
3. Leppert W. *Adv Ther*. 2010;27:714-730.

Opioid Effects on the Gastrointestinal Tract



↓ GI motility
↑ Absorption of fluid from gut
↓ Intestinal secretion
↑ Sphincter tone
↓ Defecation reflex

Leppert W. *Adv Ther*. 2010;27:714-730.
Kurz A et al. *Drugs*. 2003;63:649-671.

Contributing Factors to OIC in Advanced, Progressive Illness

- Other constipating medications (eg, vincristine, thalidomide, 5-HT_3 antagonists, anticholinergics)
- Weakness/fatigue
- Uncontrolled pain with defecation
  - Anorectal pain, bone pain, other cancer pain
- Environmental/cultural factors
  - Lack of privacy, comfort, or assistance with toileting
- Structural abnormalities (eg, anorectal fissures, pelvic tumor mass)
- Other factors
  - Dementia and delirium may contribute to constipation unawareness
  - Decreased mobility/inactivity
  - Confined to bed

However, there is little information on risk or contributing factors for OIC in individuals with chronic, non-cancer pain.

Librach SI et al. *J Pain Symptom Manage*. 2010;40:761-773.
Thomas JR et al. *J Palliat Med*. 2008;11(suppl 1):S1-S19.

Effects of OIC in Patients With Chronic, Non-cancer Pain

- **Compromises pain management[1]**
  - 35% missed, decreased, or stopped opioids to obtain relief from opioid-induced adverse effects*
  - 28% decreased opioid therapy dose to avoid opioid-induced adverse effects*
  - 33% missed, decreased, or stopped opioids to make it easier to have a bowel movement*
- **Impairs productivity and quality of life[2]**
  - 47.7% of patients experienced overall work impairment**
  - 68.1% of patients demonstrated activity impairment**
  - Mental and physical health was worse than patients who did not suffer from OIC**
- **Increases use of health care resources[2]**
  - Mean number of physician and alternative case visits was higher in OIC patients compared to patients who did not suffer from OIC**

*Results from PROBE (Patient Reports of Opioid-related Bothersome Effects) survey: 4% of survey respondents suffered from cancer-related pain.
**Data from International Health and Wellness Survey 2004 from persons aged ≥18 years taking opioids for ≥6 months.

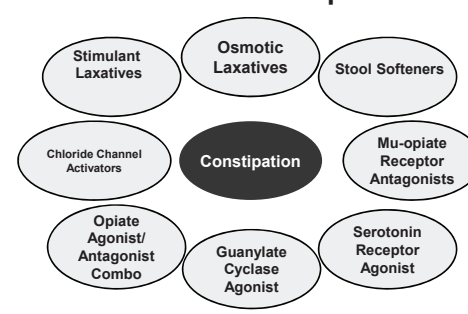
1. Bell TJ et al. *Pain Med*. 2009;10:35-42.
2. Bell TJ et al. *J Opioid Manag*. 2009;5:137-144.

Constipation Symptoms Reported in Patients Taking Opioid Therapy for Chronic, Non-cancer Pain

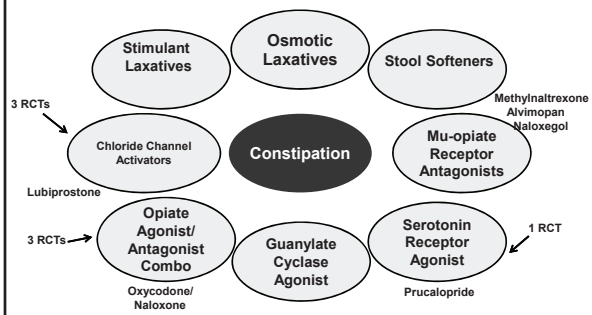
	Percentage of Patients	
Constipation Symptoms	**Tuteja AK et al[1]**	**Pappagallo M et al[2]**
Strain often	38.1%	40.0%
Hard stool	44.3%	45.4%
Feeling of incomplete evacuation	28.9%	36.1%
<3 bowel movement per week	28.4%	40.3%

1. Tuteja AK et al. *Neurogastroenterol Motil*. 2010;22:424-430.
2. Pappagallo M et al. *Am J Surg*. 2001;182(suppl 5A):11S-18S.

OIC : Treatment Options



Constipation: Therapeutics



- Standard laxatives are often insufficient for treatment of OIC and fail in ≈50% of cases[1]
- Need to look for different solutions for treating patients with chronic nonmalignant pain

Current Recommendations: Laxatives for OIC

- Laxatives are the current standard of care for the treatment of OIC[1,2]
- Historically, treatment of OIC extrapolated from recommendations for CC or palliative care[1,3,4]
- No consensus-based guidelines for the use of specific laxatives for treating OIC

CC=chronic constipation

1. Thomas JR et al. *J Palliat Med*. 2008;11(suppl 1):S1-S19.
2. Kurz A et al. *Drugs*. 2003;63:649-671.
3. Thomas J. *J Support Oncol*. 2006;4:220-223.
4. Walters JB et al. *J Opioid Manag*. 2010;6:435-444.

Bowel Function Index (BFI)

Please complete all items in this assessment.

1. Ease of defecation (NAS) during the last 7 days according to patient assessment:
   0 = easy / no difficulty
   100 = severe difficulty
   Ask the subject: *"During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"*
   If the subject requires clarification, ask: *"During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"*
2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment:
   0 = not at all
   100 = very strong
   Ask the subject: *"During the last 7 days, how would you rate any feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?"*
   If the subject requires clarification, ask: *"During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*
3. Personal judgement of patient (NAS) regarding constipation during the last 7 days:
   0 = not at all
   100 = very strong
   Ask the subject: *"During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*
   If the subject requires clarification, ask: *"During the last 7 days, how would you rate how constipated you felt on a scale from 0 to 100, where 0 = not at all and 100 = very strong"*

BFI scores for patients without constipation < 29

Consensus Recommendation:

Consider treating OIC patients with prescription medications when OTC fail and BFI >30

Argoff CE, Consensus Recommendations on Initiating Prescription Therapies for Opioid-Induced Constipation Pain Med 2015 Dec;16(12):2324-37

Lubiprostone for Treatment of OIC in Patients With Chronic, Non-cancer Pain: Phase I-III Trials

Trials I/II:

- N=869 patients, all opiates
- Lubiprostone 24 mcg BID vs placebo x 12 wk
- Primary endpoint→mean Δ from baseline SBM frequency @ Week 8
- Multiple secondary endpoints

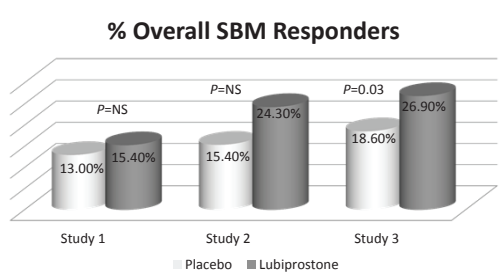
Trial III:

- N=431 patients, all opiates except methadone
- Lubiprostone 24 mcg BID vs placebo x 12 wk
- Primary endpoint→overall SBM response (≥3 SBM/wk x 9-12 wk + increase ≥1 SBM over baseline for entire trial)
- Multiple secondary endpoints

SBM=spontaneous bowel movement

Cryer BL et al. *Pain Med*. April 2014. [Epub ahead of print]. (A)
Jamal MM et al. Abstract presented at: DDW 2012; May 19-22, 2012; San Diego, CA. Abstract 848a. (A)
US FDA CDER. Lubiprostone NDA 021908 Label 4/19/13.

Lubiprostone Change From Baseline SBM Frequency in OIC (Trials I-III)



Cryer BL et al. *Pain Med*. April 2014. [Epub ahead of print]. (A)
Jamal MM et al. Abstract presented at: DDW 2012; May 19-22, 2012; San Diego, CA. Abstract 848a. (A)
US FDA CDER. Lubiprostone NDA 021908 Label 4/19/13.

Lubiprostone for OIC: Combined Adverse Events

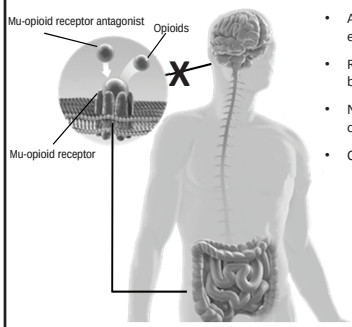
Adverse Event (AE) (N=1492 pts)	Lubiprostone (N=860 pts)	Placebo (N=632 pts)
Nausea	11%	5%
Diarrhea	8%	2%
Abdominal Pain	1%	1%

No serious AEs or deaths reported

2013 FDA approved for treatment of OIC in patients with non-cancer pain

US FDA CDER. Lubiprostone NDA 021908 Label 4/19/13.

Peripheral Mu-Opioid Receptor Antagonists



- Antagonize peripheral constipating effect of opioids
- Restricted ability to cross blood-brain barrier
- No effect on CNS-mediated effects of opioids (eg, analgesia/withdrawal)
- Currently available therapeutics:
  - Methylnaltrexone (subcutaneous)
  - Naloxegol
  - Alvimopan
  - Naloxone

Efficacy of Methylnaltrexone (MNT) in OIC

Parameter	RCT of single-dose, subcutaneous MNT in pts with advanced illness[1]			RCT of q2d subcutaneous MNT for 2 weeks followed by open-label extension trial in pts with advanced illness, insufficient response to laxatives[2]	
	MNT 0.15 mg/kg (N=47)	MNT 0.3 mg/kg (N=55)	Placebo (N=52)	MNT 0.15 mg/kg (N=63)	Placebo (N=71)
Laxation within 4h, %	62*	58*	14	48**	15
Laxation within 4h after ≥2 of first 4 doses, %	N/A	N/A	N/A	52**	8
Median time to laxation after first dose, hours	1.1	0.8	>24	6.3**	>48

Efficacy maintained for up to 3 months in open-label extension[3]

1. Slatkin N et al. *J Support Oncol*. 2009;7:39-46. (A)
2. Thomas J et al. *NEJM*. 2008;358:2332-2342. (A)
3. Lipman AG et al. *J Pain Palliat Care Pharmacother*. 2011;25:136-145. (A)

*P<.0001 vs placebo
**P<.001 vs placebo

Phase III RCT of MNT in Patients With Chronic, Non-cancer Pain

- Patients received subcutaneous MNT (QD or Q2D) or placebo for 4 weeks

Parameter	MNT 12 mg QD (N=150)	MNT 12 mg Q2D (N=148)	Placebo (N=162)
RFBM within 4h of first dose, %	33.3*	35.1*	9.9
≥3 RFBM/week during double-blind period, %	58.7**	45.3	38.3
Improvement in PAC-QOL score, %	33*	27***	18

*P<.001 vs placebo; **P<.01 vs placebo; ***P=.014 vs placebo

PAC-QOL=Patient Assessment of Constipation Quality of Life; QD=once daily; Q2D=every two days; RFBM=rescue-free bowel movement

Michna E et al. *J Pain*. 2011;12:554-562. (A)

Safety of MNT in Patients With Chronic, Non-cancer Pain

AEs occurring in ≥5% of pts, %	MNT 12 mg QD (N=150)	MNT 12 mg Q2D (N=148)	Placebo (N=162)
Abdominal pain	19.3	15.5	3.7
Diarrhea	6.0	11.5	3.7
Nausea	8.7	11.5	6.2
Hyperhidrosis	6.0	6.1	1.2
Vomiting	0.7	7.4	4.9

Michna E et al. *J Pain*. 2011;12:554-562. (A)

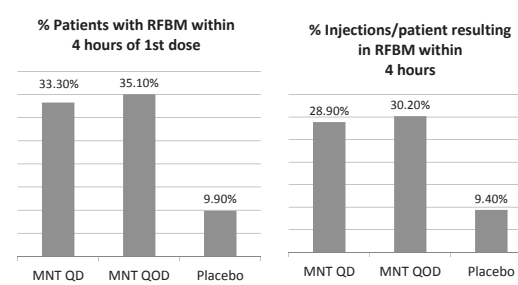
Subcutaneous MNT

- 4-week randomized, double-blind, placebo-controlled trial
- N=460 patients (61% female; 90% Caucasian)
- Placebo, MNT 12 mg QD, 12 mg QOD
- Co-primary endpoints:
  - % individuals having RFBM within 4 hours of first injection
- % of active injections per individual resulting in RFBM within 4 hours

MNT=methylnaltrexone
RFBM=rescue-free bowel movement

Michna E et al. *J Pain*. 2011;12:554-562. (A)

Subcutaneous MNT (Cont'd)



P<0.001 for all MNT comparisons to placebo

Michna E et al. *J Pain*. 2011;12:554-562. (A)

Subcutaneous MNT Adverse Events (>5%)

Adverse Event (AE)	MNT QD (N=150)	MNT QOD (N=148)	Placebo (N=162)
Abdominal pain (mild-moderate cramping)	29 (19.3%)	23 (15.5%)	6 (3.7%)
Diarrhea	9 (6%)	17 (11.5%)	6 (3.7%)
Nausea	13 (8.7%)	17 (11.5%)	10 (6.2%)
Hyperhidrosis	9 (6%)	9 (6.1%)	2 (1.2%)
Vomiting	1 (0.7%)	11 (7.4%)	8 (4.9%)

Michna E et al. *J Pain*. 2011;12:554-562. (A)

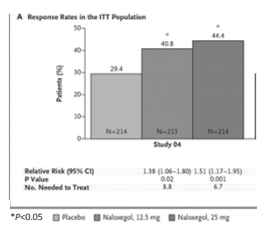
Oral MNT*

- Phase III randomized, double-blind, placebo-controlled trial
- N=804 patients (non-cancer pain)
- Placebo, MNT 150, 300, 450 mg PO QD
- For the first dose MNT: 150 (34%), 300 (41%) and 450 mg (42%) treatment groups vs PBO (23%) for rescue-free BM in first 24 hours
- Effects were maintained throughout the study
- The incidence of adverse events (AE) was similar among treatment groups and PBO

*Investigational therapy, currently not FDA-approved for the treatment of OIC.
Rauck et al. Abstract presented at: DDW 2012; May 19, 2012; San Diego, CA. Abstract 943a.

Naloxegol: Efficacy

- 2 identical, double-blind RCTs of placebo vs 12.5 mg vs 25 mg naloxegol in patients with OIC
- Primary endpoint – response rate at 12 weeks (≥3 SBM/week and increase from baseline of ≥1 SBM for ≥9 of 12 weeks and for ≥3 of final 4 weeks)



ITT=intention to treat; SBM=spontaneous bowel movements

Chey WD et al. *N Engl J Med*. 2014;370:2387-2396. (A)

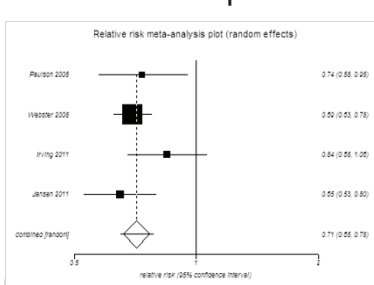
Naloxegol: Safety

Table 3. **Adverse Events.**

Adverse Event	Study 04			Study 05		
	Placebo (N=213)	Naloxegol, 12.5 mg (N=211)	Naloxegol, 25 mg (N=214)	Placebo (N=231)	Naloxegol, 12.5 mg (N=230)	Naloxegol, 25 mg (N=232)
	number of patients (percent)					
Abdominal pain	7 (3.3)	18 (8.5)	27 (12.6)	18 (7.8)	25 (10.9)	44 (19.0)
Diarrhea	9 (4.2)	7 (3.3)	20 (9.3)	10 (4.3)	18 (7.8)	21 (9.1)
Nausea	10 (4.7)	15 (7.1)	16 (7.5)	10 (4.3)	14 (6.1)	20 (8.6)
Flatulence	4 (1.9)	9 (4.3)	12 (5.6)	7 (3.0)	4 (1.7)	14 (6.0)
Upper abdominal pain	4 (1.9)	3 (1.4)	11 (5.1)	3 (1.3)	5 (2.2)	6 (2.6)
Vomiting	7 (3.3)	3 (1.4)	6 (2.8)	6 (2.6)	7 (3.0)	14 (6.0)
Headache	4 (1.9)	5 (2.4)	8 (3.7)	8 (3.5)	12 (5.2)	12 (5.2)
Back pain	5 (2.3)	0	7 (3.3)	4 (1.7)	12 (5.2)	12 (5.2)

Chey WD et al. *N Engl J Med*. 2014;370:2387-2396. (A)
Included with permission of Massachusetts Medical Society, from New England Journal of Medicine. Chey WD et al. 370:2387-2396, 2014; permission conveyed through Copyright Clearance Center, Inc.

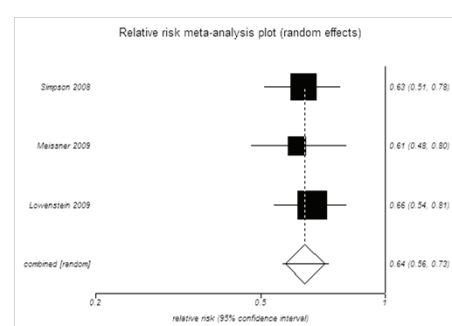
Alvimopan



**FDA approved 2008 for post-operative ileus but not approved for treating OIC

Included with permission of Nature Publishing Group, from *Am J Gastroenterol*, Ford AC et al, 108: 1566-1574; 2013; permission conveyed through Copyright Clearance Center, Inc.
**US FDA CDER. Alvimopan NDA 021775 Label 5/20/08.

Naloxone



Included with permission of Nature Publishing Group, from *Am J Gastroenterol*, Ford AC et al, 108: 1566-1574; 2013; permission conveyed through Copyright Clearance Center, Inc.

Number Needed to Treat: Currently Available Therapeutics

Therapeutic	NNT to prevent 1 patient w/OIC failing to respond to therapy
Methylnaltrexone	3-4
Alvimopan	5
Naloxone	4
Lubiprostone	15

NNT=number needed to treat

Adapted from: Brenner DM et al. Abstract presented at: DDW 2013; May 18-21; Orlando, FL. Abstract 1150. (A)

Clinical Trial Results for OIC Treatments

Drug	Study type	Study length (weeks)	Study cohort	Study endpoints	Specific outcomes	Reference
Lubiprostone	1. RCT	12	431	≥1 SBM improvement over baseline frequency and ≥3 SBMs/week for at least 9 weeks	27.1% versus 18.9% with p value < 0.030	Jamal et al. [2015]
	2. RCT	12	418	Δ from baseline in SBM no. at week 8 and overall	At 8 weeks, SBMs/week mean 3.3 versus 2.4 (plac), $p = 0.005$; overall mean, 2.2 versus 1.6 (plac) SBMs/week, $p = 0.004$	Cryer et al. [2014]
Oxycodone and naloxone (OXY PR)	1. RCT extended to open label for 52 weeks	12	278	Change in BFI at week 4 compared with baseline CSBM	40.9 BFI score at week 4 and 34.01 at week 12 compared with a baseline of 67.451% achieved CSBM in OXY PR compared with 28% in oxycodone only group at 4 weeks	Lowenstein et al. [2009]
	2. RCT	12	35	Δ from baseline in BFI during treatment	BFI score change of 23.3 compared with baseline of 61.3 ($p < 0.0002$)	Koopmans et al. [2014]
Methyl-naltrexone (MNTX)	1. RCT	4	460	Rescue-free BM (RFBM) within 4 h of first dose Time to BM within first 24 h PAC SYM	34.2% had RFBM with MNTX compared with 9.9% (plac) 46% had RFBM within 24 h with MNTX compared with 25.3% (plac)At 4 weeks, MNTX compared with placebo	Michna et al. [2011]
	2. RCT	4	460	Rectal symptoms Stool symptoms	−0.56 versus −0.30 ($p < 0.05$) −0.76 versus −0.43 ($p < 0.001$)	Ivey et al. [2011]
Naloxegol	1. RCT	4	207	Median Δ from baseline in SBMs/week after 4 weeks	25 mg naloxegol [3.0 versus 0.8 (plac), $p = 0.0022$] 50 mg naloxegol [3.5 versus 1.0 (plac), $p < 0.0001$]	Webster et al. [2013]
	2. RCT (two studies: 04 and 05)	12	641696	≥3 SBMs/week and increase of ≥1 SBM compared with baseline for ≥9 of 12 weeks3. Severity of straining3. Stool consistency	Response rates higher with 25 mg naloxegol Study 04: 44.4% versus 29.4% (plac), $p = 0.001$; study 05: 39.7% versus 29.3% (plac),$p = 0.02$Study 04: −0.73 ± 0.05; study 05: −0.80 ± 0.06 Study 04: 0.66 ± 0.07; study 05: 0.71 ± 0.07	Chey et al. [2014]

Table from: Nelson and Camilleri Ther Adv Chronic Dis. 2016 Mar; 7(2): 121–134

Potential Future Therapeutics[1]

Agent	Mechanism of Action	Phase Trials
Prucalopride	5-HT_4 agonist	Phase II
Axelopran (TD-1211)	Multivalent inhibitor of mu-opioid receptor	Phase II (+)
Linaclotide	Guanylate Cyclase C agonist	Phase II (+)
Naldemedine (S-297995)	Peripheral mu-opioid receptor antagonist	Phase III (+)

- No effects on analgesia identified throughout all trials

1. Ketwaroo GA et al. *Curr Gastroenterol Rep*. 2013;15:344.
2. Sloots CEJ et al. *Dig Dis Sci*. 2010;55:2912-2921. (A)

Summary

- OIC is a common and debilitating disorder
- Tolerance does not develop over time
- Initial therapy usually consists of fiber and laxatives though data is limited to support this recommendation
- Mu-opioid receptor antagonists have recently been approved and treat the underlying cause of constipation
- Lubiprostone has also been shown to improve OIC symptoms
- The role of other constipation therapies remains unclear

Clinical Considerations in IBS-M - is it a real entity or are mixed pts really just IBS-C or D?

Baha Moshiree, MD, MS-CI
Associate Professor
Director of Motility
University of Miami
Chester Cassel Endowed Chair in Gastroenterology

ANMS 11th Postgraduate Course on Gastrointestinal Motility & Neurogastroenterology in Clinical Practice

Patient Case

- 28 y/o with history of Campylobacter infection 1 year ago was diagnosed with IBS-D for first six months.
- Now she has alternating diarrhea and constipation with symptoms of abdominal pain and abnormal bowel habits once a week
- Complains of meal related nausea as well.
- Misses work often as she doesn't know whether to take loperamide for her diarrhea. This however causes constipation with no BM for a week if she doesn't take an OTC laxative.
- Has hard stools with straining once every 5 days (BSS 1) then 1 day of watery BM BSS 7 when episodes occur. She is very stressed she can't control the symptoms and is feeling helpless
- Tried a gluten-free die and lactose-free diet without relief

- Wants help in determining her diet and which probiotic to take

- Meds: Loperamide and PEG depending on when she has either diarrhea or constipation
- Prior testing: Colonoscopy and EGD with random bx and Duodenal Bx were negative for celiac dz
- EGD did show gastritis
- Thyroid testing and CBC are normal. No FH of IBD, colon malignancy or celiac disease
- Gastric emptying study was normal.

Defining and Characterizing IBS

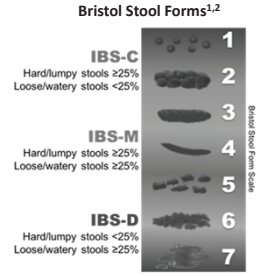
Rome IV Criteria for IBS[1]

Recurrent **abdominal pain or discomfort** on average at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

1. **Related** to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool.

Criteria should be fulfilled for the last 3 months with symptom onset ≥ 6 months prior to diagnosis

IBS Subtypes Based on Bristol Stool Forms[1,2]



IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrheal IBS-M, irritable bowel syndrome with mixed symptoms.
Lacy et al. Gastroenterology 2016 vol. 150, No. 6
O' Donnell LJD, et al. *BMJ.* 1990;300:439-440.

Rome IV

- Multidimensional Clinical Profile (MDCP)
- 5 categories
- Category A: Diagnosis w physiologic and symptom-based criteria
- Category B: Clinical modifiers included, subtype, post-infectious etc....
- Category C: Quality of life measures
- Category D: Psychosocial modifiers and medical conditions associated with IBS
- Category E: Motility parameters and biomarkers

Rome IV Diagnostic Questionnaire :
Sensitivity 62.7% (CI 57.8-67.6)
Specificity 97% (CI 96.6-97.6)
Whitehead et al. DDW Poster MO 1637

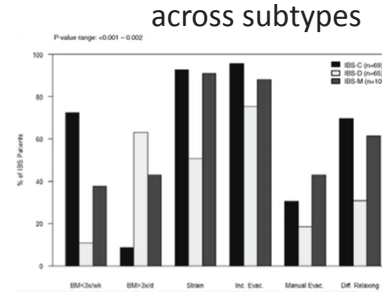
Lacy et al. Gastroenterology 2016 vol. 150, No. 6

IBS-M Definition

- More than 25% of stools with hard, lumpy stools , BSS 1 or 2 and more than 25% with BSS 6 or 7
- Keep stool diary for 14 days and be off all laxatives or anti-diarrheals.

- Diet should be on their typical diet during the 2 weeks
- Diary on typical patient diet may help to eliminate carbohydrate enzyme deficiencies

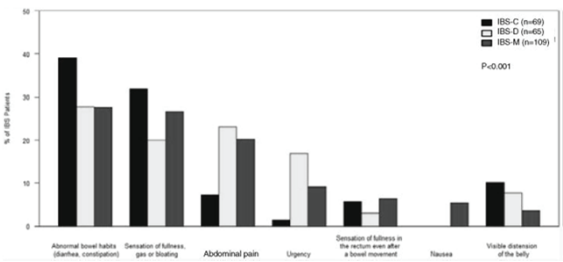
Prevalence of IBS-M and Frequency of bowel habit symptoms across subtypes



N=247 IBS pts
IBS-M (44.1%)
IBS-D (26.3%)
IBS-C (27.9%)
IBS-U (1.6%)=Unsubtyped

Su et al. Neurogastroenterol Motil (2014) 26, 36-45

Most bothersome symptom of each subtype



Su et al. Neurogastroenterol Motil (2014) 26, 36-45

Diagnostic Testing for Patients with Suspected IBS and No Concerning* Features

All IBS Subtypes[1]

CBC
Age-appropriate CRC screening

IBS-D[1,2]	IBS-M[1]	IBS-C[1]
• CRP or fecal calprotectin • IgA TtG ± quantitative IgA • When colonoscopy performed, obtain random biopsies • SeHCAT, fecal bile acids, or serum C_4 where available • Anti-CdtB/anti-vinculin antibodies??	• CRP or fecal calprotectin • IgA TtG ± quantitative IgA • Stool diary (14 days off all meds) • Consider abdominal plain film to assess for fecal loading	If severe or medically refractory, refer to specialist for physiologic testing such as anorectal manometry or transit study

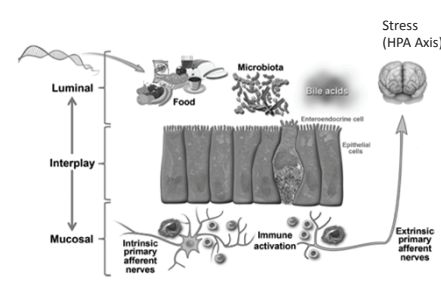
*__Alarm features__ include age ≥50 years old, blood in stools, nocturnal symptoms, unintentional weight loss, change in symptoms, recent antibiotic use, and family history of organic GI disease.
CBC, complete blood count; CRC, colorectal screening; CRP, C-reactive protein; SeHCAT, selenium homocholic acid taurine; Ttg, tissue transglutaminase.
1. Chey WD, et al. *JAMA*. 2015;313(9):949-958. 2. Pimentel M, et al. *PLoS ONE*. 2015;10(5):e0126438.

IBS-M tools for diagnosis

- Rule out mimickers of IBS (celiac disease, carbohydrate malabsorption and IBD)
- Use the ROME IV as a diagnosis of inclusion
- Clinical history should include a 14 day diet and stool diary using BSS
- Which bowel symptom dominates? Diarrhea or constipation?
- Anorectal exam to rule out pelvic floor dyssynergia
- KUB on days with worsened abdominal pain
- Anorectal manometry if more obstructive defecation history

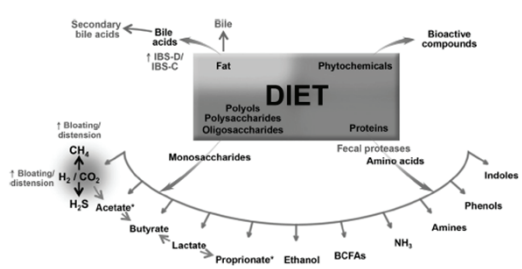
- Target treatment based on a combination of these possible factors:
  - Diet (food allergy, intolerance , carbohydrate malabsorption or gluten sensitivity)
  - SIBO, fecal or colonic microbiota and gut permeability?
  - Bile acid alteration?
  - Immune activation (mast cells or other inflammatory changes)?

IBS-M possible pathophysiologic mechanisms



Adapted from Barbara et al. Gastroenterology 2016: 150: 1305-1318.

Influence of Diet on IBS symptoms

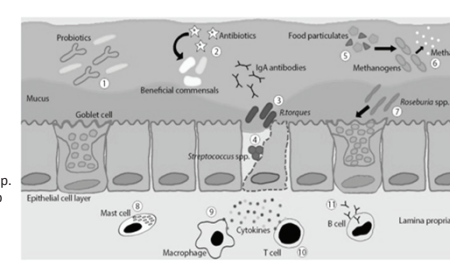


Barbara et al. Gastroenterology 2016: 150: 1305-1318.

+/- Effects of microbiota on gut barrier structure and function

R. Gnavus and R torques Mucin degraders

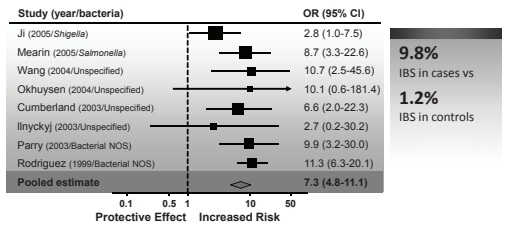
Bifidobacterium spp. & Lactobacillus spp Produce antiinflammatory metabolites



Streptococcus spp. Or Staph Aureus cause an immune response

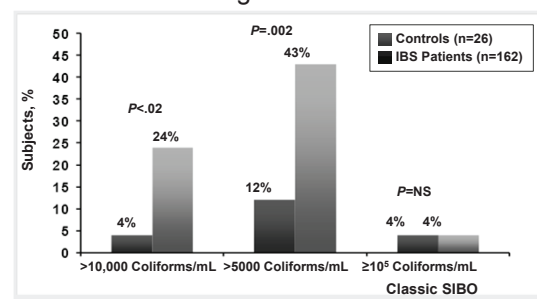
Vanner et al. Gastroenterology 2016 150, 1280-1291

Risk for PI-IBS Increases 7-fold After Infectious Gastroenteritis



OR, odds ratio; CI, confidence interval.
Data from systematic review of 8 studies involving 588,061 subjects; follow-up ranged from 3 to 12 months.
Halvorsen HA, et al. *Am J Gastroenterol.* 2006;101:1894-1899.

IBS patients have Increased Small Bowel Bacteria but this may not be Classic Small Bowel Bacterial Overgrowth



>10^3 CFU/ml threshold needed to diagnosed based on cultures
Rezaie et al. Presentation #450 DDW 2016

Posserud I et al. *Gut.* 2007;56:802-808.

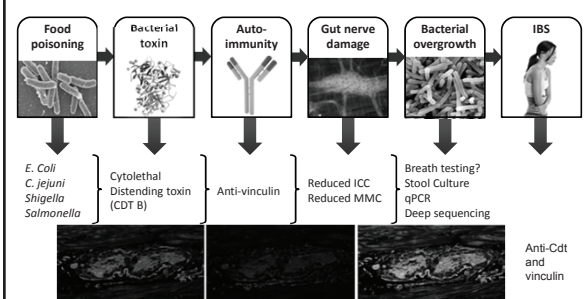
Scintigraphy Demonstrates High Rate of False-positive Results From Glucose Breath Tests for Small Bowel Bacterial Overgrowth

	All, +breath test (n = 46)	UGS, +breath test (n = 31)	NS, +breath test (n = 15)
SBBO reclassified with scintigraphy	24 (52%)	11 (35%)	13 (87%)
H+ only	19	10	9
M+ only	3	1	2
H+/M+	2	0	2
Colonic fermentation reclassified with scintigraphy	22 (48%)	20 (65%)	2 (13%)
H+ only	19	17	2
M+ only	1	1	0
H+/M+	2	2	0

- Colon fermentation caused false-positive results in 65% of patients who had undergone upper gastrointestinal surgery

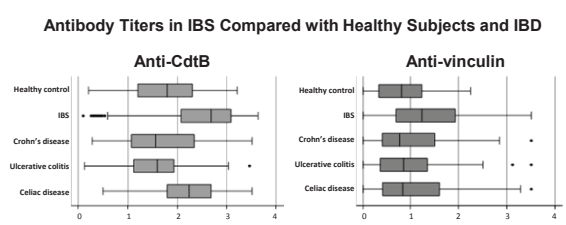
Lin et al. Clinical Gastroenterology and Hepatology 2016;14:203–208

Other Biomarkers for IBS?



Pimentel M, et al. *PLoS ONE.* 2015;10(5):e0126438. Pimental et al. Dig Dis Sci 2014

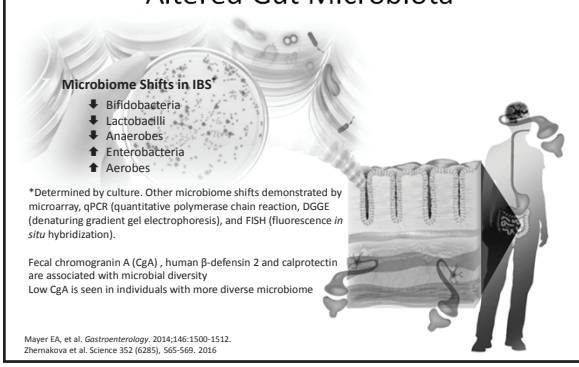
Potential Utility of Biomarkers for IBS-D and IBS-M



Optical Density	Specificity %	Sensitivity %
CdtB (cutoff ≥2.80)	91.6	43.7
Vinculin (cutoff ≥1.68)	83.8	32.6

P<0.001 for titers in IBS subjects vs other groups.
CdtB, cytolethal distending toxin.
Pimentel M, et al. *PLoS ONE.* 2015;10(5):e0126438
Rezaie et al. DDW 2016.

Patients with IBS Have Altered Gut Microbiota

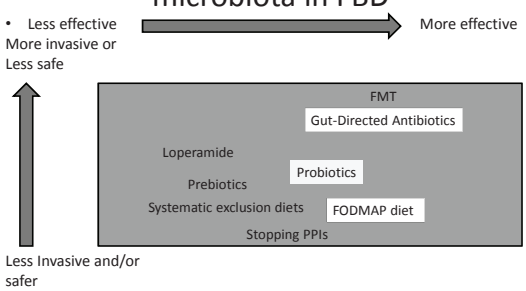


*Determined by culture. Other microbiome shifts demonstrated by microarray, qPCR (quantitative polymerase chain reaction, DGGE (denaturing gradient gel electrophoresis), and FISH (fluorescence *in situ* hybridization).

Fecal chromogranin A (CgA) , human β-defensin 2 and calprotectin are associated with microbial diversity
Low CgA is seen in individuals with more diverse microbiome

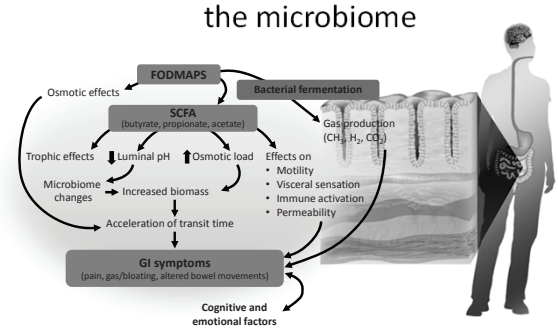
Mayer EA, et al. *Gastroenterology.* 2014;146:1500-1512.
Zhernakova et al. Science 352 (6285), 565-569. 2016

Therapeutic Strategies to modify gut microbiota in FBD



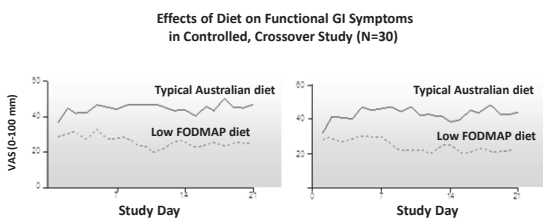
Adapted from Simrén et al. Gut 2013; 62: 159-176.

FODMAPS Influence gut transit and the microbiome



Spencer M, et al. *Curr Treat Options Gastroenterol.* 2011;12:424-440.

FODMAP Diet Reduces Functional GI Symptoms



FODMAP, fermentable oligo-di-monosaccharides and polyols.
Halmos EP et al. *Gastroenterology*. 2014;146:67-75.

Which probiotic supplement to use?

Single-Organism Probiotics:
- B infantis 35624
- B animalis DN-173010
- E coli Nissle 1917
- L Casei
- L Plantarum 299V
- L rhamnosus GG
- L salivarius UCC 4331
- Saccharomyces boulardii

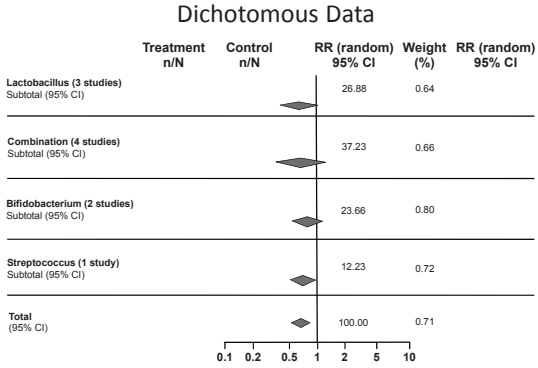
Multiple Organism Probiotics

VSL#3: (bifidobacteria, lactobacilli, Streptococcus salivarius thermophilus)

Lacteol Fort (L acidophilus LB, lactose monohydrate, calcium carbohydrate, silicic acid, talc, magnesium stearate, anhydrous lactose)

Several others: Kefir /other yogurts

Efficacy of Probiotics in IBS: Dichotomous Data



Moayyedi P et al. *Gut*. 2010;59:325-332.

Probiotics based on sub-type of IBS Specific Probiotics

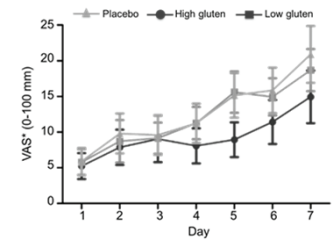
Probiotic (organism)	FBD	Significant improvements over placebo ($p < .05$)	Reference
Bifidobacterium lactis DN-173-010A	IBS-C	Bloating, abdominal girth, colon transit	Agrawal et al. 2009
B. infantis 35624 x 2 well designed studies	IBS	Composite score for abdominal pain, bloating and BM difficulty and without significant adverse events	Brenner et al. Am J Gastro 2009
VSL#3	IBS-D	Improves colon transit Bloating	Kim et al. Aliment Pharmacol Ther. 2003 Neurogastroenterol Motil. 2005
Lactobacillus acidophilus NCFM Bifidobacterium lactis Bi-07 (B-LBi07)	Non-Constipated IBS, FD, FB	Bloating	Ringel-Kulka T et al. J Clin Gastroenterol. 2011

Low FODMAP diet + probiotics (VSL#3)

- Low FODMAP diet compared with Sham diet (n=95)
- First placebo-controlled study w FODMAP diet.
- LFD resulted in lower IBS-SSS score as c/w Sham (P=0.001) and lower stool acetate (All subtypes)
- Lower abundance of Bifidobacteria was seen with LFD
- Probiotics resulted in higher stool abundance of Bifidobacteria but did not effect the IBS-SSS or HRQOL

Staudacher et al. DDW 2016

Is it Necessary to Eliminate Gluten as Part of the FODMAP Diet?



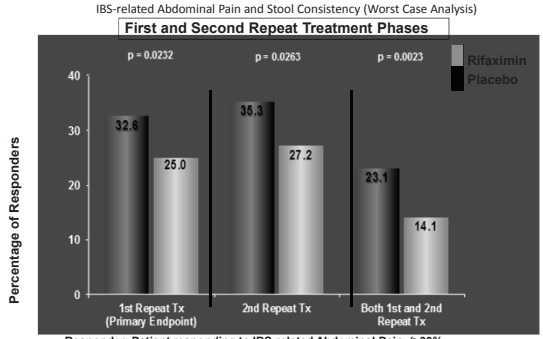
Change in symptom severity from run-in for each dietary treatment over 7-day study period. Data shown represent mean ± SEM. Differences across treatment arms were compared by Friedman test, in which overall symptoms (P=0.001) were statistically significant

SEM, standard error of the mean; VAS, visual analog scale.

Biesiekierski JR, et al. *Gastroenterology*. 2013;145:320-328.

Retreatment with Rifaximin in IBS-D

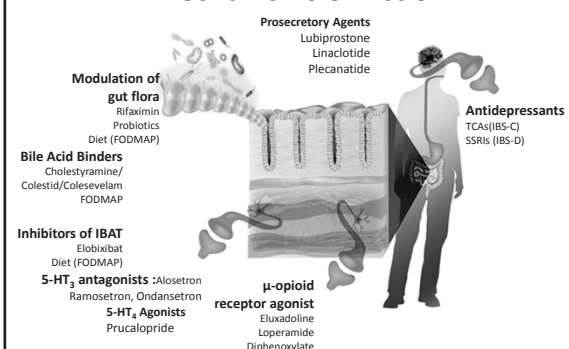
IBS-related Abdominal Pain and Stool Consistency (Worst Case Analysis)



Responder: Patient responding to IBS-related Abdominal Pain (≥30% improvement) and Stool consistency (≥50% decrease in # BMs with type 6 or 7) from baseline for ≥ 2 of the 4 weeks

Lacy BE et al. Abstract Mo1269. *Gastroenterology*. 2015;148(suppl 1):S657.

Overview of IBS Therapies: Mechanisms of Action



Efficacy of IBS-D Therapies which may be used in IBS-M

	Symptom Improvement				
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency
Antispasmodics[1]	±	+			
Loperamide[1]				+	+
Alosetron[1]	+	+	+	+	
Antidepressants[1]	+	+			
Probiotics[1]	+		+		
Newer Therapies					
Rifaximin[1]	+	+	+		+
Eluxadoline[2]	+	+		+	+
Peppermint oil[3]	+	+	+	-	–
Bile acid sequestrants[4]	+	–	–	+	+

1. Adapted from ACG Task Force on IBS. Ford AC, et al. *Am J Gastroenterol*. 2014;109(Suppl 1):S2-S26.
2. Lembo AJ et al. *N Engl J Med*. 2016;374:242-253.
3. Cash BD, et al. *Dig Dis Sci*. 2016;61:560-571.
4. Bajor A et al. *Gut*. 2015;64:84-92.

Summary of Demonstrated Efficacy of IBS-C Therapies which may be used in IBS-M

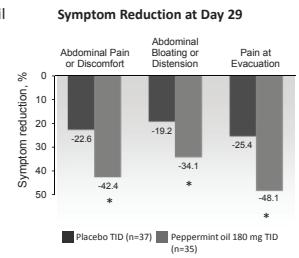
	Symptom Improvement				
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency
Fiber (psyllium)	+			+	+
Laxatives (PEG)				+	+
Lubiprostone	+	+	+		+
Linaclotide	+	+	+	+	+
Antidepressants	+	+			

PEG=polyethylene glycol.

Adapted from ACG Task Force on Functional Bowel Disorders. Ford AC et al. *Am J Gastroenterol*. 2014;109 (Suppl 1):S2-S26.

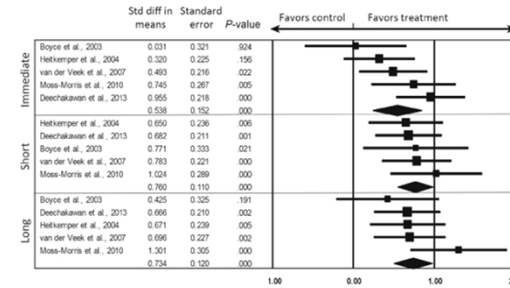
Triple-Coated Peppermint Oil for IBS

- RCT of triple-coated peppermint oil microspheres in IBS-M or IBS-D (N=72)
  - Randomized to peppermint oil 180 mg TID or placebo for 4 weeks
  - Primary analysis based on TISS
- Peppermint oil improved TISS (*P*<0.02) and frequency and intensity of individual IBS symptoms over 4 weeks
- Most frequent AEs with peppermint oil and placebo were dyspepsia and URT infection (2.9% vs 0% for each)



*P<0.05.
AEs, adverse events; TISS, Total IBS Symptom Score; URT, upper respiratory tract.
Cash BD, et al. *Dig Dis Sci*. 2016;61:560-571.

Short and Long-term efficacy of psychological therapies for IBS



Laird et al. Clinical Gastroenterology and Hepatology 2016; 14: 937-947.

Back to the patient case:

- KUB to check fecal loading
- Anorectal manometry with push maneuvers and balloon expulsion
- Treatment: probiotic, PEG and biofeedback
- FODMAP for short period with psychological support

Key Points: is IBS-M a real entity?

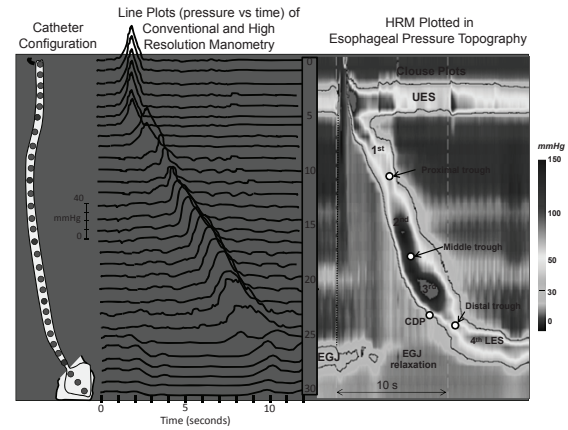
- IBS- M is a heterogeneous subgroup, the most common type of IBS subgroup and can be similar to both IBS-C and IBS-D.
- 1/3 of patients can be misclassified due to medication effects therefore all medications must be discontinued prior to subtyping
- IBS-M may be more similar to IBS-D
- A higher frequency of nausea and dyspepsia may be seen in the IBS-M subgroup
- As with D-IBS, altered intestinal and colonic microbiome and gut immune activation may be present in some IBS-M patients
- Food related symptoms are common in IBS-M and may lead to symptoms.
- Psychological therapies (cognitive, relaxation and hypnosis) are non-invasive and without side effects and may lead to both short and long-term benefits in improvement of bowel dysfunction and abdominal pain which are most commonly reported in IBS-M.
- Avoidance of medications is recommended since many patients (1/3) with IBS-M report worsening by medications started for bowel dysfunction.

Northwestern Medicine

Classification of Esophageal Motor Disorders: implications for diagnosis and treatment

"Sandhill University"
Denver, CO 2016

John E. Pandolfino, MD, MSCI
Professor of Medicine
Feinberg School of Medicine,
Northwestern University
Chief, Division of Gastroenterology and Hepatology
Northwestern Medicine
Northwestern Memorial Hospital

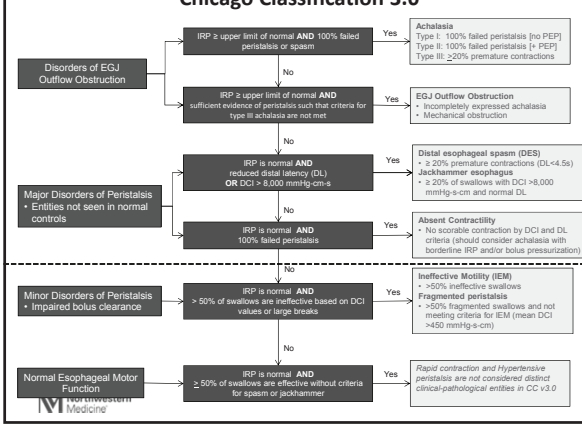


The Chicago Classification

Bridging conventional manometry and high-resolution manometry

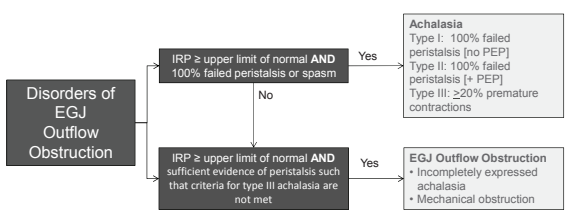
- The core of the Chicago Classification is the recognition of EPT patterns and new metrics based on EPT landmarks to better define clinically relevant phenotypes.
- Metrics
  - IRP
    - obstruction
  - Integrity
    - intact wavefront (fragmented)
  - Distal Contractile Integral
    - contractile vigor
  - Distal Latency
    - propagation and inhibition
  - Pressurization
    - type of obstruction

Chicago Classification 3.0



Pressure Topography of Esophageal Motility

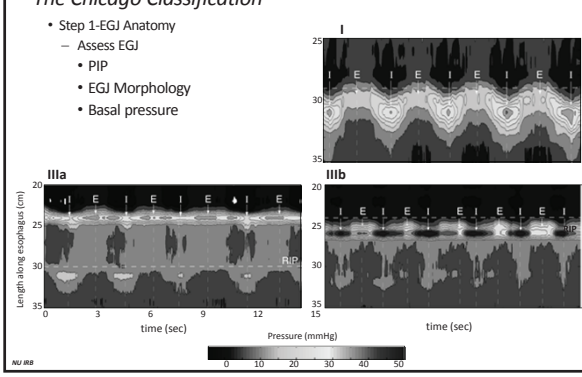
The Chicago classification



Pressure Topography of Esophageal Motility

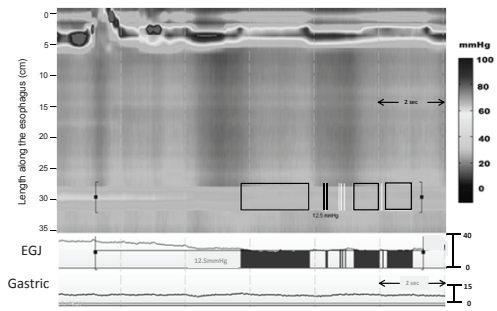
The Chicago Classification

- Step 1-EGJ Anatomy
  - Assess EGJ
    - PIP
    - EGJ Morphology
    - Basal pressure



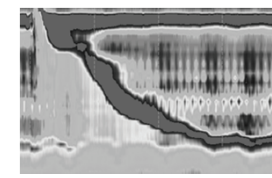
Integrated Relaxation Integral (IRP)

– **Type I should have a lower IRP threshold (> 10 mmHg) – Otherwise 15 is abnl**



Pressure Topography of Esophageal Motility
The Chicago classification

- Step 2-EGJ
  - EGJ Relaxation Pressure
    - IRP

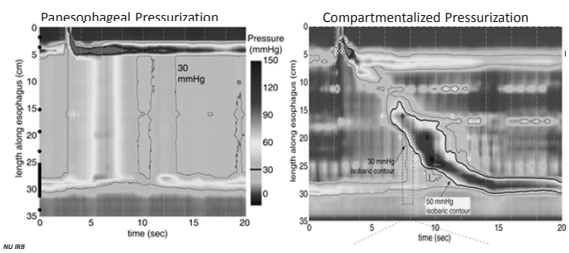


EGJ relaxation measure	Median [IQR] (mmHg)	95th percentile (high)
HRM nadir	3.6 [1.9 – 5.8]	≥ 10 mmHg
4s Integrated Relaxation Pressure	7.9 [6.4 – 10.0]	≥ 15 mmHg

NU IRB

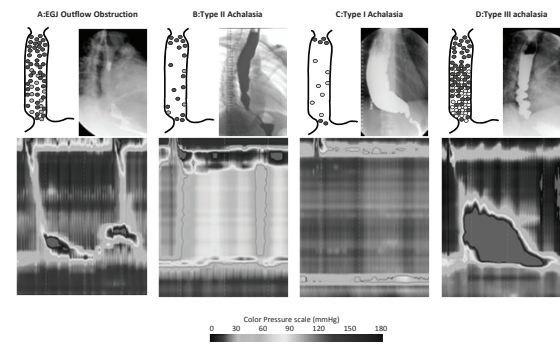
Pressure Topography of Esophageal Motility
The Chicago Classification

Assess Pressurization Pattern
- Using the IBC set at 30 mmHg
  -Panesophageal versus Compartmentalized

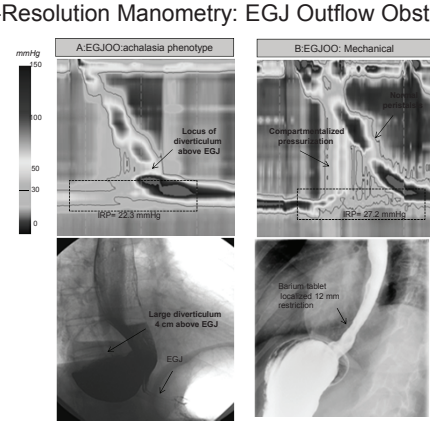


NU IRB

Esophageal Physiology: Neuromuscular Control
Concept of Inhibitory and Excitatory Balance



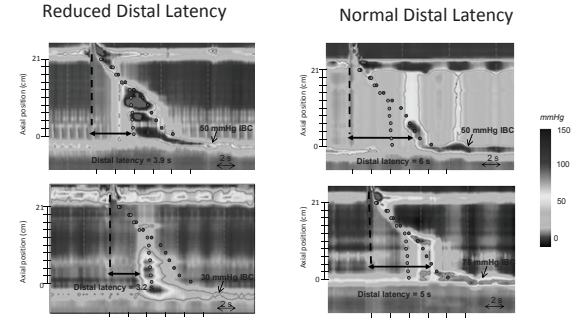
High-Resolution Manometry: EGJ Outflow Obstruction



Type III Achalasia: not all the same
Impaired EGJR, ≥20% spastic contractions

III: Premature contraction
Reduced Distal Latency

EGJ OO: Residual contraction
Normal Distal Latency



NU IRB

Pressure Topography of Esophageal Motility

The Chicago classification

Major Disorders of Peristalsis
• Entities not seen in normal controls

IRP is normal **AND** reduced distal latency (DL) **OR** DCI > 8,000 mmHg-cm-s — Yes

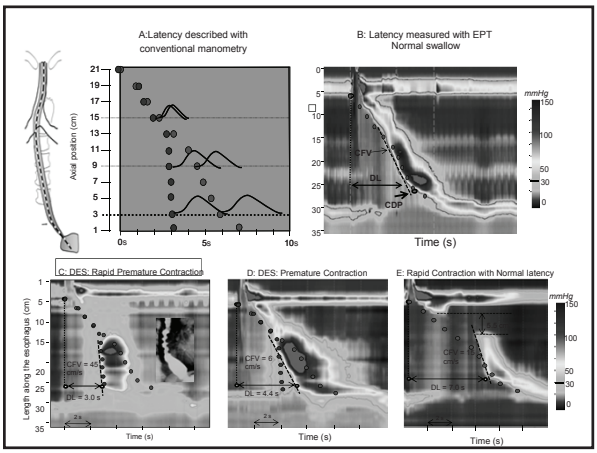
Distal esophageal spasm (DES)
• ≥ 20% premature contractions (DL<4.5s)
Jackhammer esophagus
• ≥ 20% of swallows with DCI >8,000 mmHg-s-cm and normal DL

No

IRP is normal **AND** 100% failed peristalsis — Yes

Absent Contractility
• No scorable contraction by DCI and DL criteria (should consider achalasia with borderline IRP and/or bolus pressurization)

Northwestern Medicine



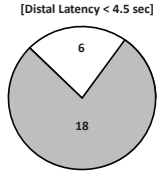
Distal Esophageal Spasm

Defining Relevant Phenotypes

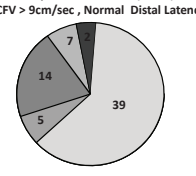
1070 consecutive patients with clinical EPT studies

91 Patients with rapid propagation

Premature Contractions (n=24)
[Distal Latency < 4.5 sec]



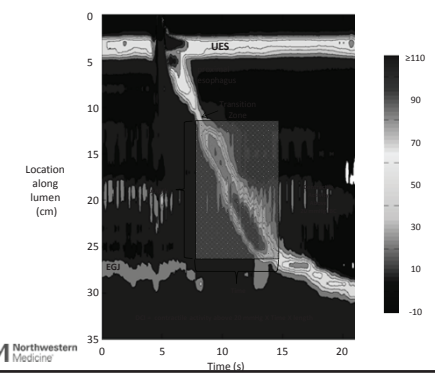
Rapid Contractions (n= 67)
[CFV > 9cm/sec , Normal Distal Latency]



Pandolfino JE, et al.Gastroenterology 2011

Pressure Topography of Esophageal Motility

Measure: Contraction pattern [DCI]

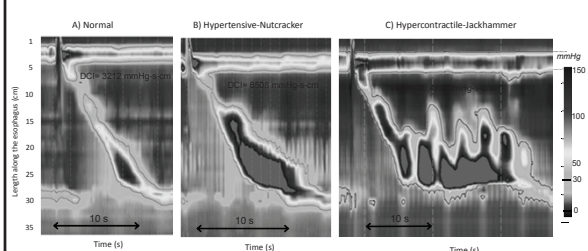


Northwestern Medicine

Nutcracker heterogeneity

Hypertensive-Hypercontractile Esophagus

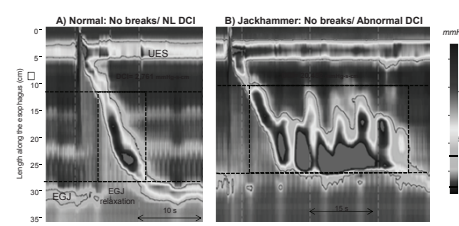
Based on DCI [mmHg•s•cm]



Northwestern Medicine

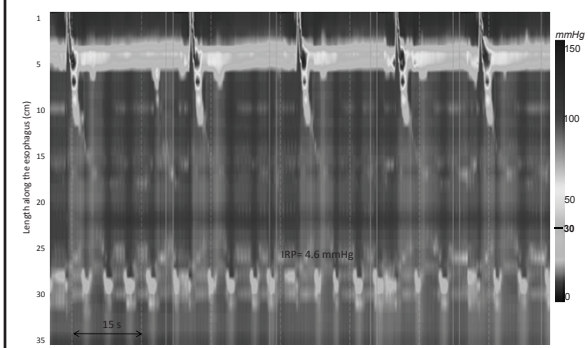
Esophageal pressure Topography

Hypercontractile/Jackhammer Esophagus



Absent peristalsis

Normal mean IRP, 100% of swallows with failed peristalsis



NU IRB

Pressure Topography of Esophageal Motility

The Chicago Classification 3.0

Minor Disorders of Peristalsis
• Impaired bolus clearance

→ IRP is normal **AND** > 50% of swallows are ineffective based on DCI values or large breaks

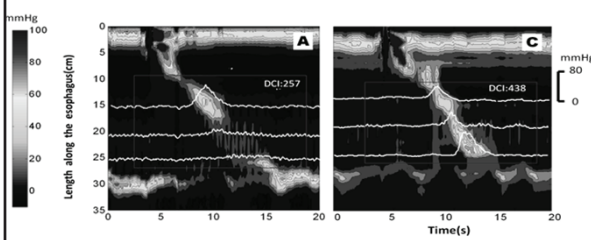
→ Yes →

Ineffective Motility (IEM)
• >50% ineffective swallows
Fragmented peristalsis
• >50% fragmented swallows and not meeting criteria for IEM (mean DCI >450 mmHg-s-cm)

Northwestern Medicine

Pressure Topography of Esophageal Motility

Not all weak swallows are the same

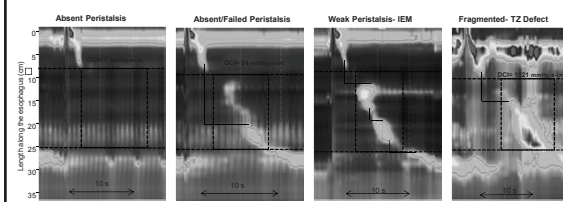


NU IRB Northwestern Medicine

Xaio et al. Am J Gastroenterol 2012 Aug 28. [Epub ahead of print]

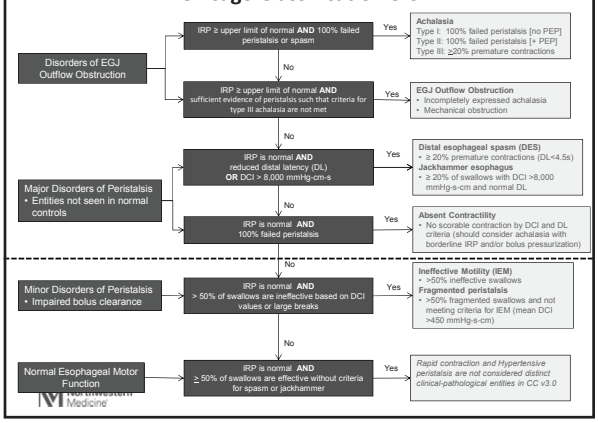
Pressure Topography of Esophageal Motility

Phenotypes of Ineffective Esophageal Motility



Northwestern Medicine

Chicago Classification 3.0



Delayed and Rapid Gastric Emptying:

Clinical and Management Implications

Henry P. Parkman, MD
Professor of Medicine
Temple University School of Medicine
Philadelphia, PA

Clinical Reasons for Obtaining a Gastric Emptying Study

Dyspeptic Symptoms
(nausea, vomiting, abdominal pain, early satiety, etc)
After excluding ulcer, obstruction

Severe Reflux Symptoms not Responding to PPIs

Identification of a pan-GI motility disorder
Patients with constipation

Evaluating a diabetic with poor glycemic control

?Evaluate response to Prokinetic Agent

Results of a Gastric Emptying Test

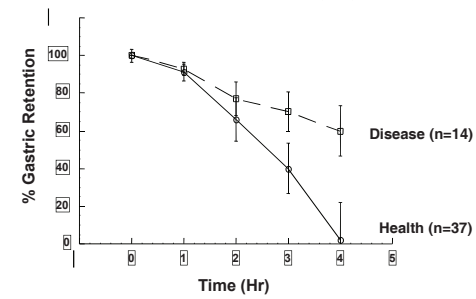
Normal Gastric Emptying

Delayed Gastric Emptying
- Gastroparesis
- Functional Dyspepsia
- Anorexia

Rapid Gastric Emptying
- Dumping Syndrome
- Post fundoplication
- Functional Dyspepsia
- Cyclic Vomiting Syndrome

Assessment of Gastric Emptying:

Percent Gastric Retention at 2, 3,or 4 hours?

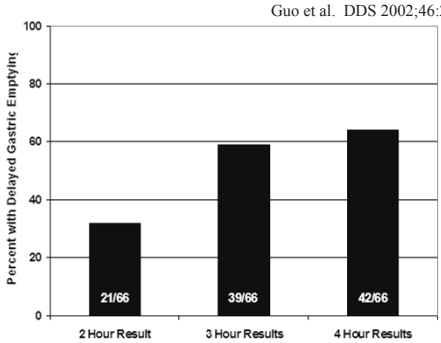


Camilleri et al. DDS 1991; 36,609-615.

Delayed Gastric Emptying in Functional Dyspepsia:

Improved Detection with 4 hour Gastric Emptying Test

Guo et al. DDS 2002;46:24-29.



Clinical Factors Suggesting Delayed Gastric Emptying in Patients with Functional Dyspepsia

Delayed gastric emptying detected in 33.5% of 343 patients with functional dyspepsia seen in referral center

Independent factors predicting delayed gastric emptying
- Female gender
- Postprandial fullness (moderate to severe)
- Vomiting (severe)

Stanghelleni, et al. Gastroenterology 1996;110:1036-1042

Correlating Symptoms to Delayed Gastric Emptying

At TUH, 1499 patients undergoing Gastric Emptying Scintigraphy from September 2007 to January 2010.

GES was performed with ingestion of a liquid egg white meal with imaging at 0, 0.5, 1, 2, 3, and 4 hours. Patients completed the Patient Assessment of Gastrointestinal Symptoms (PAGI-SYM).

629 of 1499 patients (42%) had increased retention at 4 hrs (>10%).

The symptoms correlating with gastric retention at 4 hours included

early satiety	r=0.170; p<0.01
vomiting	r=0.143; p<0.01
postprandial fullness	r=0.123; p<0.01
loss of appetite	r=0.122; p<0.01

Pathikonda, Sachdeva Maurer, Parkman . J Clinical Gastro 2012

Chronic unexplained nausea/vomiting but normal gastric emptying

425 patients with chronic nausea and vomiting, 319 (75%) delayed, 106 nl GES.

Similar symptom severity indexes for nausea, retching, vomiting, stomach fullness, early satiety, postprandial fullness, loss of appetite, bloating, visibly larger stomach.

Total GCSI scores were not correlated with gastric retention in either group.

Patients with normal gastric emptying were less likely to be diabetic.

No differences in health care utilization, quality of life, depression, trait anxiety scores. State anxiety scores were slightly higher among pts with delayed GE.

Patients with the syndrome were not adequately captured by Rome III diagnoses of chronic idiopathic nausea and functional vomiting.

CONCLUSIONS:

Patients with nausea and vomiting with normal gastric emptying represent a significant medical problem and are, for the most part, indistinguishable from those with gastroparesis.

Some Other Causes of Nausea /Vomiting

(These can be associated with delayed GE)

Disorder	Evaluation
Functional Dyspepsia	History, GES, Satiety Test
GERD	Esophageal pH, PPI Rx
Cyclic Vomiting Syndrome	History
Rumination Syndrome	Hx, Antroduodenal Manometry
Bulimia / Anorexia Nervosa	Hx, PE, ?Interview others
SMA Syndrome	UGI, CT

Contributions of Gastric Volumes and Gastric Emptying to Meal Size and Postmeal Symptoms in Functional Dyspepsia

39 patients with functional dyspepsia seen in tertiary referral practice

Gastric emptying:	**43% rapid initial GE at 1 hour (>29%)**
	41% delayed overall GE at 4 hours (<88%)
Satiety testing:	82% abnormal Maximal Tolerated Volume (<1244 ml)
Gastric volume:	?% lower fasting Gastric Volume (GV)
	56% reduced GV response to 300 ml Ensure (<449 ml)

Dyspepsia is a heterogeneous disorder with different, but additive, contributions of different gastric motor events which may provide therapeutic targets for treatment of functional dyspepsia.

Delgado-Aros, Camilleri, et al. Gastroenterology 2004;127:1685.

Cyclic Vomiting Syndrome (CVS) is Associated with Rapid Early Gastric Emptying

64 Adults with CVS; 50 met inclusion/exclusion criteria

62% (13/21) patients had accelerated GE at 1 hr
52% (11/21) patients had accelerated GE at 2 hr
19% (4/21) patients had accelerated GE at 4 hr

CVS is associated with a rapid early-phase gastric emptying.

Fajardo, Locke, Talley. ACG 2005

Gastroparesis: A chronic disorder

A motility disorder of the stomach characterized by delayed gastric emptying without evidence of obstruction.

Diagnosis
- nausea, vomiting
- early satiety
- postprandial fullness/bloating
- upper abdominal pain
- loss of appetite
- constipation

Clinical Burden of Gastroparesis is High

Nausea and Vomiting

- Nausea is present in nearly all patients (95%)
- Nausea and vomiting decrease quality of life.
- Vomiting is more prevalent and severe in DG than IG.
- Symptoms of nausea and vomiting are important symptoms that each need to be specifically addressed.

Parkman et al. NGM 2016

Abdominal pain

- Pain has largely been ignored in gastroparesis
- Pain is the predominant symptom in one fifth of gastroparetics.
- Moderate-severe abdominal pain is prevalent in gastroparesis (66%), impairs quality of life, and is associated with idiopathic etiology, but not gastric emptying.
- Pain has at least as great an impact on disease severity and quality of life as nausea/vomiting.

Hasler et al. *AJG* 2011;106:1492-502[13]

Etiologies of Gastroparesis

Diabetes
Postgastric surgery
Idiopathic

Other

Metabolic Disorders: Hypothyroidism
Medications: narcotics, anticholinergics
Rheumatologic: Scleroderma, SLE, RSD
Psychiatric: Eating disorders (anorexia, bulimia)
Generalized GI Motility Disorder:
Intestinal pseudo-obstruction
GERD

Treatment of Gastroparesis

General Items	Avoid medications that can delay stomach emptying Glucose control for diabetic patients
Diet	low fiber and roughage low in fat (fat increases CCK and delays GE) Liquid nutrients are better tolerated over solid food small meals, usually multiple 4-6/day Nutrition Consultation
Antiemetic Agents Reduce N/V	Compazine, Tigan (affect CNS vomiting center) Ondansetron, a 5-HT-3 receptor antagonist
Prokinetic Agents Speed gastric emptying	Metoclopramide, a dopamine receptor antagonist Erythromycin, a motilin receptor agonist Domperidone, a dopamine receptor antagonist

Commonly Used Prokinetic Agents

	Pros	Cons
Metoclopramide (Reglan)	Approved for gastroparesis Acts as prokinetic and antiemetic both may act for efficacy Available po, IV, SQ	Side Effects Acute/Chronic
Erythromycin	Potent gastrokinetic agent	Side Effects Acute/Chronic Tachyphylaxis (loss of effect)
Domperidone	Acts as prokinetic and antiemetic Less side effects than Reglan	Not approved in the USA Available with FDA IND

Metoclopramide to Treat Gastroparesis due to Diabetes Mellitus

Randomized, double-blind, controlled trial of metoclopramide in 10 patients with diabetic gastroparesis

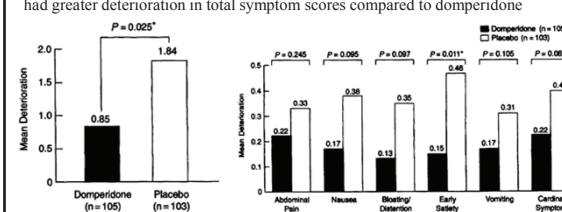
Metoclopramide increased gastric emptying
Overall symptoms and symptoms of vomiting were reduced during metoclopramide treatment.
Poor correlation between improved gastric emptying and decreased symptoms.

Metoclopramide improves symptoms of diabetic gastroparesis:
Peripheral effect of gastric smooth muscle to increase gastric emptying
Central effect on chemoreceptor vomiting zone to decrease nausea.

Snape, Battle, et al.
Ann Intern Med 1982;96:444

Domperidone in the Management of Symptoms of Diabetic Gastroparesis

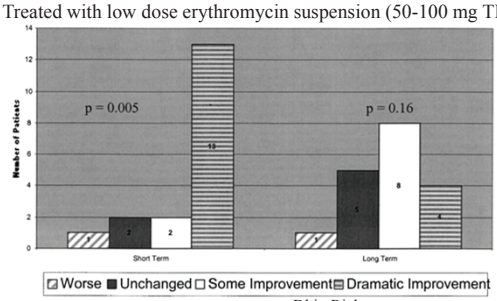
Single-Masked Study: 208/269 (77%) patients with diabetic gastroparesis improved on Domperidone 20 mg po QID
Randomized Placebo-Controlled, Double-Masked Withdrawal Phase: Placebo group had greater deterioration in total symptom scores compared to domperidone



Silvers, Kipnes, et al.
Clinical Therapeutics
1998;20:438

Erythromycin in the Short-Term and Long-Term Control of Dyspepsia Symptoms in Gastroparesis

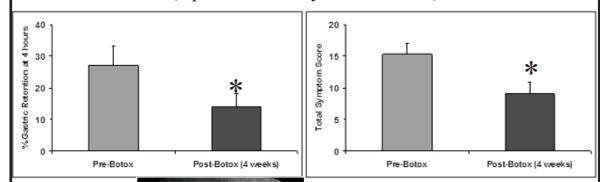
25 patients with gastroparesis
Treated with low dose erythromycin suspension (50-100 mg TID)

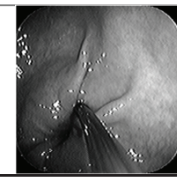


Dhir, Richter.
J Clinical Gastroenterology

Botulinum Toxin A Injection into the Pylorus for Treatment of Idiopathic Gastroparesis

(Open Label Study in 10 Patients)

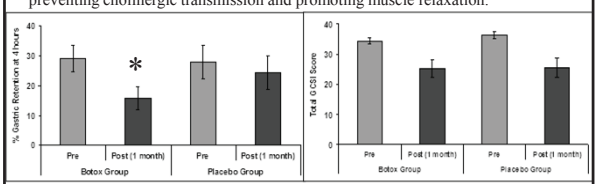


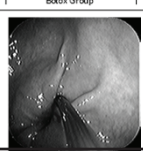


Miller, Parkman, Fisher et al.
Am J Gastro 2002;97:1653

Randomized, Placebo-Controlled Trial of Botulinum Toxin A for the Treatment of Gastroparesis

Botulinum toxin type A (Botox) binds to presynaptic acetylcholine terminals produces blockade at the level of the neuromuscular junction preventing cholinergic transmission and promoting muscle relaxation.





32 patients randomized to receive either Botox 200 units (n=16) or Saline 5 ml (n=16)

Friedenberg, Palit, Parkman, Nelson.
Am J Gastroenterology 2008

Outcomes in Gastroparesis using NIH GpR1

Patients with gastroparesis (diabetic or idiopathic) in GpR1 at the NIH Gp centers were seen every 4 months along with clinical care for their condition.

Only 28% of 262 patients symptomatically improved at 48 weeks with decrease GCSI ≥1.

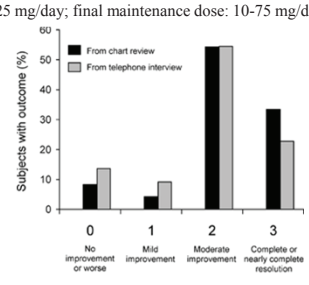
These results emphasize chronic nature of gastroparesis. The disease burden remains high.

	OR	p
Positive predictors		
age ≥ 50 years	3.35	0.001
GCSI score	2.87	0.001
antidepressant use	2.27	0.02
gastric retention > 20% at 4 hours	2.22	0.02
initial infectious prodrome	2.22	0.05
Negative predictors		
anxiolytics	0.28	0.02
pain modulator use	0.34	0.01
abdominal pain (moderate/severe)	0.40	0.04
overweight/obese	0.43	0.01
depression	0.45	0.03
smoking history	0.46	0.04
gastroesophageal reflex severity	0.66	0.01

Pasricha et al. Gastroenterology 2015

Tricyclic Antidepressants for Chronic Vomiting in Diabetic Patients

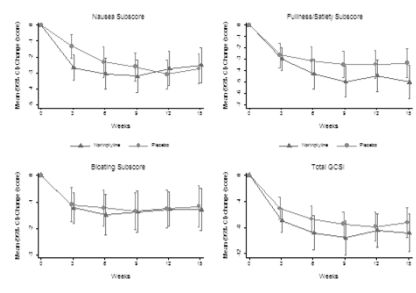
24 diabetic patients treated with tricyclic antidepressants for nausea and vomiting after an unsatisfactory response to prokinetic therapy.
TCAs: Amitriptyline, nortriptyline, desipramine.
Starting doses 10-25 mg/day; final maintenance dose: 10-75 mg/day.



Sawhney, Prakash Lustman, Clouse.
DDS 2007;52:418.

NORIG Trial: Main Outcomes

Nortriptyline did not improve overall symptoms, as defined by our primary outcome measure, in idiopathic gastroparesis over a 15 week period

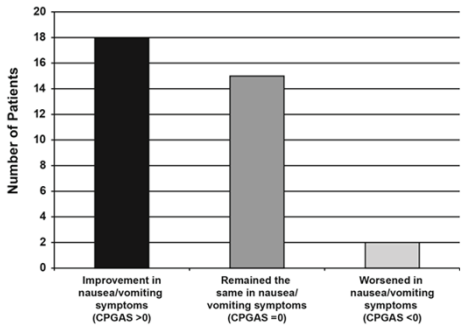


At 3 weeks:
Improvement in nausea and abdominal pain at nortriptyline (10 mg), but not sustained over time as dosing was increased.

At 15 weeks:
Higher doses of nortriptyline were associated with improvements in appetite, satiety, and body weight.

Parkman, et al. *JAMA* 2013

Granisetron (5-HT3 Receptor Antagonist) Transdermal System Improves Refractory Nausea and Vomiting in Gastroparesis



Simmons, Parkman DDS 2014

Continuous Glucose Monitoring (CGM) Plus Continuous Subcutaneous Insulin Infusion (CSII) Reduces Hypoglycemia in Diabetes (DM) with Gastroparesis (GP): A Multicenter Pilot Study (GLUMIT)

GLUMIT tested safety and efficacy of using CSII and CGM in 45 individuals with uncontrolled DM (A1c>8%) and GP (>10% 4 hr retention) (29% T1DM). CSII + CGM training was started prior to enrollment and continued throughout 24-week study. Patients were recommended to use dual wave boluses for meal boluses, adjust insulin dose based on sensor glucose trends and predictive alerts.

Diabetic Outcomes:
Baseline A1c levels (9.4±1.4 %) decreased by 1.1% at 24 weeks (P=0.0002 vs. baseline).

	Hypoglycemia (<70 mg/dl)	Euglycemia (71-180 mg/dl)	Hyperglycemia (>180)
Baseline:	3.9%	44.0%	52.1%
Follow-up:	1.7% (P<0.0001)	51.8% (p=0.004)	46.5% (p=0.04)

9 severe hypoglycemic events (third party assistance) occurred (2 during 2-8 week screening phase and 7 during 24 week treatment phase); 6 related to mismatches of insulin boluses/meal ingestion, 2 to insulin over-dosing, 1 no explanation.

Patients who had episodes of severe hypoglycemia had more severe GP at baseline, with nausea/vomiting scores 63.0% greater (p=0.002) and early satiety scores 18.2% greater (p=0.04) vs. those who did not have these episodes.

Summary: in DM patients with GP the CSII + CGM protocol for 6 months improved glycemic control with less time in hypoglycemia, more time in euglycemia and with an acceptable safety profile. Patients with more severe GP warrant more careful surveillance.

Pilot Study of the Safety, Feasibility, and Efficacy of Continuous Glucose Monitoring (CGM) and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG)

Diabetics with gastroparesis are advised to lower blood sugars to reduce symptoms. The potential of continuous glucose monitoring (CGM) coupled with intensive insulin regimens to safely reduce hyperglycemia and improve gastroparesis manifestations is unproved.

45 diabetics with gastroparesis, poorly controlled (A1c>8%) with gastroparesis (>10% 4 h retention); 29% type 1, 21±11 yr diabetes duration.

Gastroparesis Outcomes:	Baseline	Change at wk 12	Change at wk 24
Total GCSI score	29.3±7.1	-7.2±8.2 (p<0.001)	-6.6±8.8 (p<0.001)
Nausea/Vomiting subscore	8.1±4.2	-2.9±4.0 (p<0.001)	-2.8±4.1 (p<0.001)
Fullness/Early satiety	14.1±3.6	-3.1±4.5 (p<0.001)	-2.4±4.5 (p=0.002)
Bloating/Distention	7.1±2.3	-1.3±2.9 (p=0.001)	-1.5±2.5 (p=0.001)
Water load tolerance	430±207	0±243 (p=0.99)	-33±190 (p=0.31)
Liquid nutrient tolerance	420±258	15±117 (p=0.47)	59±176 (p=0.05)

Conclusions:
Symptom and nutrient tolerance benefits were maintained for the 24 week phase of intensive monitoring and therapy.
This uncontrolled pilot study shows the feasibility and potential for dual benefits improving both diabetes control and lowering gastroparesis symptom burdens.

Refractory Gastroparesis

Jejunostomy tube for feeding into small intestine
bypassing gastroparetic stomach
Gastrostomy tube for venting of stomach

Gastric electric stimulation
Gastric pacing vs high frequency stimulation
suppressing symptoms, particularly nausea, vomiting

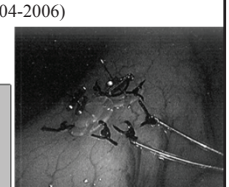
Pyloromyotomy/pyloroplasty

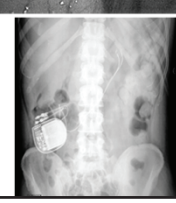
Central line for Total Parenteral Nutrition (PICC)
If long term, problems with infection, thrombosis

Gastrectomy (last resort)
near-total
completion, for post surgical gastroparesis

Clinical Improvement with Enterra Gastric Electric Stimulation Treatment for Refractory Gastroparesis
The Temple Experience (2004-2006)

Overall, 14 of 28 (50%) patients felt improved.
Nausea/vomiting subscore improved
Abdominal pain did not change.

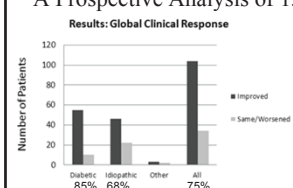


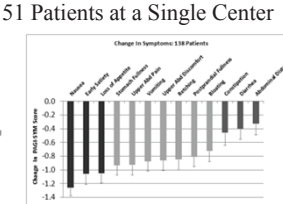


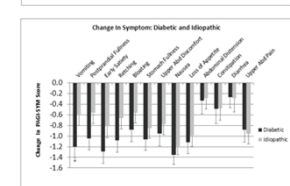
Three Predictive Factors:
Diabetic patients better than idiopathic
Chief complaint of nausea/vomiting
Not taking narcotic analgesics.

Maranki, et al. DDS 2008

Gastric Electric Stimulation for Refractory Gastroparesis: A Prospective Analysis of 151 Patients at a Single Center







Heckert, et al. DDS 2015

Effectiveness of Gastric Electrical Stimulation in Gastroparesis: Results from the Prospectively Collected Database of GpR

92 (14.5%) of patients had GES after GpR enrollment;

48-week data from these patients were compared to the remainder 542 (control group) who never had GES.

38% of patients with GES were diabetic and 54% idiopathic.

Patients with GES had more delayed gastric emptying at 4 hrs (30.9 vs 21.8) with worse GCSI scores (3.8 vs 3.0).

After 48 weeks, GCSI scores in patients with GES improved by average of 0.9 compared with 0.3 in controls ($p<0.001$) with 43.6% showing improvement of at least 1 point compared with 24.7% in controls ($p=0.004$).

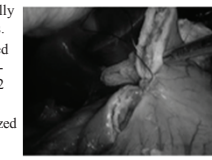
Conclusions: In this observational study in multiple practice settings, 15% of gastroparesis required GES therapy and were more likely to show clinically meaningful improvement at 48 weeks than those without GES Rx.

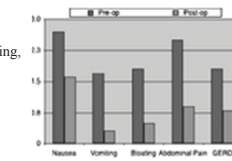
Abell et al. DDW 2015

Laparoscopic pyloroplasty for gastroparesis results in sustained symptom improvement

- Retrospective review of 28 patients underwent minimally invasive pyloroplasty as treatment for gastroparesis.
- Laparoscopic Heineke-Mikulicz pyloroplasty performed in 26 patients. Laparoscopic assisted, flexible trans-oral endoscopic circular stapled pyloroplasty used 2 patients.
- GES T1/2 decreased from 320 to 112 min and normalized in 71%.
- Improvements were seen at 1 month for nausea, vomiting, bloating, abdominal pain, and GER symptoms.
- Improvement persisted at 3 months for nausea, vomiting, bloating, abdominal pain and GERD symptoms.
- Prokinetic use was reduced from 89% to 14%.

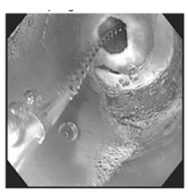
Minimally invasive pyloroplasty provides excellent outcomes for patients with gastroparesis. With technological advancements, a totally endoscopic pyloroplasty may be a less invasive option.

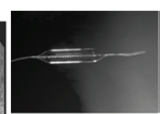




Hibbard ML., Dunst CM, Swanström LL. J Gastrointest Surg. 2011 Sep;15(9):1513

Assessing Pyloric Sphincter Pathophysiology using EndoFLIP in Patients with Gastroparesis





EndoFLIP is a novel technique that can be used to assess pyloric physiologic characteristics: pressure, diameter, length, cross sectional area, distensibility.

Early satiety and postprandial fullness were inversely correlated with diameter and cross-sectional area (CSA) of the pyloric sphincter.

No significant differences were seen comparing diabetic and idiopathic gastroparetics.

This technology may be of benefit to help select patients with pyloric sphincter abnormalities.

Malik, Sankinini et al. NGM 2015

Initiation of Enteral Nutrition
Surgical Jejunostomy

Severe weight loss
(weight loss > 10% of usual body weight over 6 months)

Repeated hospitalizations for refractory gastroparesis intravenous hydration and/or intravenous medication.

Better absorption of medications to gain therapeutic levels when vomiting prevents this.

Gastric decompression: Gastrostomy/jejunostomy tube(s).

On the Horizon for Gastroparesis

- FDA Guidance on Gastroparesis (7/2015)
- Diagnostic testing
  - Breath test for gastric emptying
- New prokinetic agents
  - Motilin receptor agonists
  - Ghrelin receptor agonists
  - 5-HT4 receptor agonists
  - Dopamine type 2 receptor antagonists
- Antiemetic agents
  - 5HT3 receptor antagonists
  - NK1 receptor antagonists
- Surgical treatments
  - Re-evaluation of gastric stimulation parameters
- Endoscopic treatments
  - Endoscopic pyloromyotomy
  - Endoscopically placed gastric electric stimulation

Dealing with Constipation & Dyssynergic Defecation

Satish SC Rao, MD, PhD, FRCP (Lon), FACG, AGAF
Professor of Medicine
Chief, Division of Gastroenterology/Hepatology
Director, Digestive Health Center
Medical College of Georgia
Augusta University, Augusta, GA

AUGUSTA UNIVERSITY

Disclosures

- Advisory Board:
  - Synergy Pharmaceuticals
  - Ironwood Pharmaceuticals
  - InTone MV
- Research Support
  - SunTrust Corporation
  - Forest/Ironwood Labs
  - Salix Pharmaceuticals
  - Synergy Pharmaceuticals
  - National Institutes of Health, NIDDK
  - Vibrant
  - InTone MV

Case Study 45-yr-old school nurse

- Increasing constipation –10 years
  - Began during college days following a bout of gastroenteritis
  - Now, B.M once a week, hard, pellet-like stool only after Fleet's enema + Suppository and laxatives
  - She describes excessive straining, often spending 20-30 min, & reports incomplete evacuation and intermittent vaginal splinting to complete BM
  - Tried OTC laxatives, MOM, PEG-no relief
  - Over past 3 years, she reports lower abdominal pain and distension sometimes better after BM, prescribed lortabs 1-2/day
  - She is also bloated and has excess gas

OBJECTIVES

- Discuss advances in Evaluation, Diagnostic Tests & Treatment:
  - Chronic Constipation
  - Dyssynergic Defecation
  - Opioid induced constipation
- Do they overlap, if so how to recognize & Treat

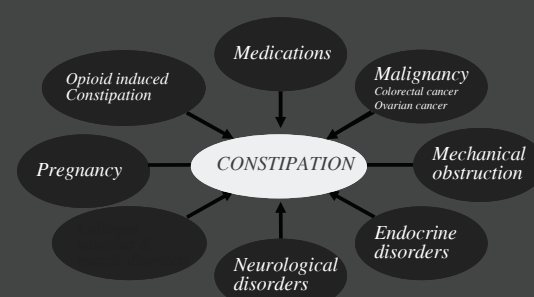
Types of Constipation

1. Occasional or Travellers constipation
2. Dietary causes- Fiber deficiency
3. Chronic Constipation
   - *Primary*
     - *Slow transit constipation*
     - *Dyssynergic Defecation*
     - *Pelvic floor disorders*
   - *Secondary*
   - *Opioid induced constipation*

Rao ssc et al Nature Revs 2016; Rao SSC. Gastroenterol Clin N Am 36 (2007) 687-711

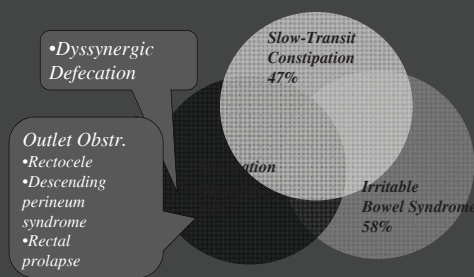
Bharucha et al, Gastroenterology 2006;130:1514

Secondary Causes of Constipation



Bytzer ML. Prim Care. 2001;28:577.
Schuffler MD. In: Sleisenger and Fordtran's Gastrointestinal and Liver Disease. 7th ed. 2002:2140.

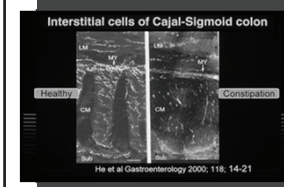
Functional Subtypes:Primary Constipation



Slow transit and IBS-C overlap in half of each group

Schiller LR. Aliment Pharmacol Ther. 2001;15:749.
Mertz H, et al. Am J Gastroenterol. 1999;94:609.

Pathophysiology-Slow Transit Constipation



Methane & STC
- *About 1/3rd of population produces CH_4*
- *Predominant organism is Methanobrevibacter smithii*
- *Increased prevalence in STC*
- *A genetic finger print*

-Rao S & Pimentel et al Am J Gastro 2012

Altered Intestinal Microbiota

Women & Constipation
- *Down-regulation of contractile proteins & Up-regulation of inhibitory G proteins caused by overexpression of progesterone receptors*

- Xiao et al Gastro 2005;128:667

Colonic Manometry
- *Absence of HAPC*
- *Loss of Gastrocolonic/Waking response*
- *Altered PRMA*
- *Sensory changes/Reflexes*

Pathophysiology-Dyssynergic Defecation

- **Impaired Rectoanal coordination**
  - **Paradoxical anal/puborectalis contraction**
  - **Inadequate rectal contraction/pushing force**
  - **Absent/Inadequate anal/puborectalis relaxation**
- **Impaired Rectoanal sensation**

Rao et al. Am J Gastroenterol 1997;92:469-75

- **Learnt = 67%**
- **Yet to Learn = 33%**

Rao et al, Gastro Clin N Am 2008

Chronic Constipation:ROME III Criteria

- **Chronic constipation must include 2 or more of the following:**
  - **Straining**
  - **Lumpy or hard stools**
  - **Sensation of incomplete evacuation**
  - **Sensation of anorectal obstruction/blockage**
  - **Manual maneuvers (eg, digital evacuation, support of the pelvic floor)**
  - **<3 defecations per week**

>25% of defecations

**Criteria fulfilled for at least 3 months with symptom onset at least 6 months prior to diagnosis*

- **Loose stools are rarely present without the use of laxatives**
- **There are insufficient criteria for irritable bowel syndrome (IBS)**

Longstreth GF, et al. Gastroenterology. 2006;130:1480.

Diagnostic Criteria-Dyssynergic Defecation

1. **The patient must satisfy diagnostic criteria for functional constipation-Rome III**
2. **During repeated attempts to defecate must demonstrate Dyssynergic pattern of defecation**
   - **Manometry**
   - **EMG**
3. **Patient must demonstrate one other abnormal test:**
   - **a. Abnormal balloon expulsion Test (> 1 minute)**
   - **b. Prolonged Colonic Transit Time (radioopaque markers or SmartPill or Scintigraphy)**
   - **c. Abnormal Defecography (≥50% barium retention)**

Rao SSC. Gastroenterol Clin N Am 36 (2007) 687-711

Bharucha et al, Gastroenterology 2006;130:1514

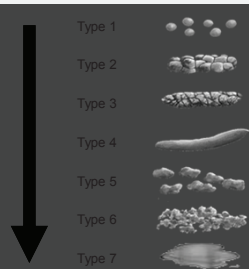
Constipation & Dyssynergia

History

- **Onset**
- **Diet**
- **Drugs**
- **Ignore call to stool**
- **Abdominal Pain & Discomfort**
- **Digital maneuvers**
- **Psychological and effects on QOL**
- **Sexual abuse / Emotional factors**
- **Injury = Obstetric / Surgery / Back**
- **Gastroenteritis**

Stool Form Correlates with Intestinal Transit Time

THE BRISTOL STOOL FORM SCALE

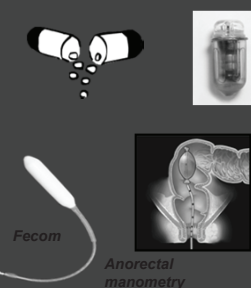


Type 1	Separate hard lumps
Type 2	Sausage-like but lumpy
Type 3	Sausage-like but with cracks in the surface
Type 4	Smooth and soft
Type 5	Soft blobs with clear-cut edges
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces

Lewis SJ, et al. Scand J Gastroenterol. 1997;32:920.
Heaton KW, et al. J Clin Gastroenterol. 1994;19:28.

Tools for Evaluation

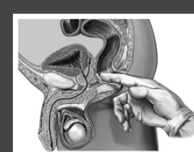
- History
- Stool diary
- Digital Rectal Exam
- Colonoscopy (particularly if aged > 50 years)
- Colonic transit study
  - radiopaque markers,
  - Scintigraphy
  - Wireless pH/Motility (SmartPill)
- Balloon expulsion test
- Defecography/MRI defecography
- Anorectal manometry
- Colonic manometry



Rao SSC, et al. Am J Gastroenterol. 2005;100:1605.

Yield of rectal exam in dyssynergia, n=209

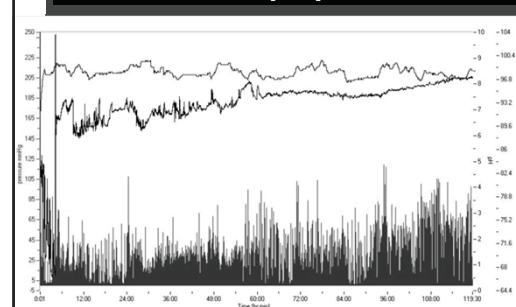
- All patients had
  - DRE
  - Anorectal manometry
  - Balloon Expulsion Test
- Data Analyzed independently

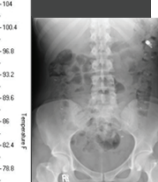


Parameter	Sensitivity (%)	Specificity (%)
Dyssynergia from DRE	75%	87%
Balloon expulsion test	49%	90%

Tantiphlachiva K, Rao S et al, CGH 2010

38 yr old Nurse, Severe Constipation, pain, gas & bloating, WMC & Radioopaque marker test

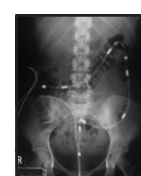




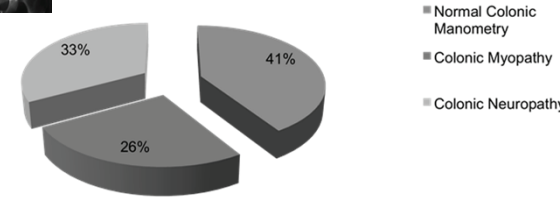
New Diagnostic Information with WMC

	Lower GI n = 50	Upper GI n = 36	Combined Group n = 86
Prolonged Gastric Emptying Time	14/50 (28%)		23/86 (27%)
Rapid Gastric Emptying Time	2/50 (4%)		5/86 (6%)
Prolonged Small Bowel Transit	7/50 (14%)		10/86 (12%)
Prolonged Colonic Transit Time	3/50 (6%)		9/86 (11%)

Rao, Mysore, Attaluri, Valestin J Clin Gastr 2011



Colonic Manometry in Slow-Transit Constipation, n=84



Singh S, Rao S et al, Neurogastro Mot 2013

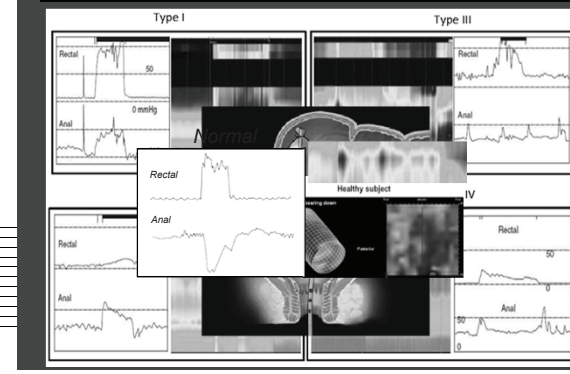
Can Symptoms Predict Dyssynergia?

100 Patients With Difficult Defecation

Symptom prevalence	Normal pattern (n = 30)	Type I (n = 32)	Type II (n = 24)	Type III (n = 14)
Excessive straining	92%	96%	89%	83%
Abdominal fullness	80%	96%	89%	67%
Incomplete evacuation	72%	96%	89%	100%
Abdominal discomfort	88%	81%	74%	75%
Digital maneuvers to defecate	28%	56%	47%	50%

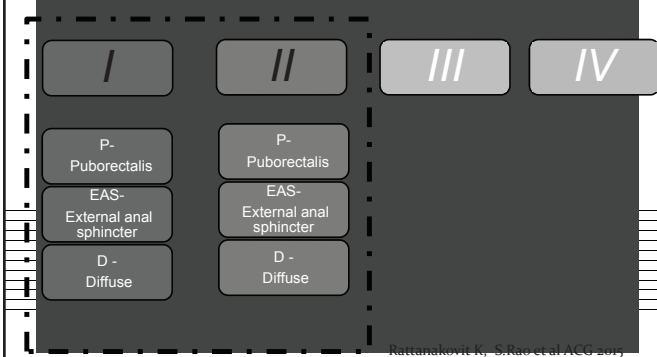
Rao SSC, et al. *Neurogastroenterol Motil.* 2004;16:589.

Types of Dyssynergic Defecation



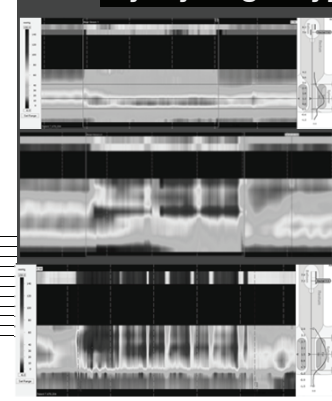
Rao et al, Neurogastroenterol Motil 2004; 16: 589

Dyssynergic patterns:



Rattanakovit K, S.Rao et al ACG 2015

Dyssynergia Type 1- Subtypes



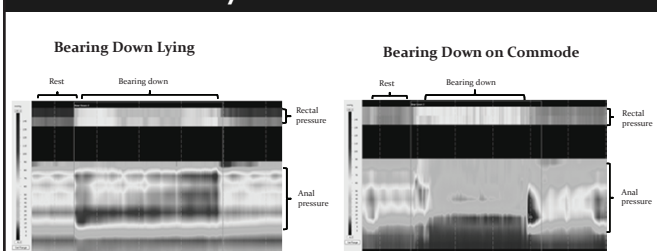
Type I- EAS

Type I-Puborectalis

Type 1-Diffuse

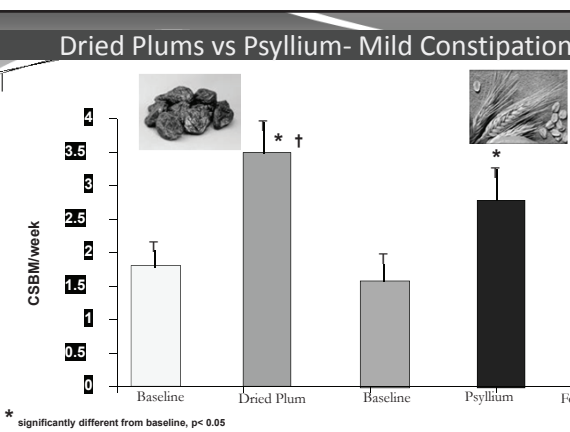
Rattanakovit K, S.Rao et al ACG 2015

Effect of Body Position on Defecation Patterns



Courtesy of S.Rao

Dried Plums vs Psyllium- Mild Constipation

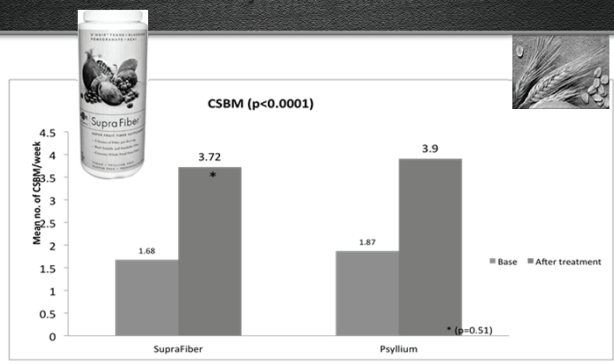


* significantly different from baseline, p< 0.05

† significantly different from psyllium, p< 0.04

Attaluri A, Rao S et al APT 2011

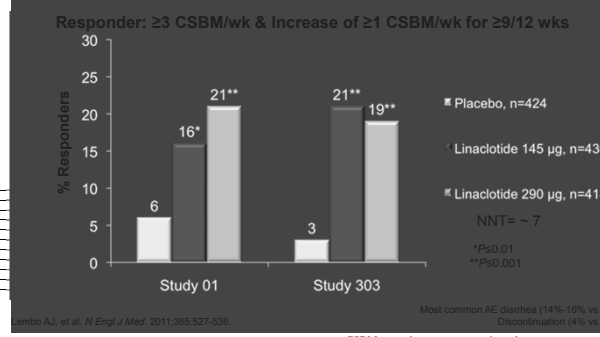
Supratiber vs Psyllium: effects on CSBM/wk



Erdogan A, Rao S et al APT 2016

25

Efficacy of Linaclotide in Chronic Constipation

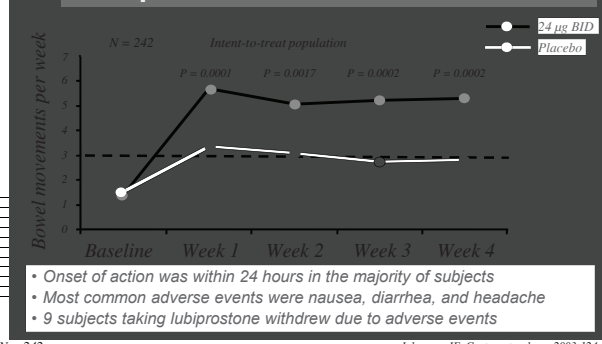


Most common AE diarrhea (14%-16% vs 4.7%); Discontinuation (4% vs 0.5%).

Lembo AJ, et al. *N Engl J Med*. 2011;365:527-536.

CSBM=complete spontaneous bowel movement.

Effects of Lubiprostone on Number of Spontaneous Bowel Movements



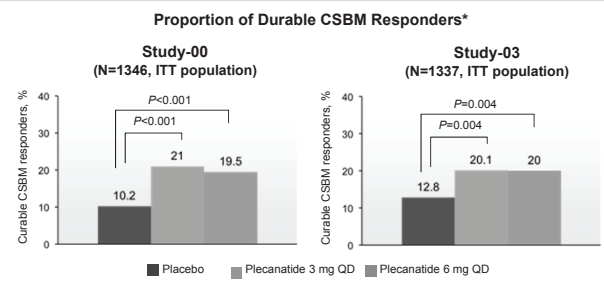
- *Onset of action was within 24 hours in the majority of subjects*
- *Most common adverse events were nausea, diarrhea, and headache*
- *9 subjects taking lubiprostone withdrew due to adverse events*

N = 242

Johanson JF. Gastroenterology. 2003;124:A48.
Johanssen et al Am J Gastroenterol 2008;103:170-7.

Efficacy of Plecanatide in CIC

Proportion of Durable CSBM Responders*

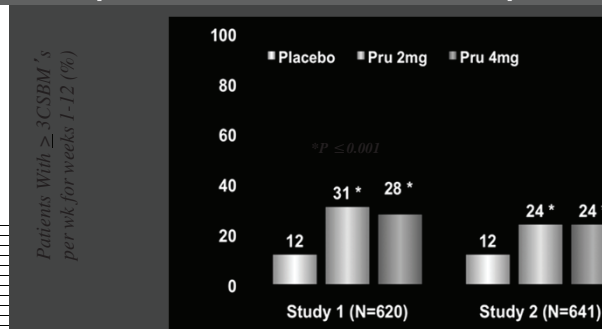


*Defined as weekly responders for at least 9 of 12 treatment weeks, for at least 3 of the last 4 weeks. Weekly responders had ≥3 CSBMs and an increase of ≥1 CSBM from baseline.

Miner PB et al. Presented at DDW 2016. Presentations Sa1440 and Su1214.

28

Prucalopride -Severe Chronic Constipation



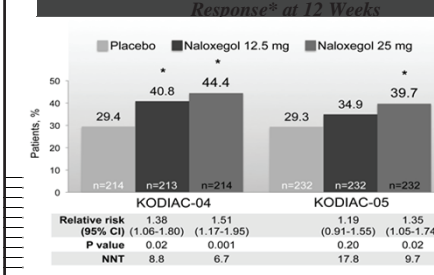
Entrance criteria: ≤ 2 CSBMs / wk

Camilleri et al. NEJM. 2008;358:2344-54

Quigley et al. Aliment Pharmacol Ther 2009;29:315-28

Naloxegol Improves OIC in Patients With Noncancer Pain: Phase 3 Trials

Response at 12 Weeks*



	KODIAC-04		KODIAC-05	
Relative risk (95% CI)	1.38 (1.06-1.80)	1.51 (1.17-1.95)	1.19 (0.91-1.55)	1.35 (1.05-1.74)
P value	0.02	0.001	0.20	0.02
NNT	8.8	6.7	17.8	9.7

*P<0.05 vs placebo

Primary End Point =

>3 SBMs/wk
+
>1SBM/wk over baseline for >9/12 wks
+
>3 SBM during last 4 wks of treatment

Chey WD, et al. N Engl J Med. 2014;370:2387-2396.

Biofeedback-Dyssynergia

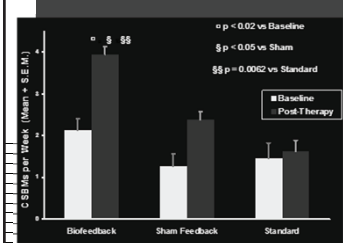
» *Goals of Therapy :*

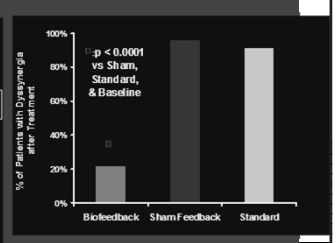
- *A) Teach Diaphragmatic breathing exercise*
- *B) Teach anal sphincter & pelvic floor relaxation*
- *C) Improve Rectal Sensation*
- *D) Eliminate Sensory Delay*
- *E) Improve Recto-anal Coordination*

Biofeedback Therapy-RCTs

- **Biofeedback Vs PEG 14.6 g for Dyssynergia**
  - *Chiarioni et al, Gastroenterology 2006; 130: 657-64*
- **Biofeedback vs Diazepam for Dyssynergia**
  - Heymen et al, Dis Col Rectum 2007
- **Biofeedback vs Sham Therapy vs Standard Therapy**
  - *Rao et al CGH 2007*
- **Biofeedback vs Standard Therapy-One Year outcome**
  - *Rao et al Am J Gastroenterol 2010*
- ***Home vs Office Biofeedback Therapy-Efficacy & Cost Effectiveness***
  - *Rao et al, Go et al, DDW 2011*

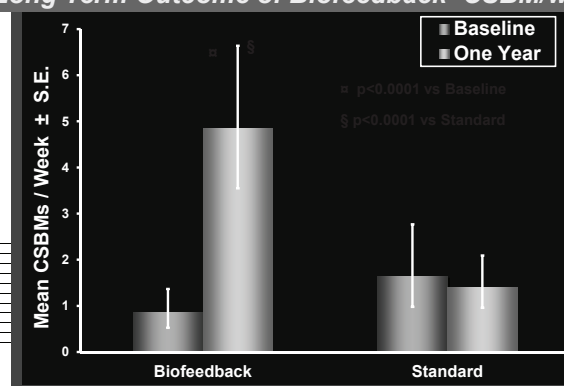
Effects of Biofeedback Therapy on CSBM & Dyssynergia- ITT Analysis





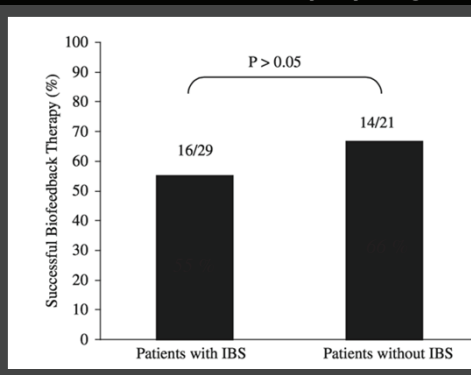
Rao et al Clin Gastro Hepatol 2007

Long Term Outcome of Biofeedback- CSBM/week



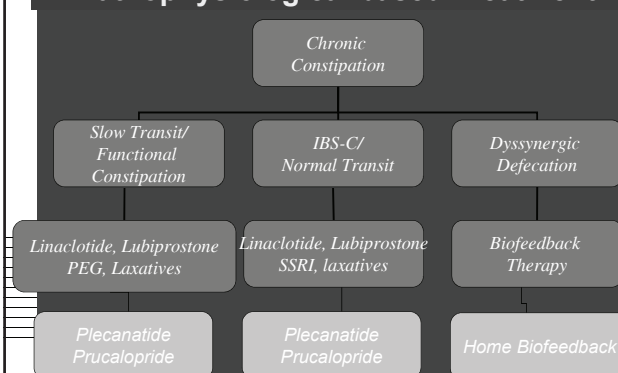
Rao et al Am J Gastro 2010

How useful is biofeedback in Dyssynergia + IBS



Patcharatrakul T, Gonlachanvit S. J Clin Gastro 2011;45:593-8

Pathophysiological based Treatment



Rao et al, Gastro Clin N Am 2009; Singh S, Rao et al, Gastro Clin N Am 2010

Take Home Points

- Chronic constipation involves multiple overlapping subtypes
- Detailed History, Physical & DRE important
- DRE is a useful bedside clinical tool
- Dyssynergic defecation is common
- Colonic Transit, ARM, defecography, Colonic manometry are complementary & helpful
- Therapeutic options will depend on a clear understanding of pathophysiology
- Linaclotide, lubiprostone, naloxegol, PEG & Biofeedback therapy are mainstay

AMS Postgraduate Course August 25, 2016

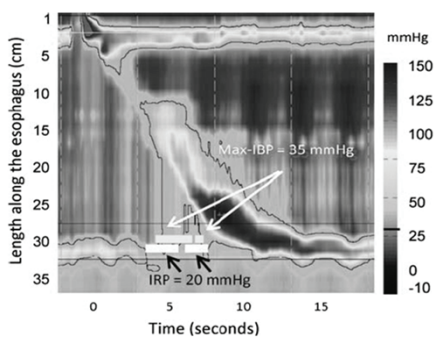
Treatment of Esophageal Hyper-and Hypomotility Disorders

Joel E Richter MD, FACP, MACG
Professor and Director
Division of Digestive Diseases and Nutrition
Joy McCann Culverhouse Center for Diseases of the Esophagus
University of South Florida Morsani College of Medicine
Tampa, Florida

Topics to Discuss

- Medical, endoscopic and surgical management
- Hyper and hypomotility disorders:
  --EGJ outflow obstruction
  --Spastic motility disorders
  --Ineffective esophageal peristalsis
  --Scleroderma esophagus
- Case studies

Esophagogastric Junction Outflow Obstruction

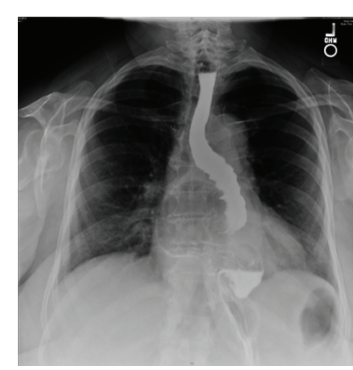


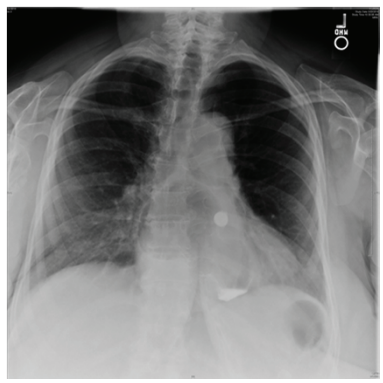
Two Types of EGJOO

- 49 patients with EGJOO-3.4% motility disorders
- Two types:
  --Anatomic (22 patients)
    Esophageal strictures (8)
    Large hiatal hernia (7)
    Eosinophilic esophagitis
    Tight fundoplication or slipped lap band
    Large esophageal varices
    Esophageal cancer
  --Functional (27 patients)
- Neither symptoms, HRM values or timed barium swallow helped to distinguish these 2 groups

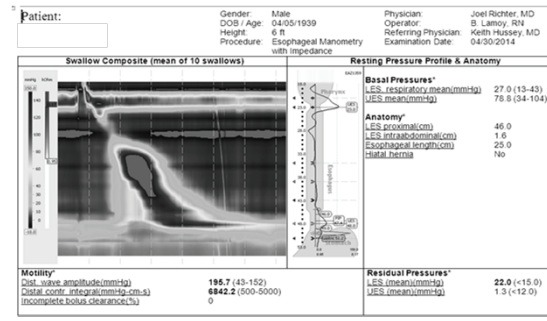
Clayton SB et al Clinical GI and Hepatology 2016

Mechanical EGJ Outlet Obstruction



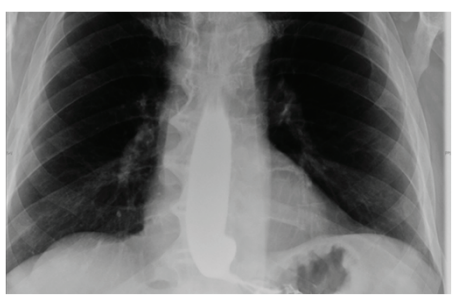


Functional EGJ Outflow Obstruction



Type IV Achalasia

Timed Barium Swallow—1 Minute

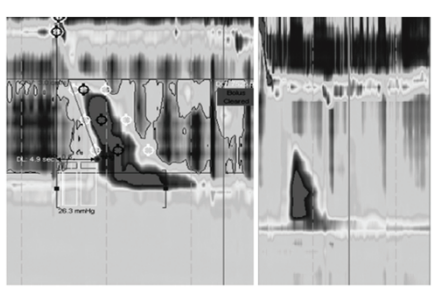


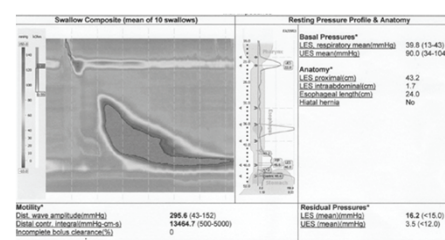
Treatment of EGJOO

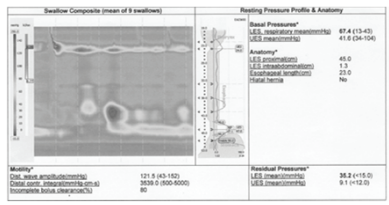
- Treat underlying anatomic problem if correctable
- Botox injections
  - 10 treated with 100 units to EGJ—2 relapsed
    - 2 initially tx with Botox evolved to type 3 achalasia
- Pneumatic dilation
  - 8 now treated with PD-30 mm
  - 2 relapsed requiring dilation with 35 mm balloon
  - No progression to type 3 achalasia
- Heller myotomy or POEMs

Clayton SB et al Clinical GI and Hepatology 2016

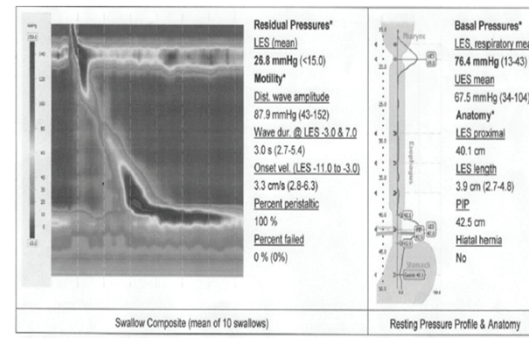
Transition of EGJOO to Type 3 Achalasia after Botox Injections





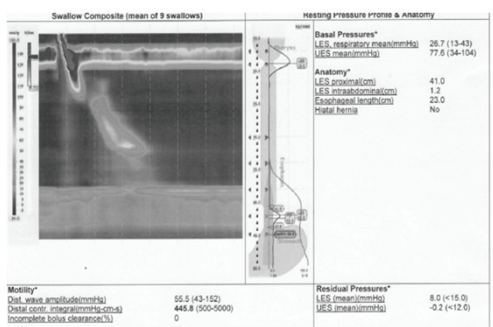


EGJOO Treated with Pneumatic Dilation—LES Only



42 yo female with dysphagia and chest pain

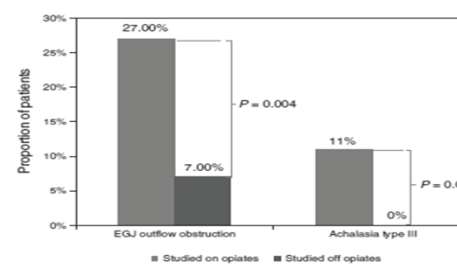
EGJOO One Month after PD 30 mm balloon



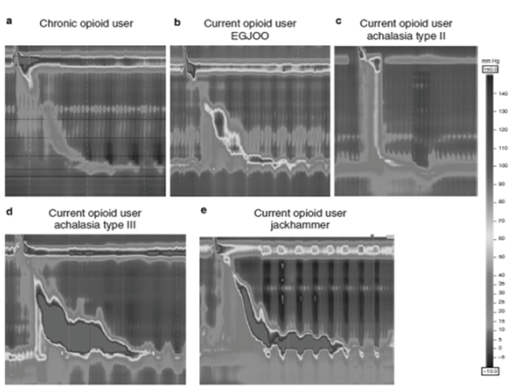
IRP decreased from 27 to 8 mm Hg and 50% decrease in DCI/amplitude

Opioid-Induced Esophageal Dysfunction

Retrospective review 121 chronic opioid users who had HRM

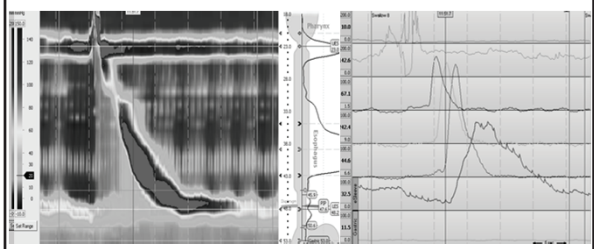


Ratuapli SK et al Am J Gastroenterol 2015



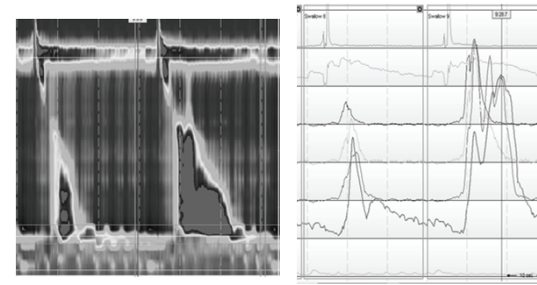
Variants of Spasm

Hypercontractile Esophagus



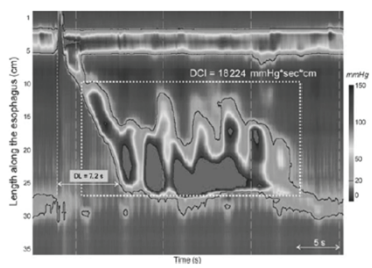
No longer DCI >5000 now must be > 8000 mmHg.sec.cm

Diffuse Esophageal Spasm



> 20% premature contractions (DL <4.5 sec)

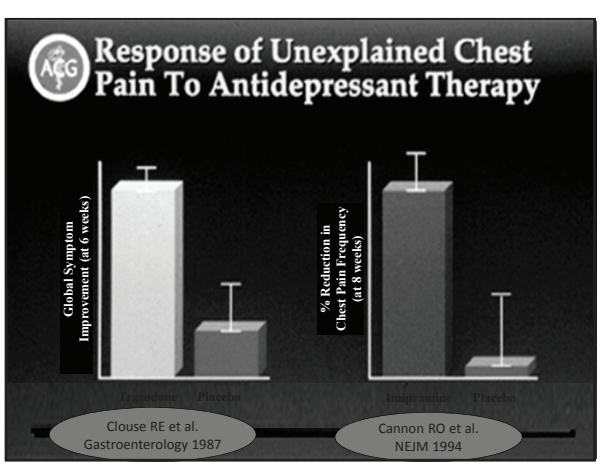
Jackhammer Esophagus with Very High Distal Contractile Integral



> 20% DCI >8000 mmHg.s.cm

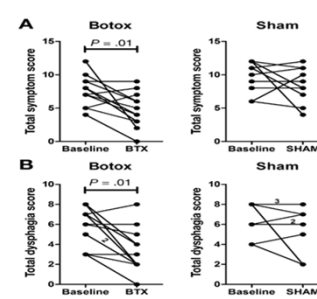
Treatment of Painful Esophageal Motility Disorders

- How do you treat what you do not understand?
- Potential medical therapies - few controlled studies
  - nitrates
  - anticholinergics
  - hydralazine
  - calcium antagonists
  - psychotropic drugs—tricyclics, SSRIs
  - botulinum toxin
  - pneumatic dilation
- Surgery - even less data



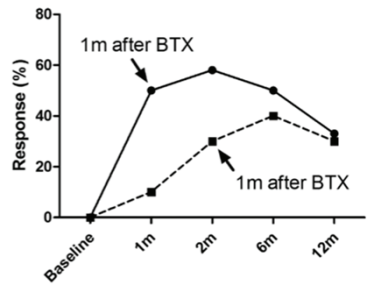
Botulinum Toxin in Treatment of Nonachalasia EMD

Double blind randomized study—22 patients with DES or nutcracker
100 units of Botox at 2 and 7 cm above LES or saline



Vanuytsel T et al. Clin Gastro and Hepatology 2013

Duration of Botox Symptom Relief



Vanuytsel T et al. Clinical Gastroenterol and Hepatology 2013

Clinical Response to Botox based on HRM Chicago Classification

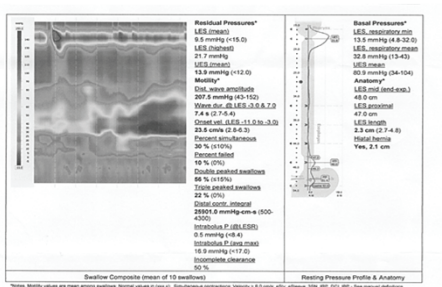
45 patients—all with dysphagia and 47% chest pain; BTX to cardia and body

	Achalasia with IRP < 15 mmHg (n = 6)	Achalasia with IRP ≥ 15 mmHg (n = 15)	Jackhammer esophagus (n = 7)	DES (n = 6)	EGJ outflow obstruction (n = 5)	Nutcracker & unclassified (n = 3)	Total (n = 42)
Responders ≥ 2 months	0 (0%)	13 (87%)	6 (86%)	6 (100%)	3 (60%)	2 (67%)	30 (71%)
Responders ≥ 6 months	0 (0%)	11 (73%)	5 (71%)	4 (60%)	3 (60%)	1 (33%)	24 (57%)

BTX, botulinum toxin; DES, distal esophageal spasm; EGJ, esophagogastric junction; IRP, integrated relaxation pressure.

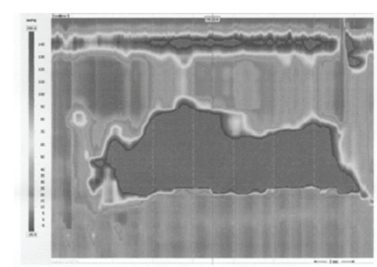
Marjoux S et al. Diseases of Esophagus 2015

JC—Severe DES with Chest Pain but no Dysphagia Treated with 200 units of Botox

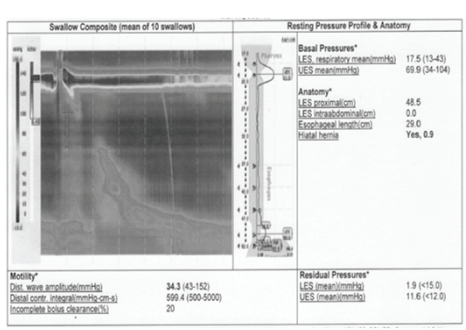


Distal contractile intergral—25,901 and 50% incomplete clearance

Single Swallow with Severe Spasm

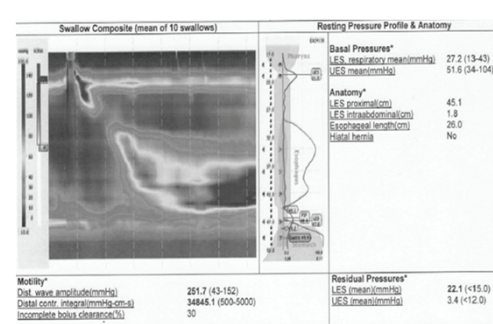


Two months after Botox—Complete Relief of Chest Pain



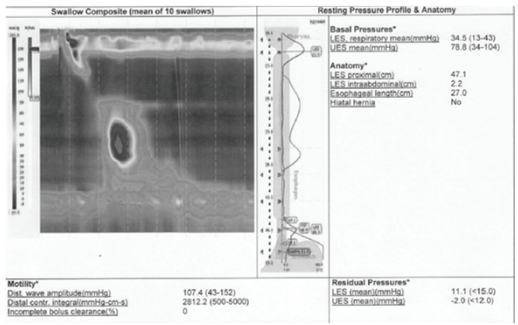
DCI now 599 and 20% impaired bolus

EGJOO with Jackhammer Esophagus



65 yo male with dysphagia—tx with pneumatic dilation 30 mm balloon at EGJ for 1 min and distal body for 30 sec

EGJOO and Jackhammer Esophagus—s/p PD



Assx 2 months after PD—Jackhammer resolved, IRP<15 mmHg and 100% clearance

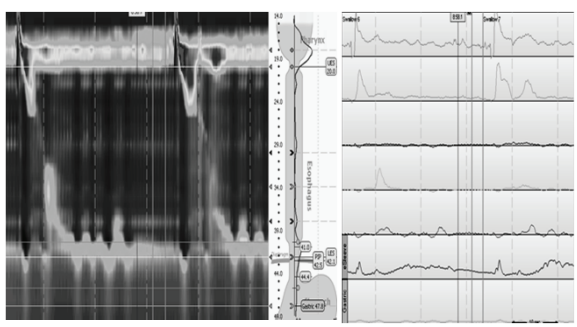
Surgical Myotomy for Spastic EMDs

- Retrospective single center study
- Success of laparoscopic myotomy
  achalasia (151)—93%
  DES (14)—86%-dysphagia 80%-chest pain
  Hypertensive LES—one patient—improved

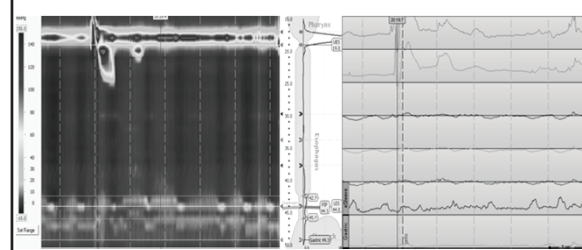
  Nutcracker (7)—80%-dysphagia
  50%-chest pain

Patti M et al. Archives of Surgery 2005

Ineffective Esophageal Peristalsis



Failed Peristalsis in Scleroderma

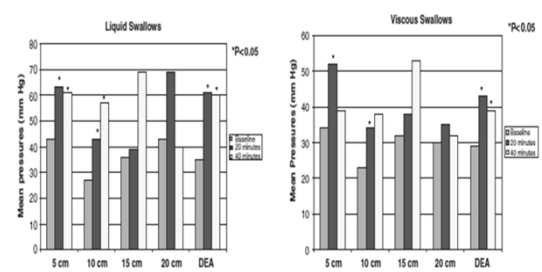


DCI < 100 mmHg.s.cm

Treatment of Hypomotility Disorders

- Treat GERD aggressively with PPIs
- Prokinetic drugs:
  --little data—focus on motility—not symptoms
  --bethanechol
  --pyridostigmine
  --cisapride and mosapride
  --capsaicin

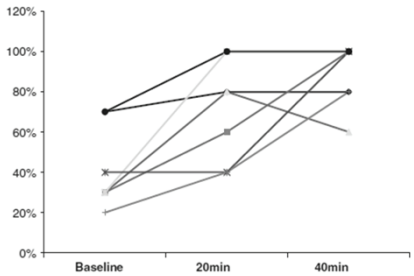
Esophageal Amplitude Change after Bethanechol 50 mg Orally



7 patients with severe ineffective esophageal motility

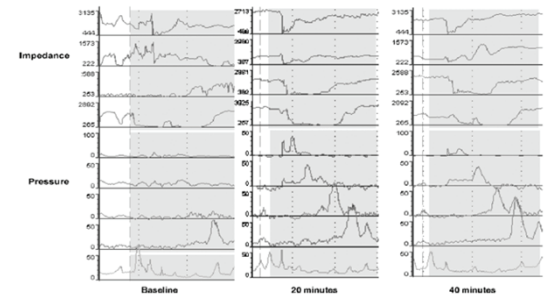
Agrawal A et al. J Clin Gastro 2007

Percentage of Swallows with Complete Bolus Clearance after Bethanechol 50 mg



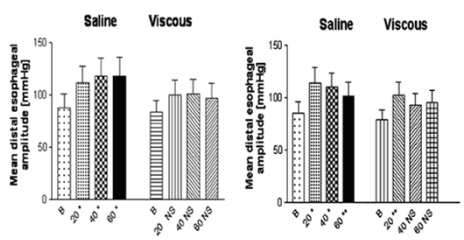
Agrawal A et al J Clin Gastro 2007

Increased Contraction Amplitude and Complete Bolus Clearance after Bethanechol 50 mg



Agrawal A et al. J Clin Gastro 2007

Amplitude Changes in 10 Healthy Volunteers after Pyridostigmine and Buspirone



Pyridostigmine 60 mg

Buspirone 20 mg

Blonski

SCLERODERMA AND THE ESOPHAGUS CLINICAL FEATURES

- Dysphagia
  - due to distal motility disorder
  - seen in approximately 50% of patients
  - usually mild, if severe → peptic stricture
- Heartburn
  - due to low LESP and aperistalsis
  - mild → worse disease I've ever seen
  - erosive esophagitis - 60% all have motility disorders
  - Barrett's and adenocarcinoma reported

Esophageal Testing: When, Why, and How?

Rachel Rosen M.D., M.P.H.

Center for Motility and Functional Gastrointestinal Disorders
Aerodigestive Center
Boston Children's Hospital

Case

- 5 yo with chronic cough
- 6 courses of antibiotics/steroids per year for "bronchitis" or "early pneumonia"
- Otolaryngologist sees erythematous airways and prescribes PPI
- Family seeks second opinion with GI
- What will you do?

Cost of Extraesophageal Reflux

Francis et al Am J Gastro 2013

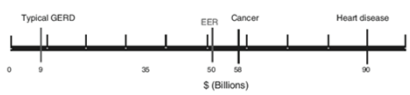


Figure 1. Comparison of estimated economic burden of extraesophageal reflux (EER) with typical GERD, cancer, and heart disease.

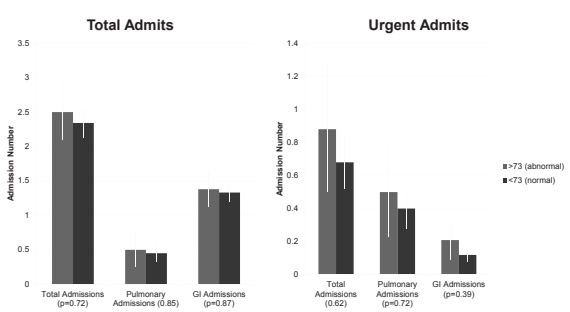
Cost is being driven by:
-Testing
-Therapy
-Side effects from therapy

What do we know?

- Correlating symptoms with reflux events is difficult
- Esophageal acid may not reflect lung exposure
- Does reflux testing improve outcomes?

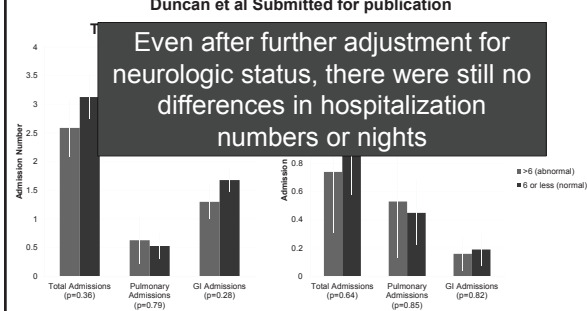
Abnormal number of reflux episodes by pH-MII does not predict number of admissions

Duncan et al JPGN 2016



pH probe results do not predict number of admissions, even after adjustment for aspiration

Duncan et al Submitted for publication



Even after further adjustment for neurologic status, there were still no differences in hospitalization numbers or nights

Full Column Reflux Matters

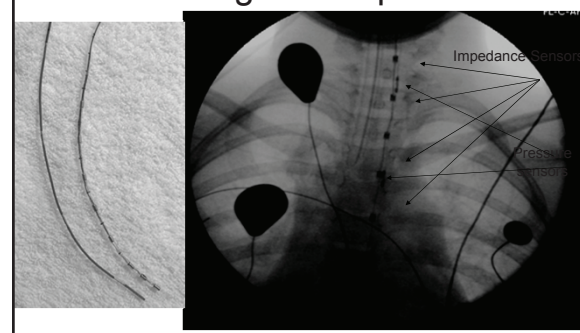
Jadcherla et al Am J Gastro 2008

Extent of Refluxate (# AREs)	Composite SSI	Respiratory
Pharynx (N = 30)	77% (23/30)	47% (14/30)
Proximal esophagus (N = 36)	50% (18/36)	22% (8/36)
Middle esophagus (N = 36)	50% (18/36)	28% (10/36)
Distal esophagus (N = 409)	27% (109/409)	11% (44/409)

SSI value >10% was considered to be abnormal (8).

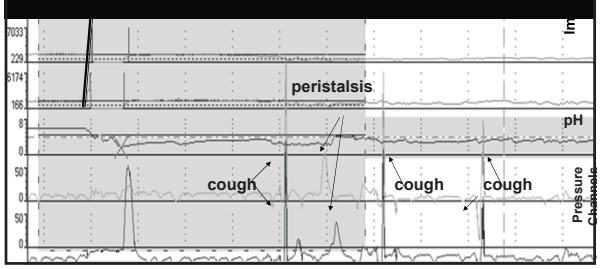
SSI: Number of Reflux Events associated with Symptoms
Total Number of Reflux Events

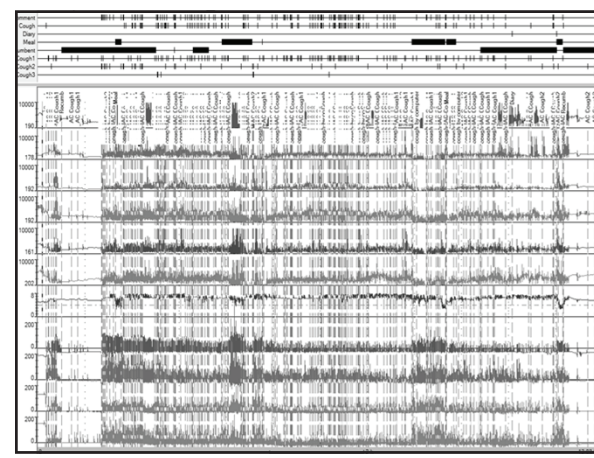
Esophageal Pressure Recording with impedance

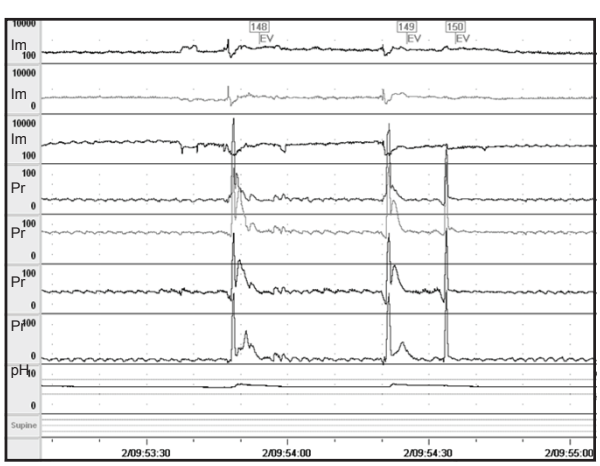


Patients only record 39% of all coughs on the log Addition of manometry increases cough detection by 100%

Sifrim, Gut 2005
Rosen et al JPGN 2013







Goal of Testing

- Correlate reflux events with respiratory symptoms
- Disprove reflux so PPIs are not needed

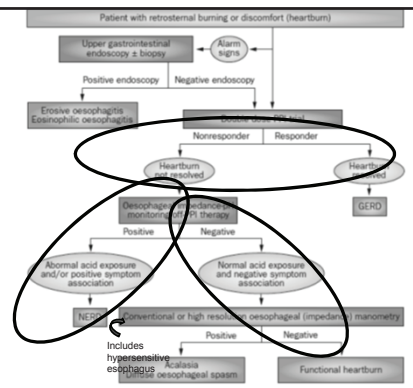
"All right pal, just hand over the nose and nobody gets hurt."

Case

- 16 yo with chest pain
- Slight improvement after 4 weeks on BID PPI
- Feels reflux coming up
- Family comes in asking about fundoplication
- Now what?

New Definitions

	Typical Symptoms	Erosions Endoscopically	Abnormal amount of acid reflux	+ Symptom association with acid or non-acid reflux
ERD	+	+	+	+/-
NERD	+	-	+	+/-
Hypersensitive Esophagus	+	-	-	+
Functional Heartburn	+	-	-	-



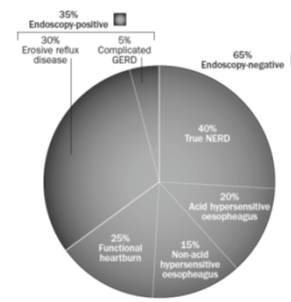
NERD Algorithm
Savarino et al Nat Reviews Gastro 2013

Adults suggest functional heartburn is not NERD

NERD by definition needs some abnormal reflux testing, not just symptoms

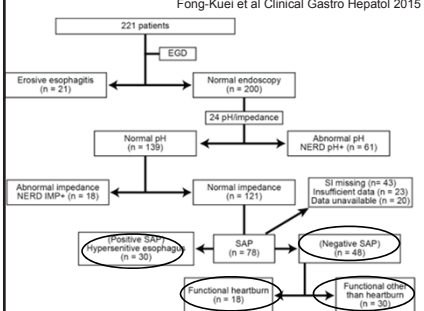
Incidence of subtypes

Savarino Nat Med Rev 2013



Incidence of functional heartburn and hypersensitive esophagus

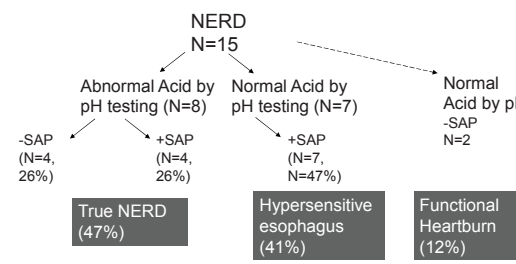
Fong-Kuei et al Clinical Gastro Hepatol 2015



54% of patients do not have a diagnosis that responds to PPI therapy

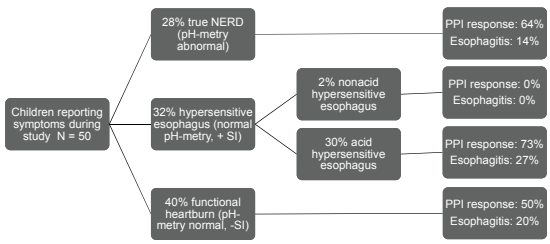
Frequency of Subtypes in Pediatrics

Borelli et al NGM 2012



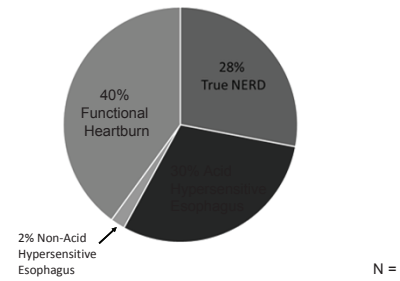
NERD in Pediatrics

Mahoney et al Submitted for Publication



NERD in Pediatrics

Mahoney et al Submitted for Publication



Baseline impedance and NERD

Kandulski et al CGH 2015

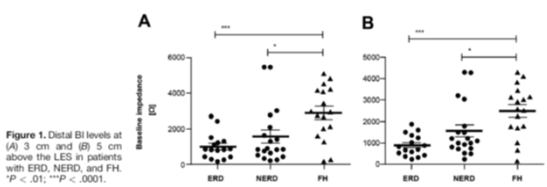
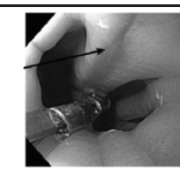


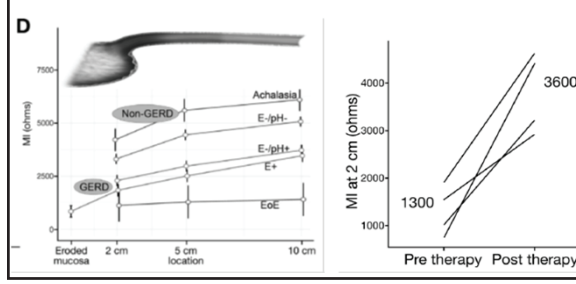
Figure 1. Distal BI levels at (A) 3 cm and (B) 5 cm above the LES in patients with ERD, NERD, and FH. *$P < .01$; ***$P < .0001$.

- A cut-off value of less than 2100 U, BI identified patients with NERD/ERD with 78% sensitivity and 71% specificity, with positive and negative predictive values of 75%.

Single impedance measurement

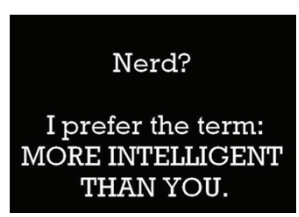
Ates et al Gastro 2015





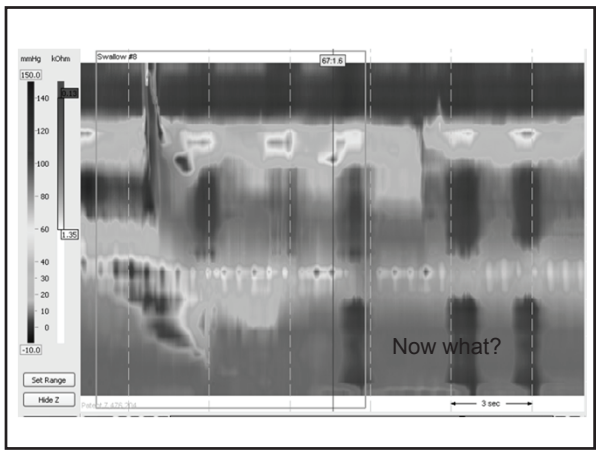
Goal of Testing

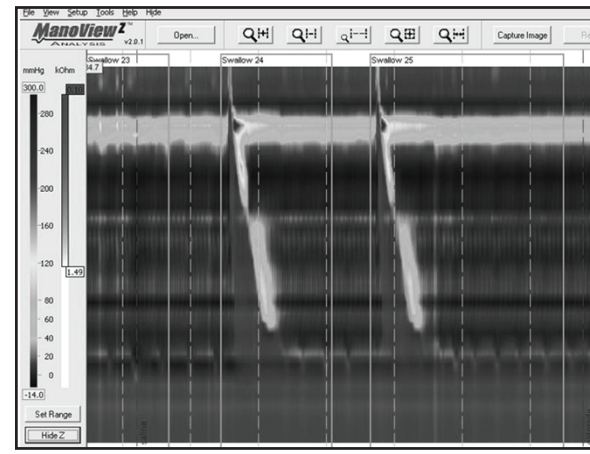
- Provide a diagnosis
- Open the door to alternative therapies besides PPI



21 yo lung transplant patient with graft rejection

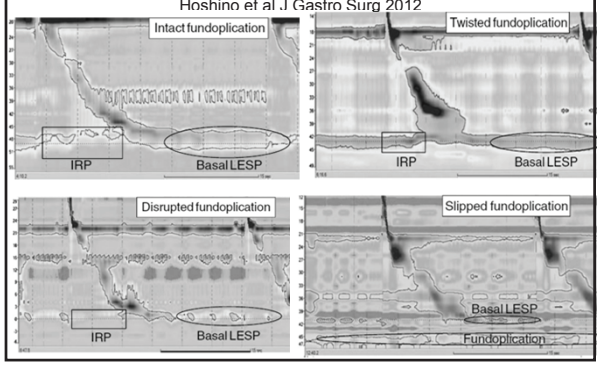
- 21 yo with CF who had significant reflux symptoms prior to first transplant.
- Underwent fundoplication 3 months after transplant
- Was lost to follow up for 1 year
- Returned with graft failure and dysphagia





Post-Fundoplication Complications and HRM

Hoshino et al J Gastro Surg 2012



HRM before and after fundoplication

Loots et al J Peds 2014

Table 1. Comparison before and after fundoplication

	Presurgery	Postsurgery	*P* value
24-hour pH-impedance			
Total GER episodes	97 (69-172)	66 (18-87)	.012
Acid GER episodes	37 (32-120)	10 (2-39)	.013
Weakly acid GER episodes	18 (8-33)	20 (9-43)	NS
Acid exposure, %	12.5 (8.0-22.7)	3.1 (1.0-6.1)	.005
SAP, %	86 (17-100)	45 (9-100)	NS
Impedance baseline most distal channel (Ohm)	874 (611-1415)	1001 (617-2452)	.028
Manometry impedance			
PeakP, mm Hg	57 (49-72)	67 (47-71)	NS
Peristalic contractions, %	73 (36-96)	64 (33-91)	NS
LES resting pressure, mm Hg	11 (7-21)	14 (9-27)	NS
Complete LES relaxation, %	92 (76-100)	65 (29-91)	.038
LES nadir pressure, mm Hg	1 (0-5)	3 (0-5)	NS
Bolus transit time (entrance → exit), seconds	13.4 (10.3-21.5)	16.0 (9.9-23.4)	NS
TLESRs/hour	1.9 (0.7-4.4)	0.3 (0.0-2.4)	.086
GEBT			
Gastric-emptying half time, minutes	64 (45-96)	63 (48-78)	NS

NS, not significant; *SAP*, symptoms association probability.
P values are based on a paired Wilcoxon signed rank test.

Tight Fundoplications: A common Pediatric Problem

Schneider et al Eur J Ped Surg 2012

Table 2 Factors Associated with Esophageal Dilation (Multivariate COX Hazards Model with Stepwise Selection)

	HR[a]	95% CI	*p* Value
Dumping syndrome	4.46	2.61–7.61	<0.0001
Surgical revision	2.60	1.49–4.57	0.0008
Oral feeding	2.23	1.25–3.97	0.0064

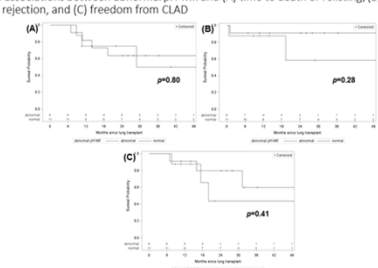
Note: Statistical significance: $p \leq 0.05$.
[a]HR, adjusted hazard ratio (ratio of risk of Nissen dilation per unit of time).
95% CI, 95% confidence interval.

25% of all patients required dilation of the fundoplication

A quick side note… Reflux testing in pediatrics does not predict outcome

Dy et al Submitted for Publication 2016

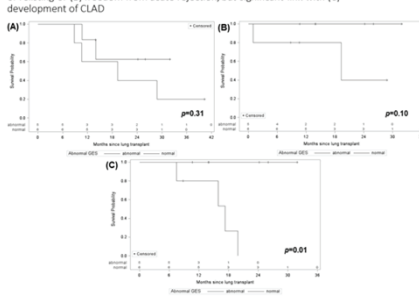
Figure 3. Kaplan-Meier analysis of pediatric lung transplant patients **without** Nissen fundoplication showing no associations between abnormal pH-MII and (A) time to death or relisting, (B) freedom from acute rejection, and (C) freedom from CLAD



A quick side note… Gastric dysmotility does predict outcome

Dy et al Submitted for Publication 2016

Figure 4. Kaplan-Meier analysis of pediatric lung transplant patients **without** Nissen fundoplication showing no associations between abnormal GES and (A) time to death or relisting or (B) freedom from acute rejection, but significant link with (C) development of CLAD

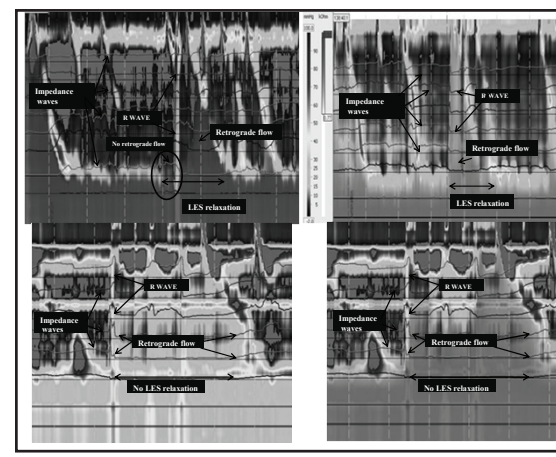


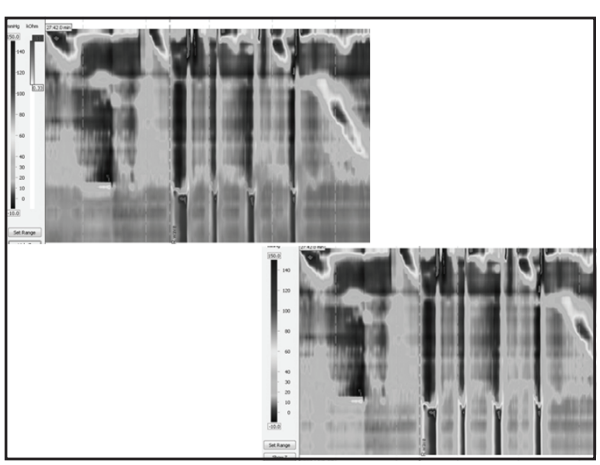
Goal of Testing

- Assess for stasis, differentiate reflux from stasis
- Identify patients who may benefit from dilation or redo/takedown of fundoplication

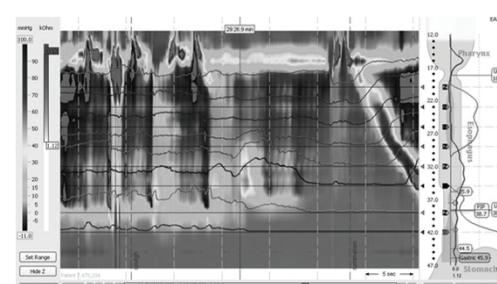
Case

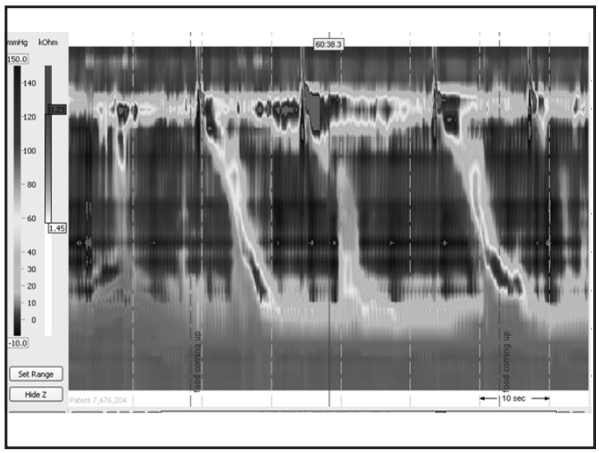
- 12 yo with intractable reflux
- Unable to sit at the table without spitting up into a thermos he carries
- No response to PPI





Cough versus Rumination: You need impedance or you need to be there





Impact of Baclofen on TLESRs

Omari et al J Peds 2006

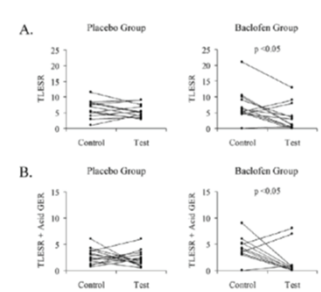


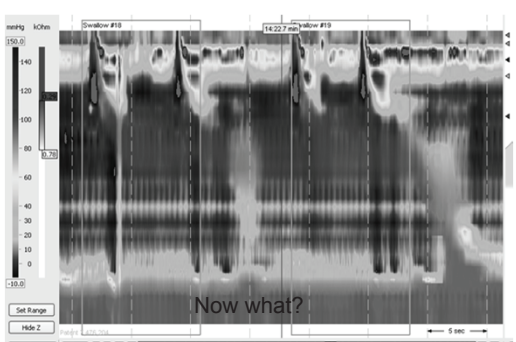
Figure 2. Individual data for the number of (A) TLESRs and (B) TLESRs triggering acid GER recorded during the control and test periods of the trial in patients receiving placebo or baclofen.

Goal of Testing

- Make an affirmative diagnosis
- Avoid unnecessary fundoplication
- Potentially guide therapy

Case

- 12 yo with dysphagia
- History of EA
- Recurrent respiratory infections
- Patent anastomosis, no erosions grossly, 3 eos per hpf below anastomosis, normal above anastomosis



Diagnosis changes when age and height are considered

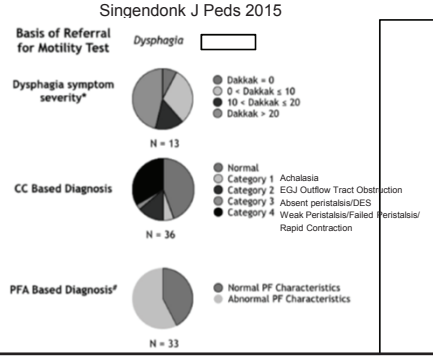
Singendonk et al NGM 2014

Table 2 De novo classification of 76 studies into motor disorder category using established criteria and after applying criteria adjusted for age and length from nose till the LES upper border margin

Chicago Classification	Original criteria [n studies, %]	Revised criteria – based on age [n studies, %]	Revised criteria – based on length [n studies, %]
Category 1 - Achalasia	2 (2.6)	2 (2.6)	2 (2.6)
Achalasia type I	0 (0)	0 (0)	0 (0)
Achalasia type II	2 (2.6)	2 (2.6)	2 (2.6)
Achalasia type III	0 (0)	0 (0)	0 (0)
Category 2			
EGJ outflow obstruction	13 (17.1)	5 (6.6)	4 (5.3)
Category 3	13 (17.1)	3 (3.9)	6 (7.9)
Distal esophageal spasm	11 (14.5)	1 (1.3)	4 (5.3)
Absent peristalsis	2 (2.6)	2 (2.6)	2 (2.6)
Hypercontractile esophagus	0 (0)	0 (0)	0 (0)
Category 4	22 (28.9)	28 (31.5)	28 (31.5)
Weak peristalsis with large breaks	11 (14.5)	12 (15.8)	12 (15.8)
Weak peristalsis with small breaks	8 (10.5)	12 (15.8)	12 (15.8)
Frequent failed peristalsis	2 (2.6)	2 (2.6)	2 (2.6)
Rapid contractions with normal latency	2 (2.6)	2 (2.6)	2 (2.6)
Hypertensive peristalsis	0 (0)	0 (0)	0 (0)
Normal	26 (34.2)	38 (50.0)	36 (47.4)

Relationship between symptoms and diagnoses

Singendonk J Peds 2015



Relationship between HRM and fundoplication patients with and without dysphagia

Loots et al J Peds 2014

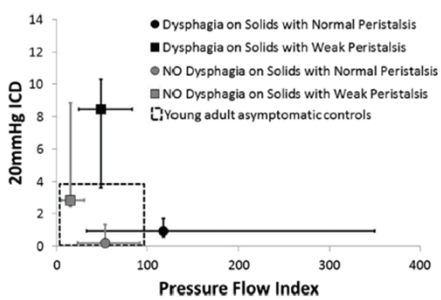
Table II. Comparison of patients with and without postoperative dysphagia

	With dysphagia	Without dysphagia	*P* value
Conventional GER measures			
Total GER episodes	125 (70-169)	96 (66-199)	NS
Acid exposure, %	14.5 (2.7-24.1)	12.5 (8.9-22.8)	NS
SAP, %	100 (69-100)	80 (0-96)	NS
Manometry			
PeakP, mm Hg	64 (46-90)	57 (54-63)	NS
Peristaltic contractions, %	93 (75-99)	53 (19-81)	.11
Complete LES relaxation, %	94 (43-100)	92 (76-100)	NS
Gastric emptying			
Gastric-emptying half time, minutes	96 (71-104)	48 (26-68)	.032
AIM analysis			
PeakP, mm Hg	48 (36-86)	39 (25-48)	NS
IBP, mm Hg	7.7 (5.1-11.3)	5.3 (4.3-5.7)	.11
IBP slope, mm Hg/sec	6.0 (1.6-10.4)	2.3 (0.9-6.1)	NS
Tradimp-Peak, seconds	3.4 (3.1-3.8)	3.4 (3.0-4.3)	NS
Dysphagia risk index	55.6 (14.9-105.0)	2.0 (1.7-5.9)	.016

Tradimp-Peak, the time between the point of nadir impedance and the time of PeakP.

Dysphagia and HRM in Pediatrics

Rommel et al Eur J Peds 2015



Relationship between dysmotility and bolus clearance in patients with esophageal atresia

Van Wijk et al J Peds Surg 2013

Table 2 Bolus clearance as detected by multichannel intraluminal impedance.

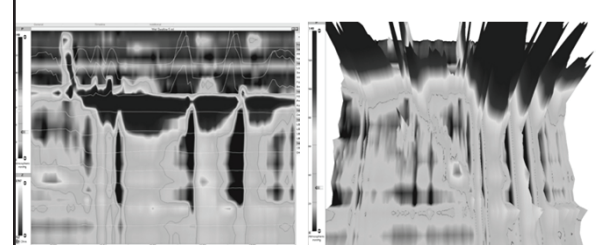
	Infants				Adults			
	Liquid		Viscous		Liquid		Viscous	
	Supine	Upright	Supine	Upright	Supine	Upright	Supine	Upright
Normal clearance	13 (46%)	11 (55%)	9 (33%)	12 (38%)	16 (41%)	19 (45)%	11 (33%)	17 (40%)
TBTT	14 (6–141)	13 (3–86)	18 (12–224)	15 (4–111)	14 (5–64)	13 (5–162)	16 (9–48.4)	13 (4–121)

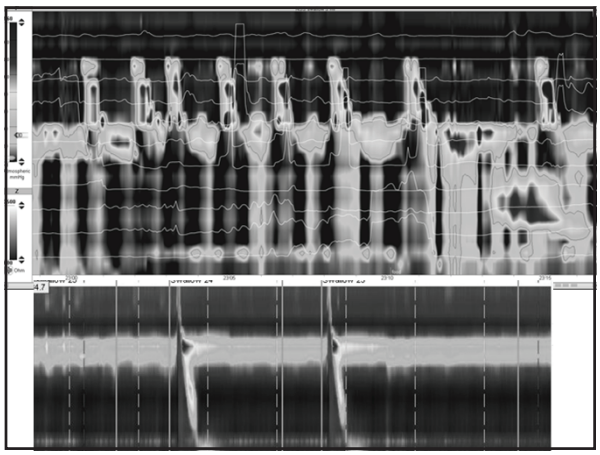
Normal clearance is shown as number of patients (%). Total bolus transit time (TBTT) is shown as median (range). Note that in the latter parameter boluses infused in the proximal esophagus are not included in the analysis.

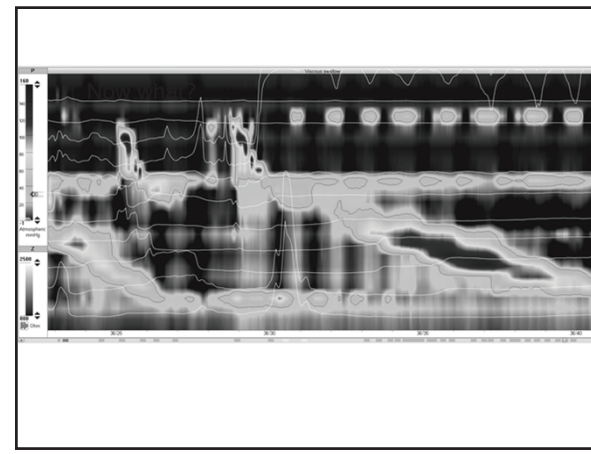
Swallows with intact motility has complete bolus clearance 85% of the time
Swallows with abnormal motility has complete bolus clearance 30% of the time

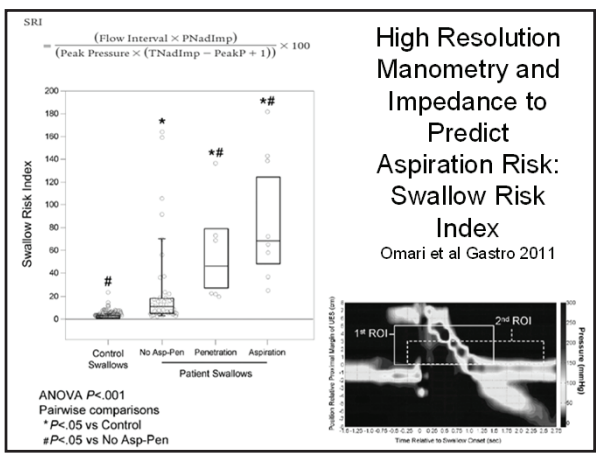
Case

- 13 month old with noisy breathing
- Chronic respiratory infections
- VFSS with prominent cricopharyngus but bolus passes well, aspiration with thin and nectar liquids









HRM-MII for the diagnosis of aspiration

Rommel et al JPGN 2014

TABLE 1. Summary data of 58 liquid bolus swallows of 20 paediatric patients showing the relations among pressure–flow variables and the presence of aspiration–penetration as assessed by videofluoroscopy

	Patients with no aspiration–penetration	Patients with aspiration–penetration	Patients with aspiration only
No. of patients	8	12	6
Peak pressure, mmHg	165 [118–206]	111 [89–207]	196 [95–263]
Pressure at nadir impedance, mmHg	34 ± 7	48 ± 7	61 ± 12 (0.06)
Flow interval, ms	974 ± 196	1404 ± 158	1617 ± 215*
Time nadir impedance to peak pressure, ms	244 ± 67	193 ± 28	197 ± 41
Swallow risk index	17 ± 5	42 ± 7*	43 ± 9*
UES relaxation interval, ms	579 [409–757]	774 [573–1043]	675 [529–957]
UES intrabolus pressure, mmHg	28 ± 6	39 ± 6	47 ± 9
UES nadir pressure, mmHg	11 ± 5	18 ± 5	26 ± 7
UES resistance, mmHg/s	31 [19–93]	40 [26–77]	74 [44–86]
UES impedance, Ω	413 ± 58	523 ± 54	510 ± 76
UES pressure at nadir impedance, mmHg	17 ± 6	29 ± 5	38 ± 6*
iNadImp/Imp ratio	265 ± 36	407 ± 45*	379 ± 75

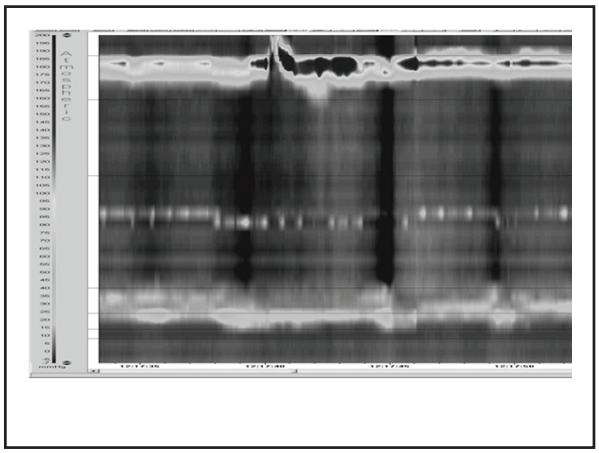
Data are presented as median [interquartile range] or mean ± SD. *P* values of Mann–Whitney rank sum test or *t* test for control versus aspiration/penetration and no aspiration versus global aspiration shown in parentheses. Data for which $P < 0.05$ are marked with an asterisk. iNadImp/Imp ratio = integrated ratio of nadir impedance to impedance; UES = upper oesophageal sphincter.

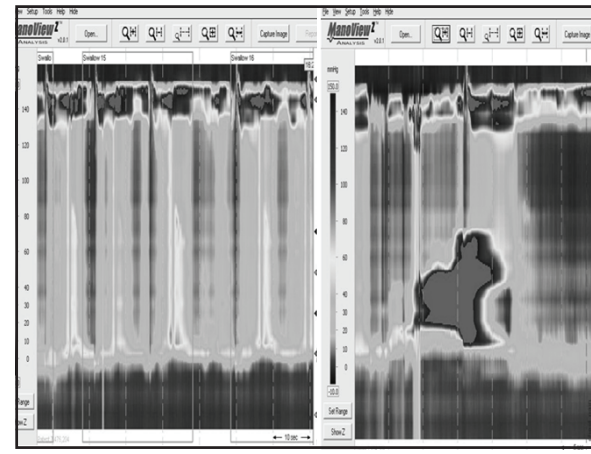
Goal for Testing

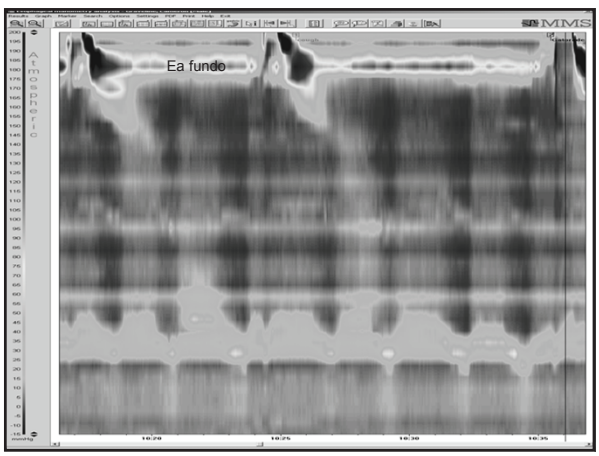
- To determine if dilation or BoTox is an option
- To potentially determine if aspiration is related to swallowing dysfunction or anatomy

12 yo with nocturnal cough

- 5 years of worsening cough
- Wet productive cough at night
- Symptoms of early satiety such that she ate small amounts during the day
- Some periodic vomiting
- 3-4 course of antibiotics per year for “bronchitis”







HRM with achalasia predicts response to therapy

Pandolfino et al Gastro 2008

Table 4. Response to Therapeutic Interventions Among Achalasia Subtypes

Achalasia subtype	Type I (n = 16)	Type II (n = 46)	Type III (n = 21)	All (n = 83)
Number of interventions, mean (*SD*)	1.6 (SD, 1.5)	1.2[a] (SD, 0.4)	2.4[a,b] (SD, 1.0)	1.8 (SD, 0.7)
Success with BoTox (first intervention) (%)	0 (0/2)	86 (6/7)	22 (2/9)	39 (7/18)
Success with dilation (first intervention with 30-mm balloon) (%)	38 (3/8)	73 (19/26)	0 (0/11)	53 (24/45)
Success with myotomy (first intervention) (%)	67 (4/6)	100 (13/13)	0 (0/1)	85 (17/20)
Success with first intervention (total) (%)	44 (7/16)	83 (38/46)	9 (2/21)	56 (47/83)
Success with last intervention (%) (last intervention type)	56 (B-0, P-10, M-6)	96[a] (B-6, P-25, M-15)	29[a,b] (B-8, P-8, M-5)	71 (B-14, P-43, M-26)

NOTE. Pneumatic dilation was initially done with a 30-mm Microvasive balloon in all instances. If this failed, it was usually followed by a 35-mm dilation accounting for the difference in success rate for pneumatic dilation when applied as an initial or as the last intervention. Overall, type II patients exhibited better response to all therapies: Botox (B), pneumatic dilation (P), or surgical myotomy (M).
[a]$P < .05$ *vs* type I.
[b]$P < .05$ *vs* type II.

Endoflip and its role in achalasia

Rohof et al Gastro 2012

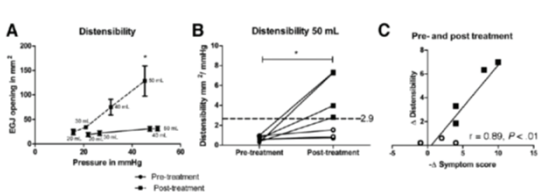


Figure 4. The effect of initial treatment is depicted (n = 7), showing increased distensibility at the different volumetric distentions after treatment in *A*, which is statistically significant at the largest volumetric distention (*P < .05; Wilcoxon signed rank test). Additionally, *B* and *C* show that the effect of treatment on distensibility differs and that an increase correlates excellently with the decrease in symptoms (r = 0.89; P < .01; Spearman rank correlation). The 3 patients marked with an *open symbol* in *B* and *C* have an impaired distensibility after therapy (<2.9 mm²/mm Hg). All 3 patients needed additional therapy due to persistent symptoms.

Dilation improves distensibility but does not predict ourcomes

Smeets et al NGM 2015

Table 3 Effect of single pneumatic balloon dilation (30 mm) on EGJ distensibility in newly diagnosed achalasia patients (n = 26)

	Before pneumatic balloon dilation (30 mm)	After pneumatic balloon dilation (30 mm)	*p* value
EGJ distensibility 30 mL (mm²/mmHg)	1.2 (0.8–1.6)	1.6 (1.4–2.2)	<0.01
Pressure (mmHg)	17.6 (12.7–26.6)	16.2 (13.9–25.5)	0.14
CSA (mm²)	20.2 (19.9–20.7)	28.7 (21.1–42.7)	<0.01
EGJ distensibility 40 mL (mm²/mmHg)	0.8 (0.7–1.4)	3.2 (2.2–4.0)	<0.01
Pressure (mmHg)	26.5 (21.1–36.1)	24.0 (19.8–30.3)	0.01
CSA (mm²)	24.1 (20.1–31.6)	77.6 (55.0–104.3)	<0.01
EGJ distensibility 50 mL (mm²/mmHg)	0.9 (0.7–1.5)	4.2 (3.0–5.7)	<0.01
Pressure (mmHg)	46.8 (42.2–57.1)	39.1 (31.4–45.0)	<0.01
CSA (mm²)	47.6 (40.4–65.1)	173.0 (112.6–206.3)	<0.01

EGJ, esophagogastric junction; CSA, cross-sectional areas.

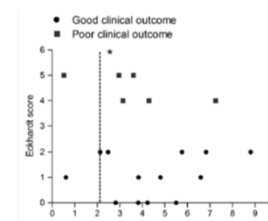
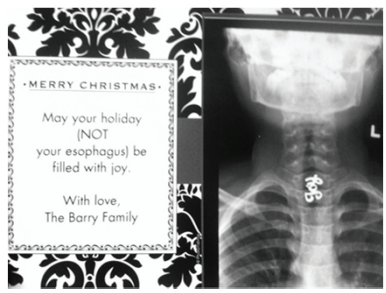


Figure 3 Distensibility of the esophagogastric junction directly after 30-mm pneumatic dilation in patients with a good and poor clinical outcome at 1-year follow-up. *Dotted line represents cutoff value for normality (2.1 mm²/mmHg).

Goals for Testing

- To make an affirmative diagnosis
- To give an idea of prognosis



Summary

- Lots of exciting tests
- Many studies but whether the test change outcomes is not known in the majority of studies

Psychopharmacology Augmenting the Benefits of Antidepressants in Patients with FGID

Gregory S. Sayuk, MD, MPH
Associate Professor of Medicine and Psychiatry
Division of Gastroenterology

Washington University in St. Louis

Disclosure

- The following are my disclosures. Potential conflicts of interest have been resolved.

Research Support / Grants	None
Stock/Equity	None
Consulting / Employment	Synthetic Biologics, Synergy
Speakers Bureau / Honoraria	Salix, Allergan/Ironwood
Other	None

Objectives

- Overview of refractory functional abdominal pain
- Strategies for using antidepressants (ADs) in patients FGID
- Scenarios where ADs often fail in FGIDs
- Strategies for augmenting AD therapy

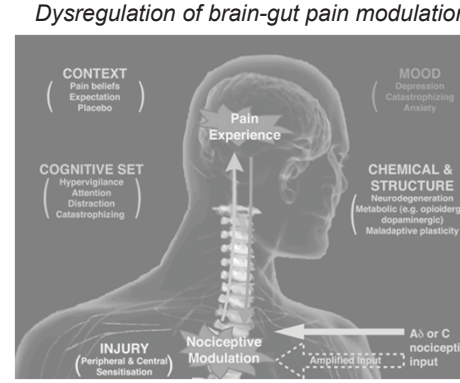
Objectives

- Overview of refractory functional abdominal pain
- Strategies for using antidepressants (ADs) in patients FGID
- Scenarios where ADs often fail in FGIDs
- Strategies for augmenting AD therapy

Chronic abdominal pain
A big medical challenge

- Chronic pain affects 20% of the adult population
  - Abdomen a common location, FGID frequent cause
- Objective diagnostic approaches to decrease reliance on subjective pain reports are lacking
- Total annual costs in US >$30 billion ($20 indirect costs) for IBS alone
- Needs of chronic pain patients largely unmet

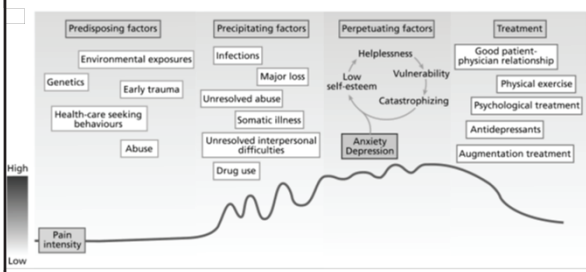
Chronic pain disorders
Dysregulation of brain-gut pain modulation



Adapted from: Tracey I and Mantyh PW. *Neuron* 2007.

Conceptual biopsychosocial model

Interaction of factors triggering chronic abdominal pain



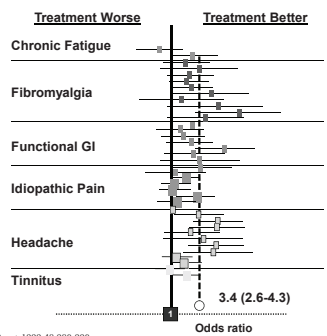
Adapted from: Tornblom H and Drossman D. *NGM* 2015. See also: Perera TD *et al Neuroscientist* 2008 and Perera TD *et al*. *J Neurosci* 2007.

Objectives

- Overview of refractory abdominal pain
- Strategies for using antidepressants (ADs) in patients FGID
- Scenarios where ADs often fail in FGIDs
- Strategies for augmenting AD therapy

Antidepressants for Somatic Pain Syndromes

Multiple controlled trials demonstrate benefit



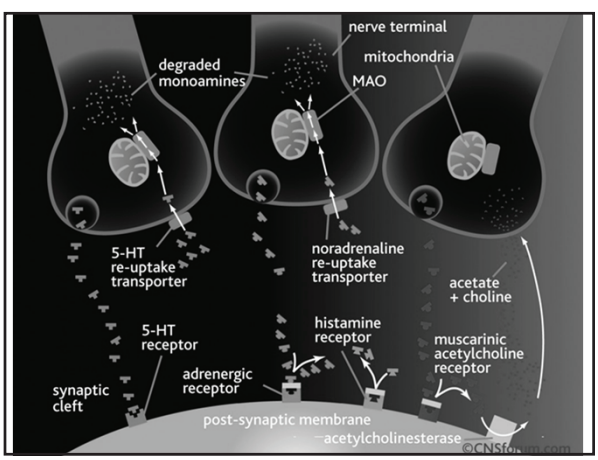
O'Malley PG, et al. *J Fam Pract.* 1999;48:980-990.

Antidepressants

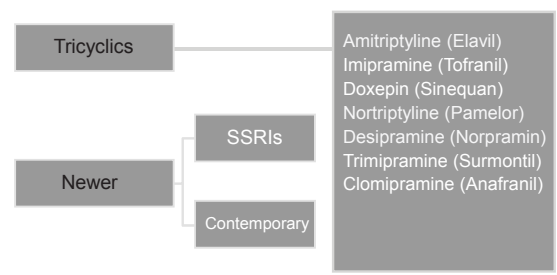
Putative effects on abdominal pain

- Central effects
  - Alterations in pain perception (analgesia, antihyperalgesia)
  - Modified attention to pain
  - Decreased stress responses
  - Improvement of mood, psychiatric disorders
  - Treatment of sleep disturbances
- Peripheral effects
  - Alterations in visceral afferent signaling
  - Effects on GI physiology
    - Smooth muscle relaxation
    - Decreased secretion

Grover M and Drossman DA. *Gastroenterol Clin N Am* 2011.



Antidepressants for the Non-Psychiatrist



Meta-analysis: TCAs in IBS

Study or sub-category	Treatment n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Tricyclic antidepressants					
Heefner 1978	10/22	12/22		5.94	0.83 (0.46 to 1.51)
Myren 1982	5/30	10/31		2.66	0.52 (0.20 to 1.33)
Nigam 1984	14/21	21/21		14.74	0.67 (0.49 to 0.90)
Boerner 1988	16/42	19/41		7.63	0.82 (0.50 to 1.36)
Bergmann 1991	5/19	14/16		3.82	0.30 (0.14 to 0.65)
Vij 1991	14/25	20/25		10.67	0.70 (0.47 to 1.04)
Drossman 2003	60/115	36/57		16.77	0.83 (0.63 to 1.08)
Talley 2008	0/18	5/16		0.33	0.08 (0.00 to 1.36)
Vahedi 2008	8/27	16/27		5.02	0.50 (0.26 to 0.97)
Subtotal (95% CI)	**319**	**256**		**67.56**	**0.68 (0.56 to 0.83)**

Total events: 132 (treatment), 153 (control)
Test for heterogeneity: X^2 = 10.92, df=8, (*P*=.21), I2 = 26.9%
Test for overall effect: Z=3.86 (*P*=.0001)

Ford AC et al. *Am J Gastroenterol.* 2009;104:1831-1843; quiz 1844.

Meta-analysis: TCAs in IBS

Number needed-to-treat (NNT) using TCAs in IBS ≈ 4

Higher doses (>50 mg) may be more effective in IBS-D

1. Ford AC et al. Gut 2009. 2. Lesbros-Pankoflickova et al. Aliment Pharmacol Ther 2004.

Study	Treatment	Control	RR (random)	Weight	RR (random)
Vij 1991	14/25	20/25		10.67	0.70 (0.47 to 1.04)
Drossman 2003	60/115	36/57		16.77	0.83 (0.63 to 1.08)
Talley 2008	0/18	5/16		0.33	0.08 (0.00 to 1.36)
Vahedi 2008	8/27	16/27		5.02	0.50 (0.26 to 0.97)
Subtotal (95% CI)	**319**	**256**		**67.56**	**0.68 (0.56 to 0.83)**

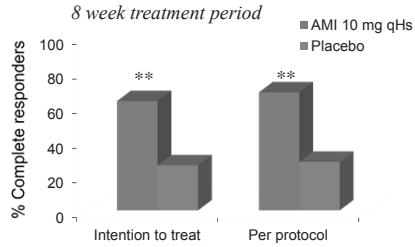
Total events: 132 (treatment), 153 (control)
Test for heterogeneity: X^2 = 10.92, df=8, (*P*=.21), I2 = 26.9%
Test for overall effect: Z=3.86 (*P*=.0001)

Ford AC et al. *Am J Gastroenterol.* 2009;104:1831-1843; quiz 1844.

Amitripyline for IBS

TCAs effective at low doses

8 week treatment period



*** p<0.01 for each*
No significant difference in adverse events between groups

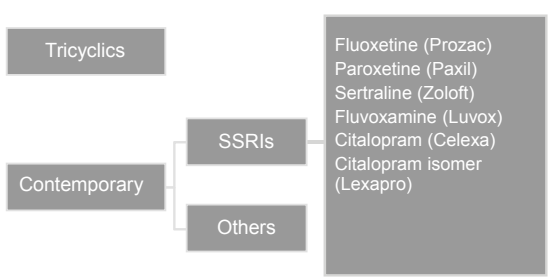
Vahedi H *et al. AP&T* 2007.

Recent Tricyclic Antidepressant Trials for IBS

Study	Drug (mg/day)	Design	Abdominal pain relief	Global IBS symptoms	Well-being
Rajagopalan1998	Amitriptyline (25→75)	12-wk DB RCT n=40	+	+	+
Drossman 2003	Desipramine (50→150)	12-wk MC CC RCT n=216	-	NA	+*
Morgan 2005	Amitriptyline (50)	4-wk RCT n=19	+	NA	NA
Vahedi 2008	Amitriptyline (10)	8-wk DB RCT n=50	-	+	+
Bahar 2008	Amitriptyline (10-30)	13-wk DB RCT n=33 (adolescent)	+	-	+
Abdul-Baki 2009	Imipramine (25)	12-wk RCT n=56	-	+	+

*Per protocol analysis NA = not assessed DB=double-blinded RCT=randomized controlled trial
CC=comparator-controlled MC=multi-center study

Antidepressants for the Non-Psychiatrist



Clouse RE and Lustman PJ. *GUT* 2006.

Meta-analysis: SSRIs in IBS

Selective serotonin reuptake inhibitors				
Kuiken 2003	9/19	12/21	5.85	0.83 (0.45 to 1.51)
Tabas 2004	25/44	36/46	14.90	0.73 (0.54 to 0.98)
Vahedi 2005	6/22	19/22	4.52	0.32 (0.16 to 0.64)
Tack 2006	5/11	11/12	4.90	0.50 (0.25 to 0.97)
Talley 2008	5/17	5/16	2.27	0.94 (0.33 to 2.65)
Subtotal (95% CI)	**113**	**117**	**32.44**	**0.62 (0.45 to 0.87)**

Total events: 50 treatments; 83 controls
Test for heterogeneity: X^2 = 6.46, df = 4, (*P*=.17), I2 = 38.1%
Test for overall effect: Z = 2.74 (*P*=.006)

Ford AC et al. *Am J Gastroenterol.* 2009;104:1831-1843.

Meta-analysis: SSRIs in IBS

Number needed-to-treat (NNT) using SSRIs in IBS ≈ 3.5

Fewer, smaller studies to date.

Anecdotally, *less* effective than TCAs for abdominal pain.

Ford AC et al. Gut 2009.

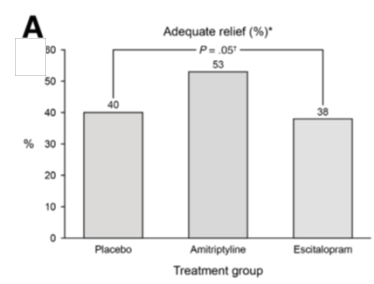
Subtotal (95% CI)	113	117		32.44	0.62 (0.45 to 0.87)

Total events: 50 treatments; 83 controls
Test for heterogeneity: $X^2 = 6.46$, df = 4, (P=.17), I2 = 38.1%
Test for overall effect: Z = 2.74 (P=.006)

Ford AC et al. *Am J Gastroenterol.* 2009;104:1831-1843; quiz 1844.

Antidepressants for Functional Dyspepsia

Results of the Functional Dyspepsia Treatment Trial (FDTT)

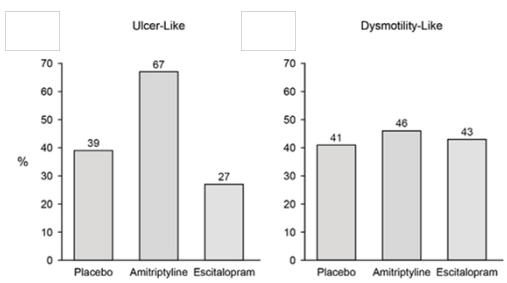


* ≥5 weeks of adequate relief
† p value from logistic regression model controlling for confounders

Talley *et al. Gastroenterol* 2015.

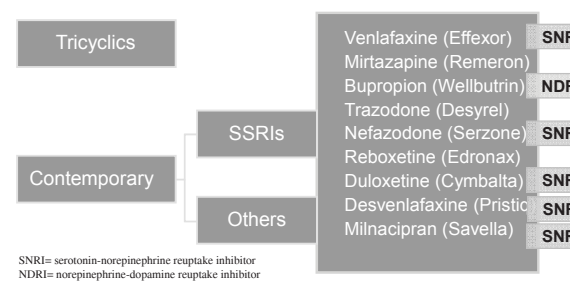
ADs for Functional Dyspepsia

All FD patients do not respond equally



Talley *et al. Gastroenterol* 2015.

Antidepressants for the Non-Psychiatrist

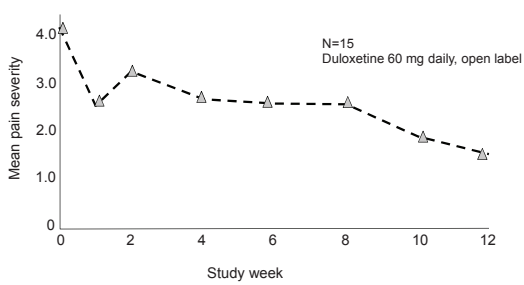


SNRI= serotonin-norepinephrine reuptake inhibitor
NDRI= norepinephrine-dopamine reuptake inhibitor

Clouse RE and Lustman PJ. *GUT* 2006.

Duloxetine for IBS

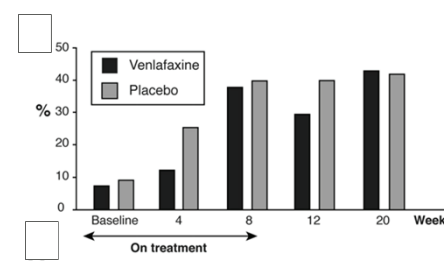
Improvement in pain severity



Brennan BP *et al. Human Psychopharmacol* 2009.

Venlafaxine for FD

No treatment difference in 'symptom free' patients



Van Kerkoven LAS *et al. Clin Gastro Hepatol* 2008.

Antidepressants in FGID

Overview of options

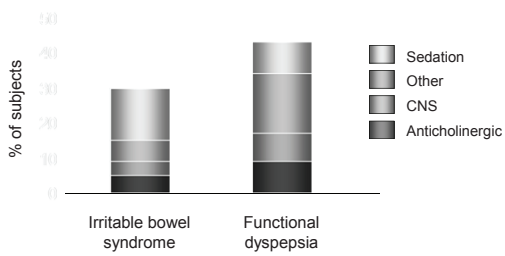
	TCAs	SSRIs	SNRIs
Agents	Amitriptyline, Imipramine, Doxepin, Desipramine, Nortriptyline	Fluoxetine, Sertraline, Paroxetine, Citalopram	Duloxetine, Venlafaxine Desvenlafaxine, Milnacipran
Dose range	10-200 mg	10-100 mg	30-90 mg (duloxetine) 75-225 mg (venlafaxine)
Adverse effects	Sedation Constipation Dry mouth/eyes Weight gain Hypotension Sexual dysfunction	Insomnia Diarrhea Night sweats Weight loss Agitation Sexual dysfunction	Nausea Agitation Dizziness Fatigue Liver dysfunction Constipation
Time to action	Few days to 2 weeks (low doses) 2-6 weeks (high doses)	3-6 weeks	3-6 weeks
Efficacy	Good	Moderate	Limited studies
Dose adjustments	Common	Usually not needed	Common

TCA=tricyclic antidepressant; SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin-norepinephrine reuptake inhibitor
Grover M, Drossman DA. *Gastrointest Endoscopy Clin N Am.* 2009;19:151-170.

Objectives

- Overview of refractory abdominal pain
- Strategies for using antidepressants (ADs) in patients FGID
- Scenarios where ADs often fail in FGID
- Strategies for augmenting AD therapy

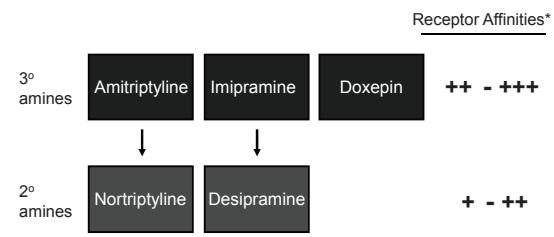
Side-effects from TCA Treatment of FGIDs are Common



Clouse RE *et al. Dig Dis Sci* 1994; Prakash C *et al. Dig Dis Sci* 1998.

Tricyclic Antidepressants

Receptor affinity predicts side effects

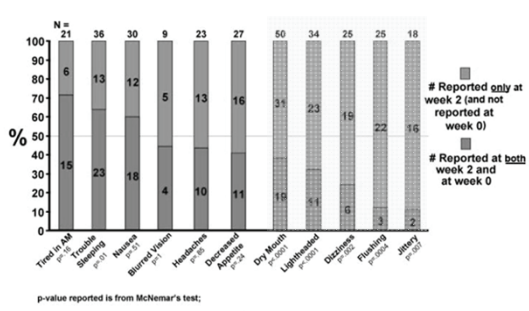


* For acetylcholine, histamine, and α-adrenergic receptors

Clouse RE and Lustman PJ. *GUT* 2006.

Antidepressant Therapy for FGIDs

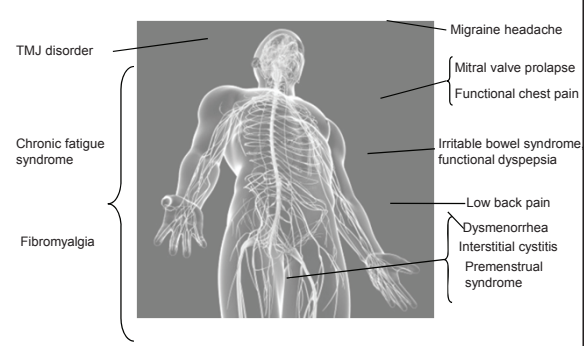
Side effect observations



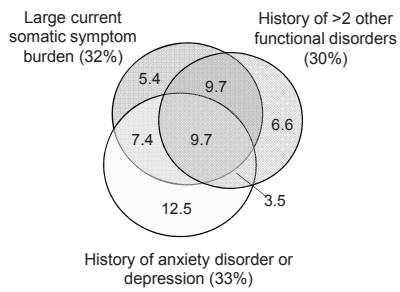
p-value reported is from McNemar's test;
A significant value (p<0.05) indicates disagreement between reporting at both time points

Thiwan S. *Clin Gastroenterol Hepatol* 2009.

Multiple **functional pain syndromes in the same patient *("somatization")***

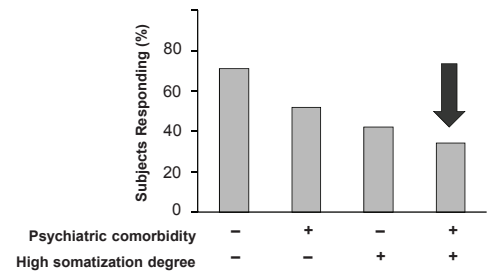


Functional GI Disorder (FGID) Comorbidity
High Symptom Burdens and Psychiatric Diagnoses



Sayuk GS. *Clin Gastroenterol Hepatol*. 2007.
Sayuk GS. *Psychosom Med*. 2007.

Antidepressants in FGIDs
Satisfactory Responses Predicted by Comorbidity*



* *At least 'moderate response' on a 4-part Likert scale*

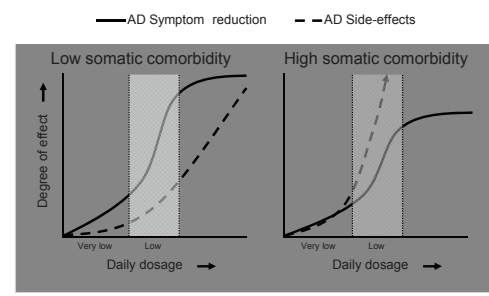
Sayuk GS. *Psychosom Med*. 2007

Abdominal pain patients with high comorbidity
Keys to antidepressant tolerance

- Very slow titration to final AD dosage
- Use of agents with favorable side effect profiles
  - Discuss anticipated side-effects
- Adjunct non-pharmacological therapies
  - Diet, exercise, psychological
- Frequent telephone contact and office visits

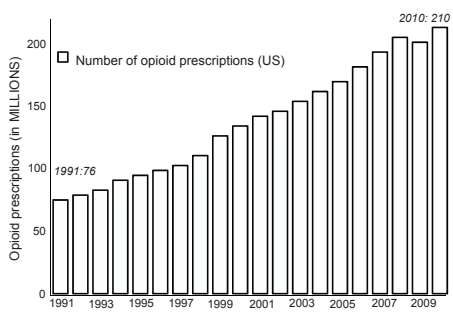
Sayuk GS. *Psychosom Med*. 2007.

AD Benefits and Side-effects
Vary by Somatic Comorbidity



Sayuk GS. *Psychosom Med*. 2007.

Narcotic Prescription Use
An iatrogenic epidemic

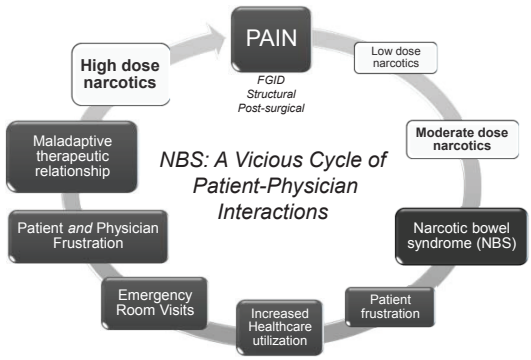


www. Drugabuse.gov; Source: SDI Vector One: National 2010.

What is Narcotic Bowel Syndrome (NBS)?

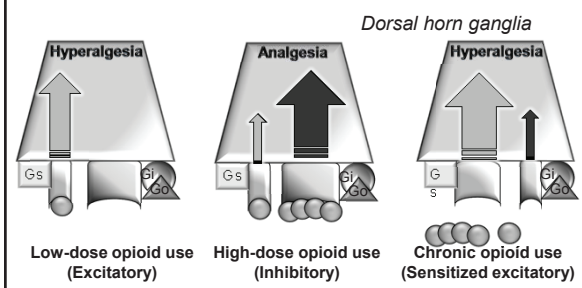
- Subset of opioid bowel dysfunction
- Chronic or recurring abdominal pain
- Pain worsens *despite* ongoing narcotic use, typically with *escalating dosages*
- Under-recognized, and likely increasing in prevalence

Drossman DA, et al. *Am J Gastroenterol* 2012.



Adapted from Grunkemeier *et al. Clin Gastroenterol Hepatol* 2007.

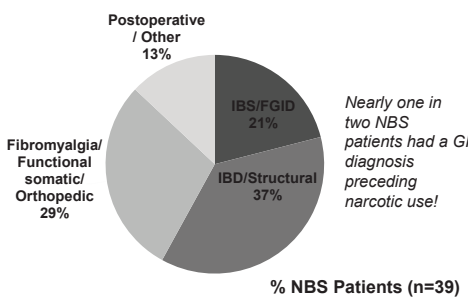
Bimodal opioid modulation: Narcotics *causing* pain



Crain SM *et al. Pain* 2000.

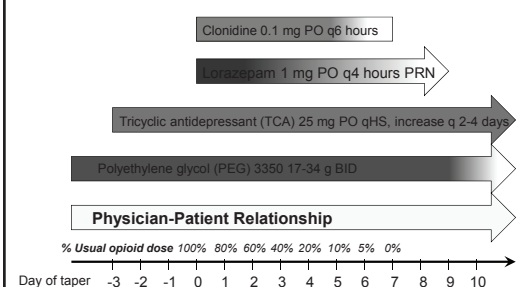
Patient diagnoses preceding NBS

"Creating our own monster"



Drossman DA, et al. *Am J Gastroenterol* 2012.

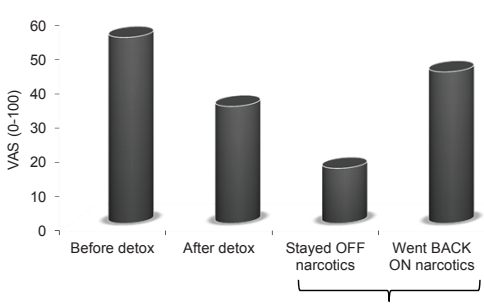
Withdrawing the NBS patient from narcotics



Adapted from Grunkemeier *et al. Clin Gastroenterol Hepatol* 2007.

NBS Abdominal pain scores

Before and after detoxification



Drossman *et al. Am J Gastroenterol 2012.*

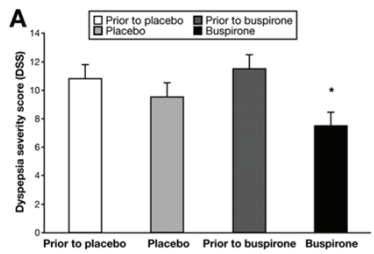
Objectives

- Overview of refractory abdominal pain
- Strategies for using antidepressants (ADs) in patients FGID
- Scenarios where ADs often fail in FGID
- Strategies for augmenting AD therapy

Buspirone, a 5-HT_{1D} agonist

Improvement in dyspeptic symptoms

Buspirone 10 mg tid for 2 weeks



Pain benefit associated with changes in gastric accomodation

Tack J *et al. CGH* 2011.

Buspirone, a 5-HT_{1D} agonist

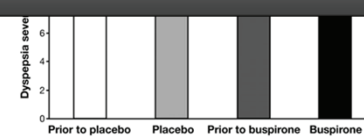
Improvement in dyspeptic symptoms

Buspirone 10 mg tid for 2 weeks

Anecdotally, good adjunct with TCAs for abdominal pain

Few drug interactions, very well tolerated

Need to titrate slowly (start 5 mg qd for 1 wk, then 5-7.5 mg bid)



Pain benefit associated with changes in gastric accomodation

Tack J *et al. CGH* 2011.

Alpha 2 delta (α2δ) Ligands

Gabapentin and pregabalin

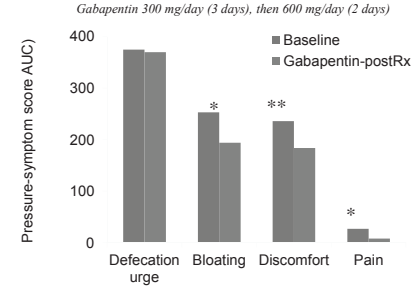
- High affinity binding to α2δ subunits of voltage-gated Ca channels
- Structurally related to inhibitory neurotransmitter, ɣ-aminobutyric acid (GABA)
- Established utility in neuropathic pain, migraine prophylaxis, anxiety
- Preclinical (animal) models suggest benefit at decreasing visceral hypersensitivity, particularly with superimposed stressors

Gale JA and Houghton LA. *Front Pharmacol* 2011.

Gabapentin for IBS pain

Reductions in rectal mechanosensitivity

Gabapentin 300 mg/day (3 days), then 600 mg/day (2 days)



** p<0.05 vs before study medication*

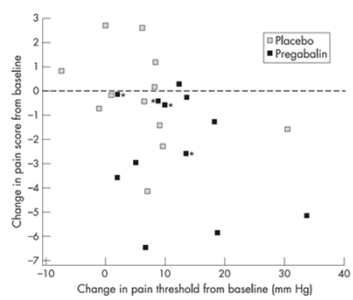
*** p<0.01 vs before study medication*

Lee KJ *et al. AP&T* 2005.

Pregabalin for IBS pain

Improvement in pain scores

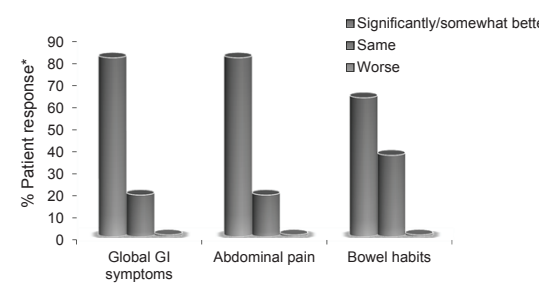
Pregabalin titrated 50→200 mg tid over a 3-week course



Houghton LA, *et al. Gut* 2007.

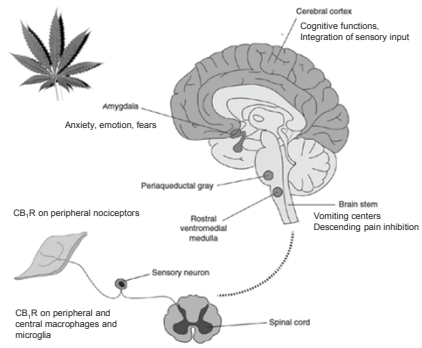
Atypical antipsychotics (quetiapine) in refractory abdominal pain

**10/21 (48%) IBS subjects discontinued quetiapine*



Grover M *et al. Dig Dis Sci* 2009.

Cannabinoids for pain
CNS Targets



Modified from: Starowicz K *et al. WIREs Membr Trans Sig* 2013.

Cannabinoids
An option for abdominal pain?

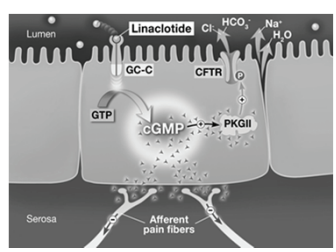
- Dronabinol (synthetic Δ^9-THC analog) available
- Benefits in both subjective and objective measures of pain, particularly neuropathic, in clinical trials
- Improvements in HRQOL
- Minimal data on abdominal pain to date
  - Pilot data showing improvement in non-cardiac chest pain symptoms and esophageal sensory thresholds
  - 5 mg po bid x 4 weeks

THC = tertahydrocannabinol

Rahn EJ and Hohmann AG. *Neurotherapeutics* 2009.
Malik Z *et al. Curr Gastroenterol Rep* 2015.

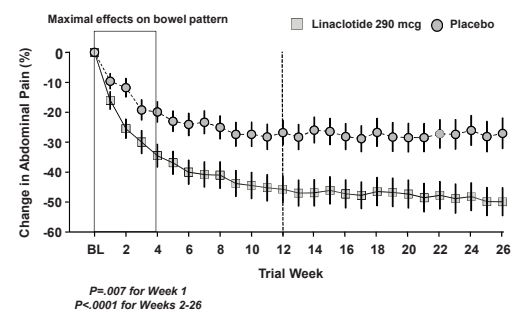
Linaclotide
A peripherally acting GC-C Agonist

- Stable peptide analog of guanylin and uroguanylin
- Via activation of GC-C receptor, increases intracellular and extracellular cGMP
- Extracellular cGMP may inhibit firing of enteric afferent pain fibers



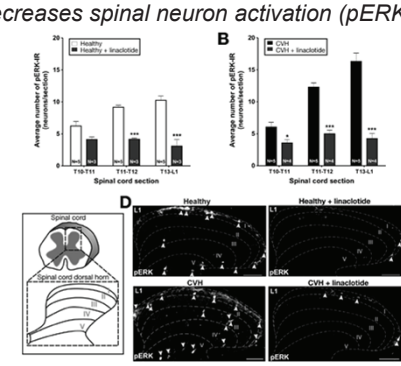
Wensel TM, Luthin DR. *Ann Pharmacother.* 2011;45:1535-1543.

Linaclotide in IBS-C
Abdominal pain continues to improve over 26 weeks



Chey WD *et al. Am J Gastroenterol* 2012.

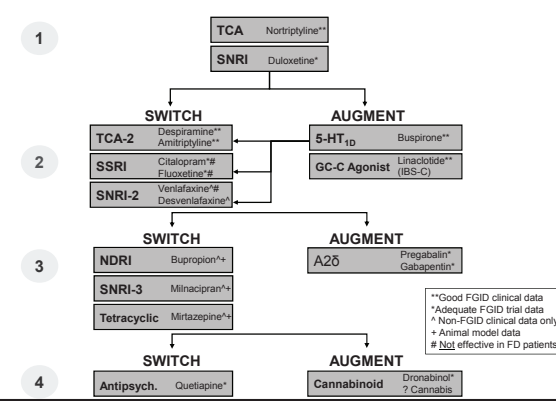
Linaclotide effects at spinal cord
Decreases spinal neuron activation (pERK-IR)



CVH = chronic visceral hypersensitivity

Castro J *et al. Gastroenterol* 2013.

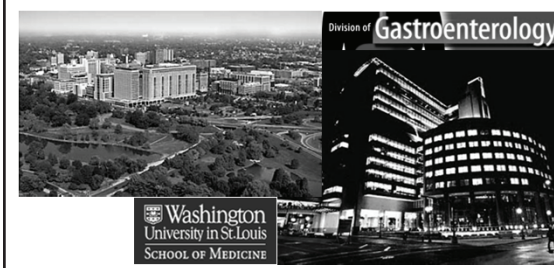
"Switch & Augment" Neuromodulator Strategy for FGID



Antidepressants in FGID

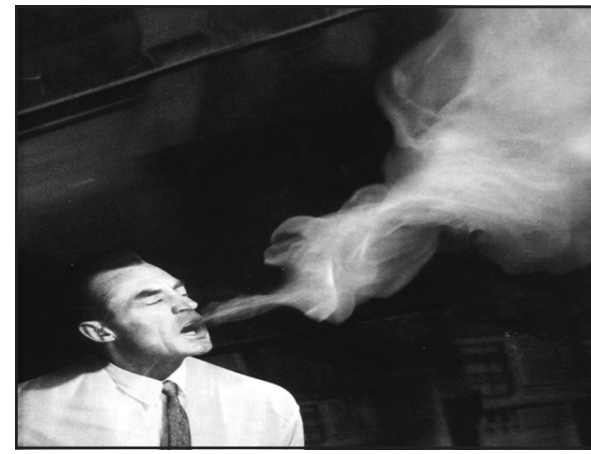
Prescriptions for success

- Biopsychosocial model of chronic abdominal pain forms rationale for antidepressant (AD) use in FGID
- ADs are not simple analgesics; address global symptoms, well-being
- Anticipate challenges (side effects, narcotics, multiple comorbidities)
- TCA>SNRI>SSRI; "Start low, go slow"
- Embrace "switch & augment" strategies to optimize FGID patient outcomes



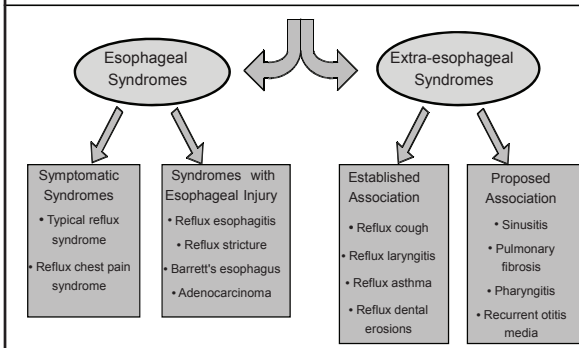
ADVANCES MANAGEMENT OF LARYNGEAL, PHARYNGEAL AND PULMONARY MANIFESTATIONS OF GERD

Michael F. Vaezi, MD, PhD, MSc, FACG
Professor of Medicine and Otolaryngology
Clinical Director, Interim Chief
Division of Gastroenterology, Hepatology and Nutrition
Vanderbilt University Medical Center

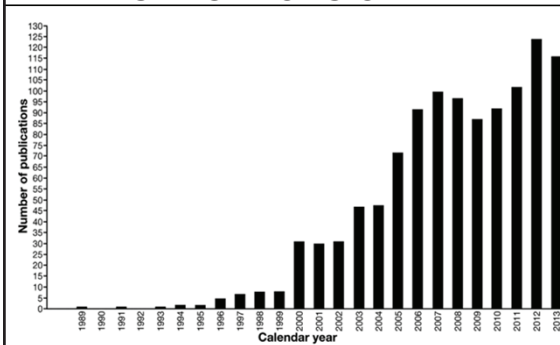


Silent GERD

GERD

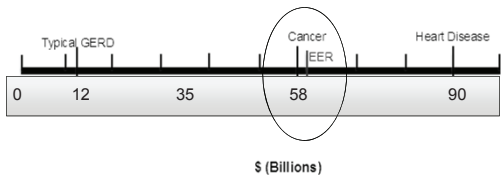


PUBLICATIONS ON EER



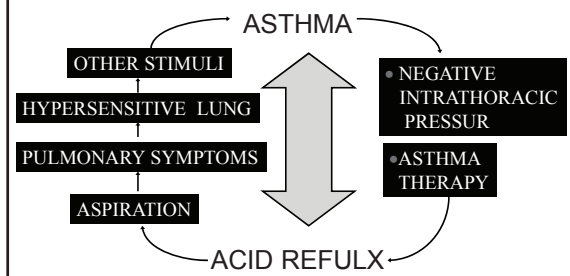
Francis and Vaezi, CGH 2015

Estimated Economic Burden of Extraesophageal Reflux

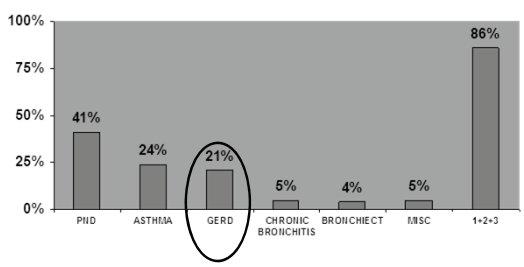


Francis and Vaezi, AJG 2013

GERD/ASTHMA RELATIONSHIP

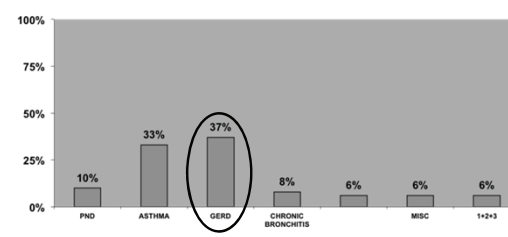


CAUSES OF CHRONIC COUGH



Irwin et al. Am Rev Respir Dis 1990; 141:640

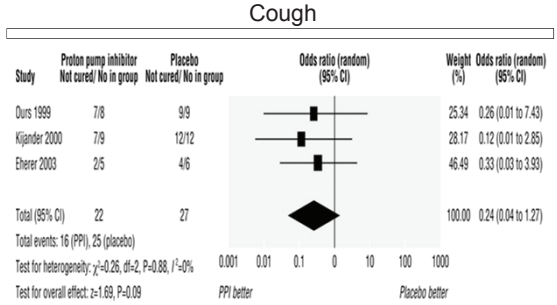
CAUSES OF CHRONIC COUGH



Ojoo et al. Cough 2013

META ANALYSIS

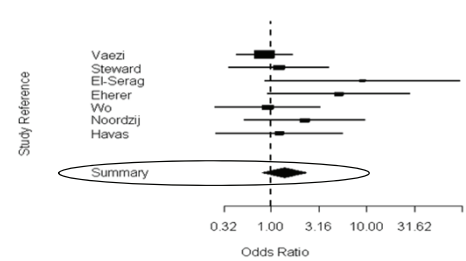
Cough



Chang et al, BMJ 2005

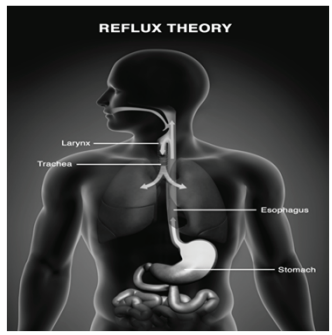
META ANALYSIS

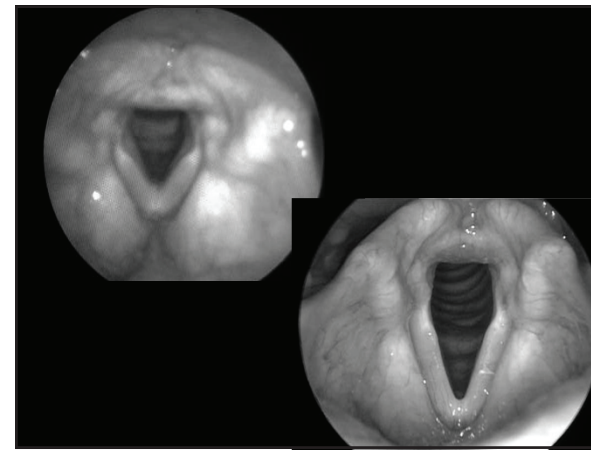
LPR



Qadeer and Vaezi, AJG 2007

Aspiration Theory





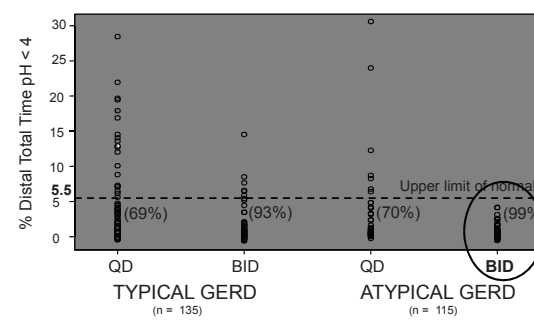
Laryngeal Signs in Healthy Volunteers

- At least one "abnormal" finding: 91/105 (87%)

	Prevalence
Interarytenoid bar	75/105 (71%)
Arytenoid medial wall erythema	31/105 (30%)
Post. pharyn. wall cobblestoning	22/105 (21%)
Interarytenoid bar erythema	16/105 (15%)
Arytenoid medial wall granularity	14/105 (13%)

Hicks and Vaezi, J Voice 2003

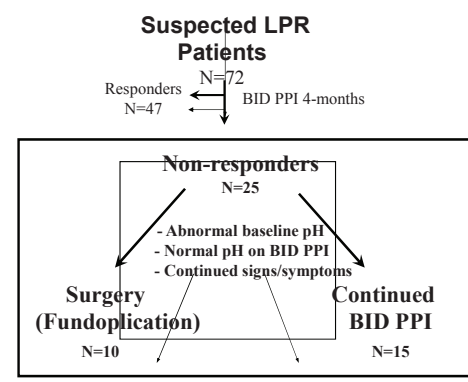
PH MONITORING ON PPI THERAPY



Charbel and Vaezi. Am J Gastroenterol 2005

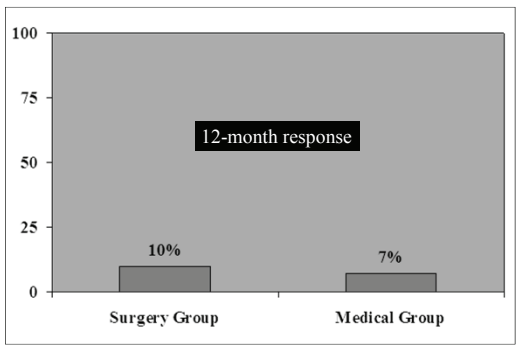
What About Surgery?

- Poor Test Sensitivity
- Intermittent Reflux
- Pepsin is the devil



Swoger and Vaezi, CGH 2005

Surgery Does not Improve Symptom

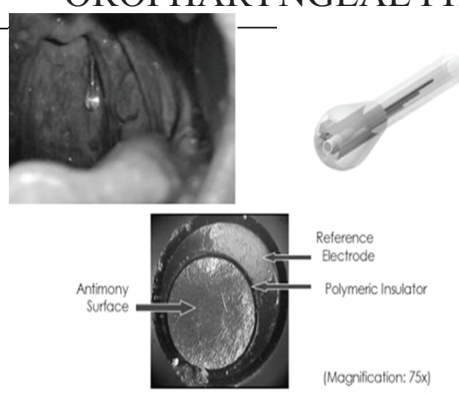


Swoger and Vaezi, CGH 2005

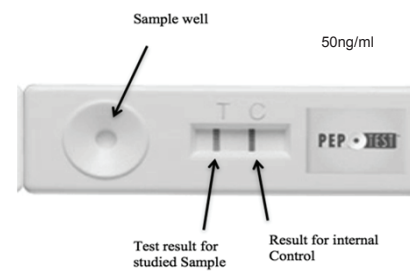
TESTING EXPECTATIONS

	NORMAL FINDINGS
• *EGD ----------→*	*> 80%*
• *pH on therapy ----------→*	*> 90%*
• *Impedance/pH:*	
– *On bid PPI therapy-----→*	*70%*
– *Off PPI therapy--------→*	*60%*

OROPHARYNGEAL PH

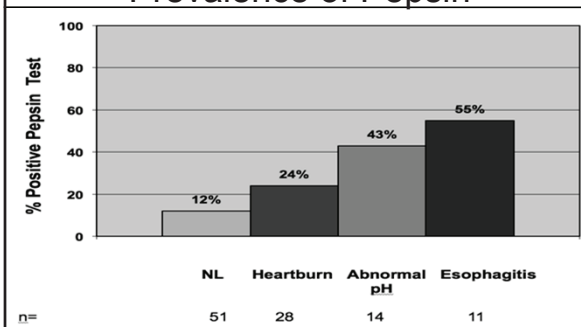


Salivary Pepsin



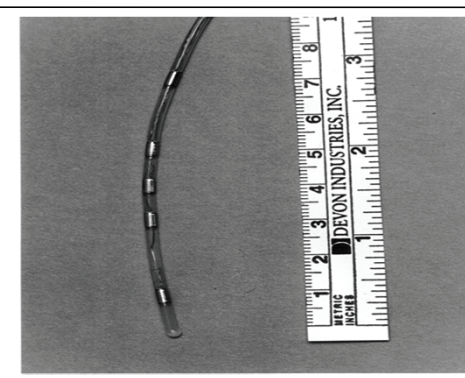
Yuksel and vaezi, laryngoscope 2012

Prevalence of Pepsin

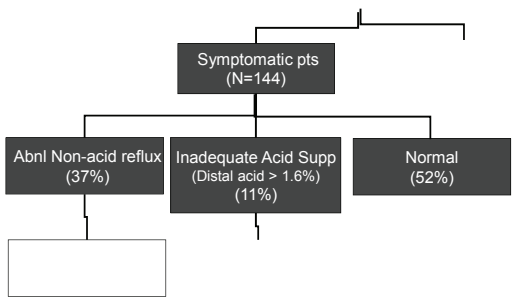


Yuksel and vaezi, laryngoscope 2012

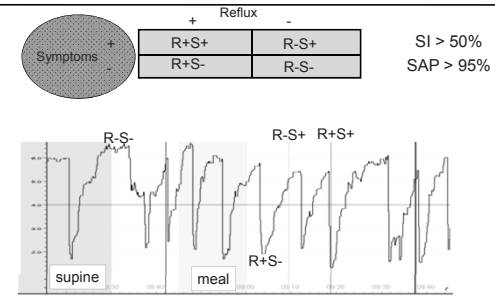
AMBULATORY 2.3 mm MII-pH CATHETER



Impedance-pH in Refractory to BID PPI

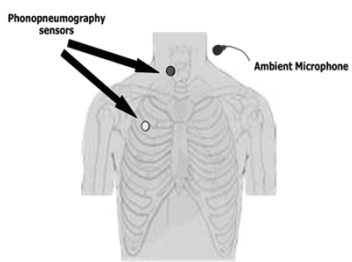


Mainie et al. Gut 2006; 55:1398-1402.



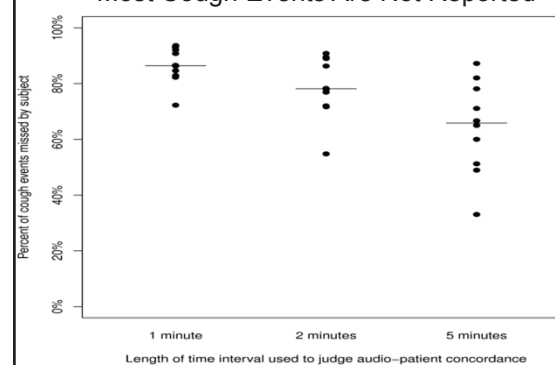
Kavitt and Vaezi, Gastroenterology 2012

Audio Recording and pH Monitoring



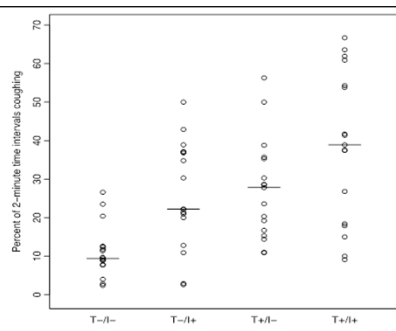
Kavitt and Vaezi, Gastroenterology 2012

Most Cough Events Are Not Reported



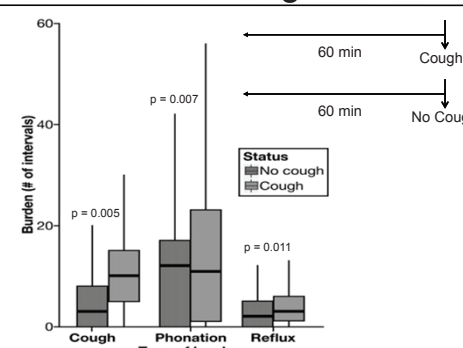
Kavitt and Vaezi, Gastroenterology 2012

Affect of Talking and Reflux on Cough



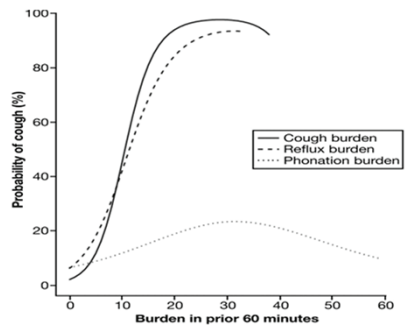
Francis and Vaezi, CGH 2016

Burden of Cough



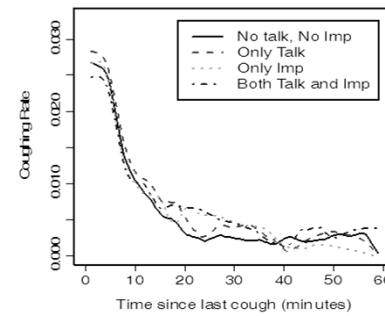
Francis and Vaezi, CGH 2016

Burden of Cough



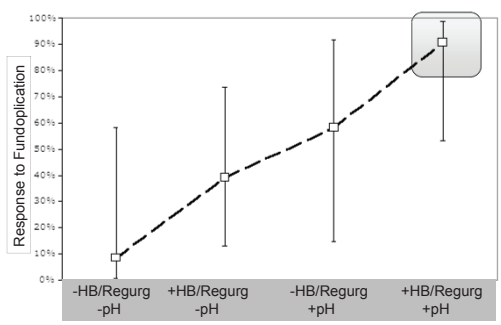
Francis and Vaezi, CGH 2016

Cough Induces More Cough



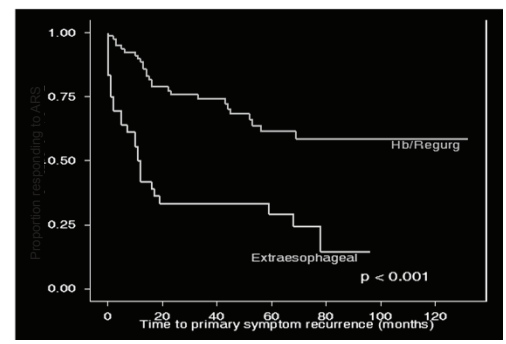
Francis and Vaezi, CGH 2016

HB/Regurg/Acid

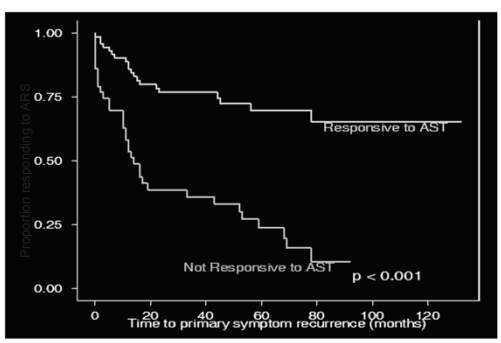


Francis and Vaezi, Laryngoscope 2011

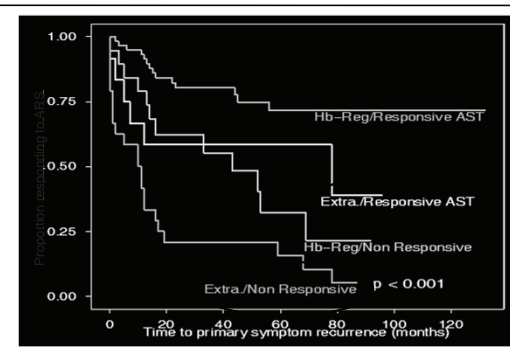
Outcome by presenting symptom



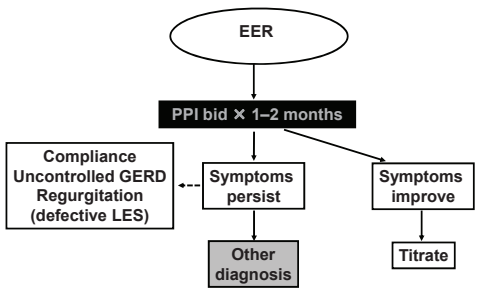
Outcome by response to AST

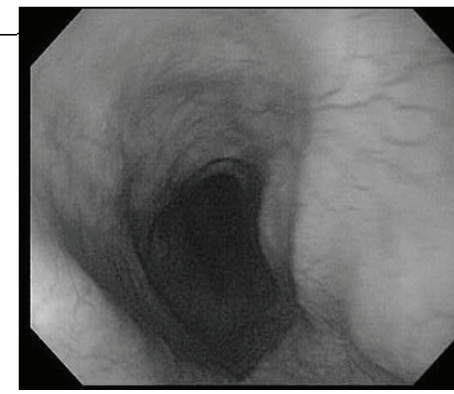


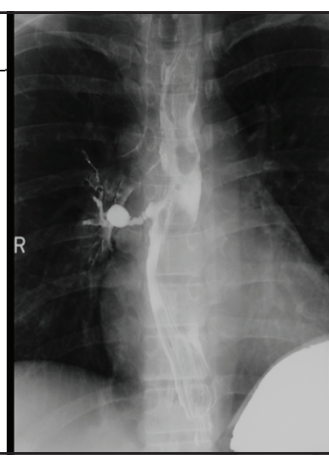
Outcome by presenting symptom and response to AST

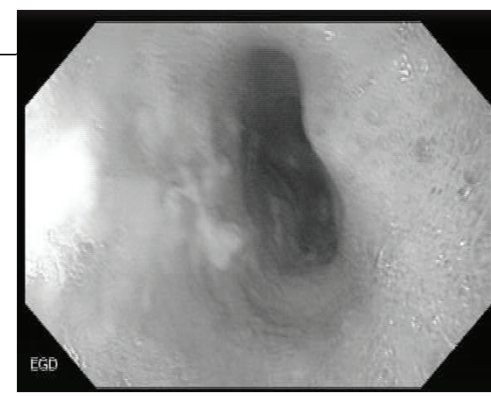


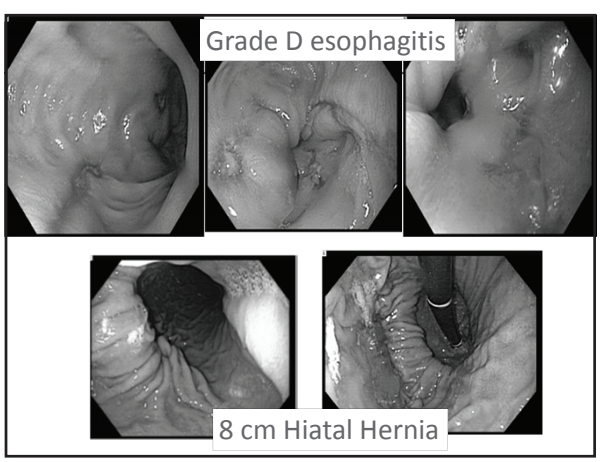
Algorithm


EER
PPI bid × 1–2 months
Compliance
Uncontrolled GERD
Regurgitation
(defective LES)
Symptoms persist
Symptoms improve
Other diagnosis
Titrate




R


EGD


Grade D esophagitis
8 cm Hiatal Hernia

Reflux Monitoring: pH and Impedance-pH

Marcelo F. Vela, MD, MSCR
Mayo Clinic Arizona
Scottsdale, AZ, USA

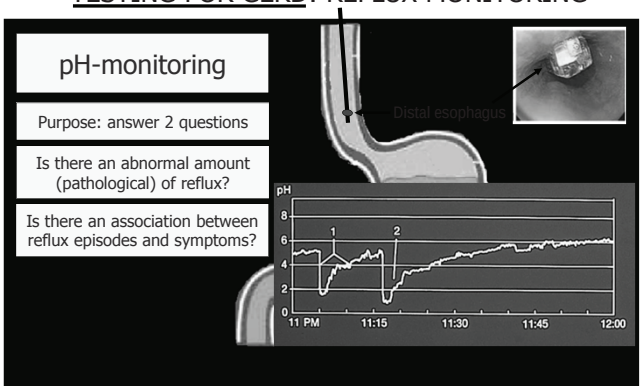
COMMON INDICATIONS FOR REFLUX MONITORING

- As pre-operative evaluation before anti-reflux surgery
- Establish whether reflux may play a role in those with extraesophageal presentations
- Work-up of patients with incomplete response to PPI

AVAILABLE TOOLS

- Catheter-based pH monitoring
- Wireless pH monitoring
- Impedance-pH monitoring

TESTING FOR GERD: REFLUX MONITORING



DEFINITION OF PATHOLOGIC REFLUX

- **Percent acid exposure (pH <4.0)**
  - **Upright**
  - **Recumbent**
  - **Total**
- **Total number of reflux episodes**
- **Number of episodes > 5 minutes**
- **Time of single longest episode**

Johnson LF, DeMeester TR: Am J Gastroenterol 62:325, 1974

USEFULNESS OF pH MONITORING

- Robust indicator of GERD when abnormal

Test OFF PPI

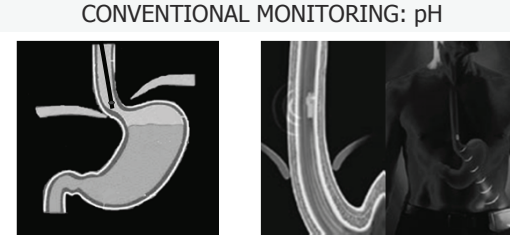
- Abnormal 24-hour pH score predicts a successful outcome of fundoplication
- Patients with normal preoperative pH score had worse symptomatic outcomes

Campos et al. J Gastrointest Surg 1999
Khajanchee et al. Am J Surg 2004

- Likelihood of abnormal pH test ON PPI
  - 10% typical symptoms
  - 1% atypical symptoms

Charbel et al. Am J Gastroenterol 2005

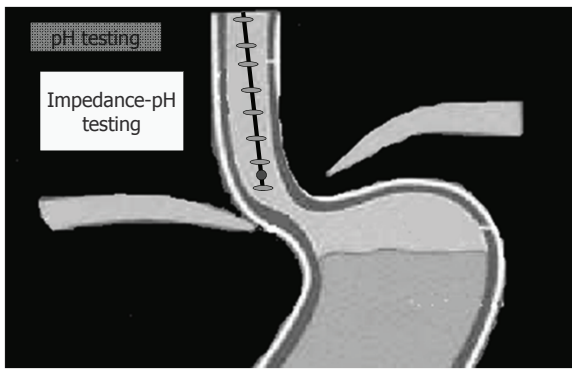
CONVENTIONAL MONITORING: pH



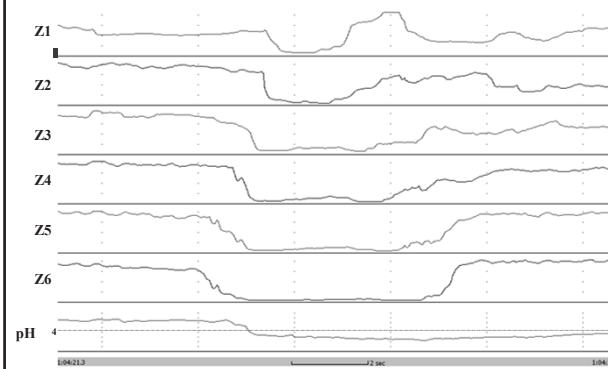
ACID REFLUX

- In patients with ongoing symptoms despite adequate acid suppresion → **Reflux with pH>4** ***weakly acidic nonacid***

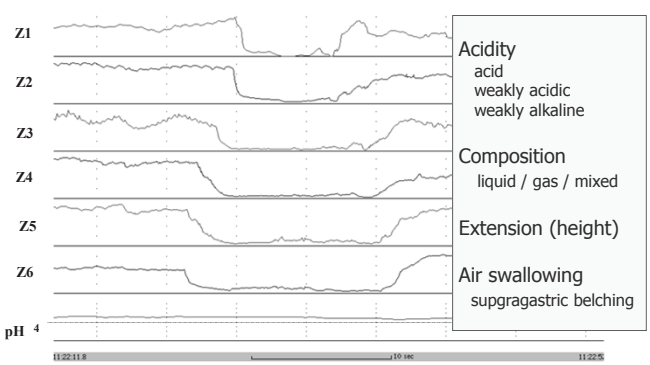
TESTING FOR GASTROESOPHAGEAL REFLUX

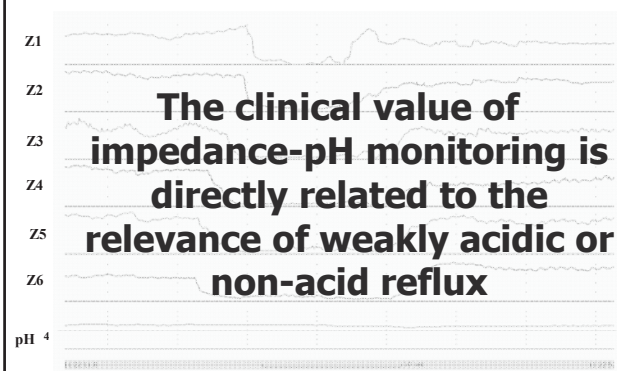


ACID REFLUX



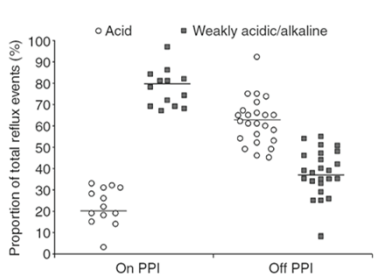
NON-ACID REFLUX (pH > 4)





SYSTEMATIC REVIEW: ROLE OF ACID, WEAKLY ACIDIC AND WEAKLY ALKALINE REFLUX IN GERD

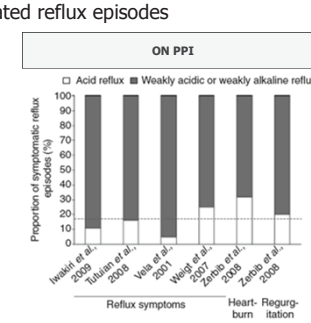
- 21 studies involving 664 patients
  - 374 patients on PPI / 382 patients off PPI



Boecksxtaens and Smout Aliment Pharmacol Ther 2010

SYSTEMATIC REVIEW: ROLE OF ACID, WEAKLY ACIDIC AND WEAKLY ALKALINE REFLUX IN GERD

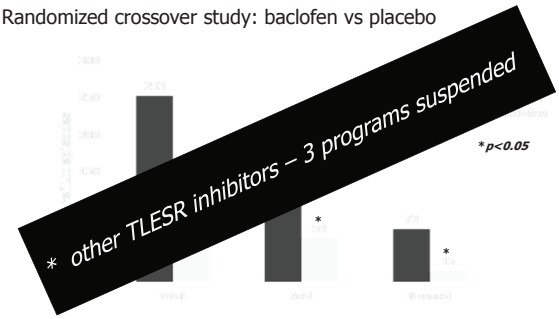
- Symptom-related reflux episodes



Boecksxtaens and Smout Aliment Pharmacol Ther 2010

EFFECT OF BACLOFEN ON ACID AND NONACID REFLUX

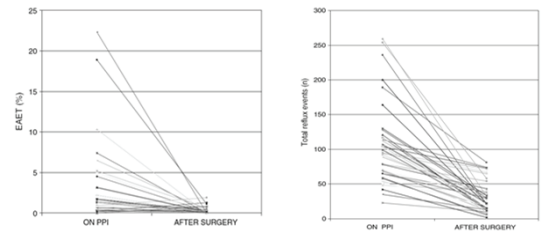
- 18 subjects with heartburn
- Randomized crossover study: baclofen vs placebo



Vela, Aliment Pharmacol Ther 2003

Nissen Fundoplication in Refractory GERD

- **40 patients with heartburn / regurgitation despite PPI**
- **Impedance-pH monitoring:**
  - **on PPI before surgery**
  - **off PPI 3 months after fundoplication**



Esophageal Acid Exposure Time | Number of reflux episodes

Frazzoni et al. Dig Dis Sci 2011;56:1099

Nissen Fundoplication in Refractory GERD

- 3-year follow-up in 38 patients recently published
  - Good symptom control in 34 of 38
  - Reflux parameters improved

Characteristic	Before surgery	After surgery	*P*
LES tone, mmHg	13 (8–20)	19 (14–25)	0.001
Total refluxes	68 (45–94)	8 (4–17)	0.001
Abnormal %EAET	6 (16 %)	3 (8 %)	0.480

Frazzoni Surg Endosc 2013

NON-ACID REFLUX: CLINICAL RELEVANCE?

Measurable
Provokes symptoms
Treatable
Further research (RCTs) needed

24-hour impedance-pH monitoring: Report

Impedance-pH Monitoring Details
Reflux Study

Acid Exposure (pH)

	Upright	Upright Normal	Recumbent	Recumbent Normal	Total	Total Normal
Clearance pH : Channel 7						
Number of Acid Episodes	2		0		2	
Time	1.5 min		0.0 min		1.5 min	
Percent Time	0.2%	(<1.5 %)	0.0%	(<0.5 %)	0.1%	(<1.3 %)
Mean Acid Clearance Time	46 sec		0 sec		46 sec	
Longest Episode	1.2 min		0.0 sec		1.2 min	

Acid Exposure normal values in parentheses are valid for PPI medicated 95th percentile adult.

Reflux Episode Activity (Impedance)

	Upright	Recumbent	Total	Normal
Acid	8	1	9	
Nonacid	72	5	77	
All Reflux	80	6	86	(<48)

NOTE: Reflux episodes are detected by Impedance and categorized as acid or nonacid by pH.

Symptom Correlation to Reflux (Impedance)

Symptom	Occurrences	Acid Related	Nonacid Related	All Reflux Related	Unrelated
Belch	7	1	5	5	2
Acid regurgitation	1	0	1	1	0

Reflux Symptom Index (Impedance)

Symptom	Acid	Nonacid	All Reflux
Belch	14%	71%	71%
Acid regurgitation	0%	100%	100%

Patient History
Symptom(s):
Belching
Medications:
Pantoprazole 40 mg BID

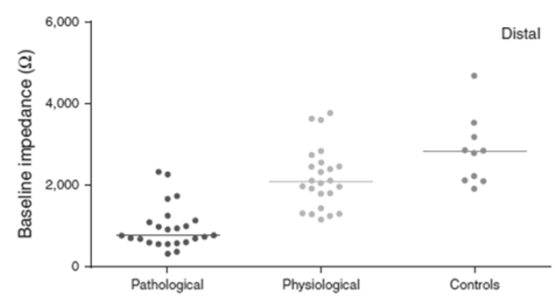
Impressions

Esophageal Acid Exposure: normal

Total Number Reflux Episodes: increased, predominantly nonacid

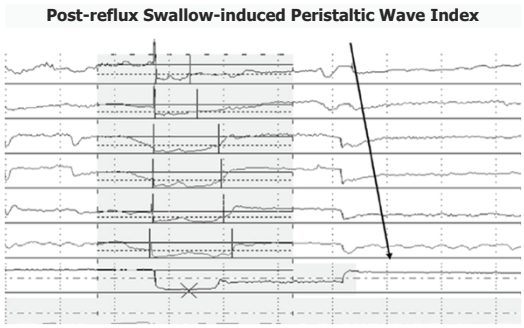
Symptom Association: good for reflux episodes with belching and acid regurgitation

NEW impedance-pH parameters: Baseline impedance



Kessing, Am J Gastroenterol 2011

NEW impedance-pH parameters: PSPW Index



Frazzoni, Clin Gastroenterol Hepatol 2016

CHOOSING BETWEEN pH and IMPEDANCE-pH

Mode of testing

- OFF PPI: any technique, primary outcome is acid reflux by pH
- ON PPI: must use impedance-pH to account for weakly acidic reflux

Indication

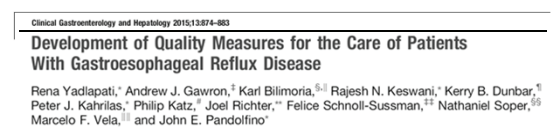
- As pre-operative evaluation before anti-reflux surgery
- Role of reflux in extraesophageal presentations
- Belching
- Work-up of patients with incomplete response to PPI

Impedance-pH Monitoring

"Reflux monitoring ON PPI should be performed with impedance-pH monitoring"

Am J Gastroenterol 2013

Impedance-pH Monitoring



"If planning to perform reflux monitoring on antireflux medication, then impedance-pH monitoring should be performed to enable measurement of persistent acid or nonacid reflux"

Clin Gastroenterol Hepatol 2015

IMPEDANCE-pH MONITORING

ISSUES AND UNANSWERED QUESTIONS

- No controlled studies of surgery for nonacid or weakly acidic reflux
- How best to define an abnormal test?
- What parameters predict response to therapy?
- Value of new parameters (PSPW, baseline impedance)

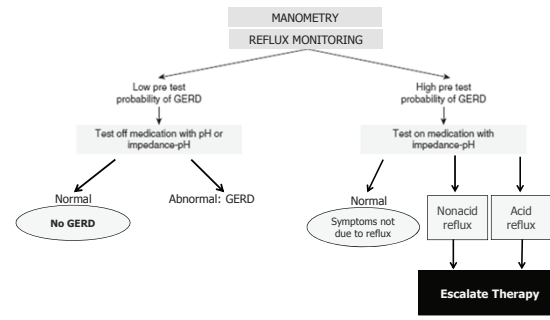
PERSISTENT SYMPTOMS DESPITE ACID SUPPRESSION

- Ongoing acid reflux:
  therapeutic failure– medication does not achieve sufficient acid suppression
- Nonacid reflux:
  adequate acid suppression, reflux of nonacidic material
- NO reflux at all:
  other etiologies (eosinophilic esophagitis, functional heartburn, etc)

PERSISTENT SYMPTOMS DESPITE ACID SUPPRESSION

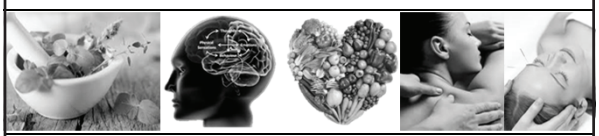
1. Optimize PPI dosing
2. Exclude other potential etiologies (EGD, ENT/Pulmonary consultation, etc.)
3. Perform reflux monitoring

PERSISTENT SYMPTOMS DESPITE ACID SUPPRESSION



Katz P, Gerson L, Vela MF, Am J Gastroenterol 2013

Complementary and Alternative Medicine Therapies for Functional Gastrointestinal Disorders

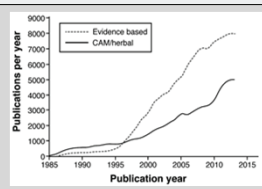


Jasmine Zia, MD
Acting Assistant Professor, University of Washington
ANMS 11th Postgraduate Course, San Francisco, CA
August 25, 2016

Complementary and Alternative Medicine (CAM)

"A group of diverse medical and healthcare systems, practices and products that are not generally considered to be part of conventional medicine."

Why should we learn about CAM?

Patients	• **Up to 44% of GI patients use CAM** • Women, higher education, anxiety, symptom severity • $30.2B yearly out-of-pocket expenses on CAM (2012 NHIS)
Researchers	
Funding	• The "National Center for Complementary and Alternative Medicine" was established as part of NIH in 1998 • Annual budget: $19.5M (1998) -> **$124.1M** (2015)

Holtmann G et al. *Clinical Gastroenterology and Hepatology* 2015;13:422-432.
Hung et al. *Dig Dis Sci* 2015;60:1883-1888.

Why are FGID patients seeking CAM?

"Want to feel better"

- Dissatisfied with conventional treatment
- 62% experienced improved GI symptoms
- Most common CAM:
  – Ginger, massage therapy, & yoga

Hung et al. *Dig Dis Sci* 2015;60:1883-1888.

CAM Therapies for FGIDs


Herbal Medicines


Mechanical Interventions


Behavioral Therapies

Diet & Lifestyle Modifications

Herbal Medicines for FGIDs

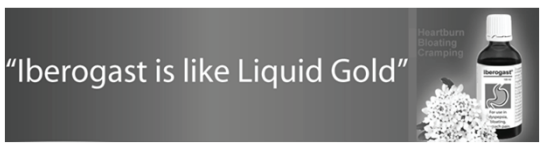
STRONG EVIDENCE

Both FD & IBS	IBS	FD
STW 5 (Iberogast®)	Peppermint Oil	Peppermint Oil + Caraway Oil

WEAK EVIDENCE

Both FD & IBS	IBS	FD
Ginger	Padma Lax	Xiaoyao San (MXS)
Artichoke Leaves	Carminatives	Xinwei Decoction
	Tong Xie Yao Fang	Chiois Mastic Gum
	Tumeric	

STW 5 (Iberogast®) for FD & IBS



STRONG EVIDENCE

STW 5 (Iberogast®)

- Proprietary blend of herbs
  - Bitter candytuft, angelica root, chamomile, caraway fruits, milk thistle, lemon balm, peppermint, celandine, licorice
- Dose: 20 drops before each meal
- Cost: $32 USD for 100ml bottle (~1 month)
- Adverse drug reaction: 0.04%
- Possible interaction with Coumadin?

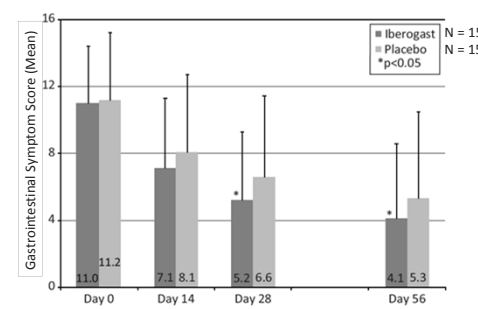
STW 5 (Iberogast®)

- Meta-analysis with 12 clinical trials
- 6 RCTs (N = 413)
  - 5 in FD: 4 placebo & 1 cisapride
  - 1 in IBS: 1 placebo

Efficacy of Symptom Reduction:
- Iberogast > Placebo
- Iberogast = Cisapride

Von Arnim U et al. *Am J Gastroenterol* 2007;102(6):1268-75.

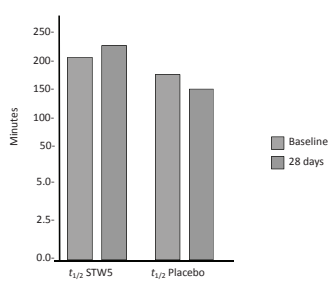
STW 5 (Iberogast®) for FD



Von Arnim U et al. *Am J Gastroenterol* 2007;102(6):1268-75.

STW 5: Mechanisms of Action

Not from: Gastric Emptying of Solids

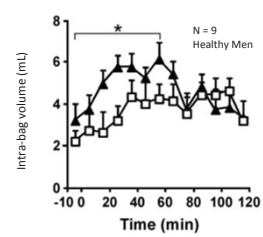


Braden B et al. *Neurogastroenterol Motil* 2009;21:632-e25.

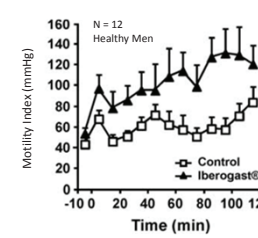
STW 5: Mechanisms of Action

Possibly from:

⇧ Gastric Relaxation



⇧ Antral Motility Index



Pilichiewicz AN et al. *Amer J Gastroenterol* 2007;102:1276-1283.

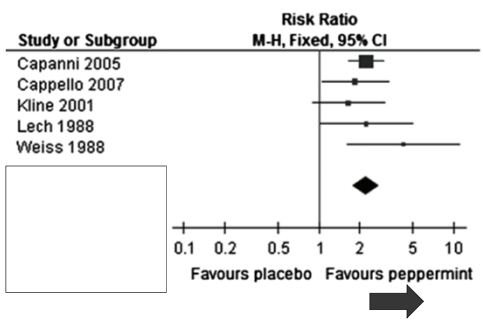
Peppermint Oil for IBS

STRONG EVIDENCE

Peppermint Oil Capsules

Brand/Formulation	Directions	Cost per day
Peppermint Oil	5 drops in a glass of water QD	$0.09
Colpermin	1 capsule TID	$0.99
Peptogest	2 capsules TID	$1.07
Heather's Tummy Tamers	2 capsules TID	$0.90
IBgard	1-2 capsules TID	$3.75

Peppermint Oil



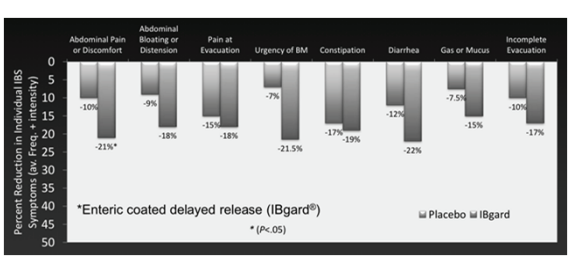
Khanna R et al. *J Clin Gastroenterol*, 2014;48:505-512.

Efficacy of Peppermint Oil

IBS treatment	NNT vs placebo
Alosetron	8
Antidepressants	4
Antispasmodics	5
Fiber	11
Linaclotide[b]	8
Lubiprostone	12
"Placebo without deception"[c]	4
Peppermint oil	2.5
Rifaximin	11
Tegaserod	10

Spiegel BMR. *Clinical Gastro and Hep*, 2011;9:461-469.

Enteric-Coated Delayed Release Peppermint Oil Capsules: IBgard®



Epstein et al. *DDW*, 2015.

Peppermint Oil

- Mechanism of action:
  - Decreases smooth muscle contractility by calcium channel blockade
- Side effects:
  - Heartburn, respiratory depression, stomatitis, anal burning

Grundmann O et al. *World J Gastroenterol* 2014;20(2):346-362.

Peppermint + Caraway Oil

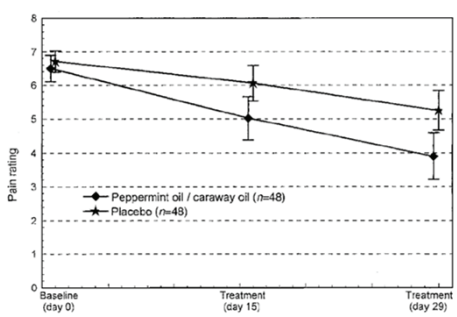
STRONG EVIDENCE

Peppermint + Caraway Oil for FD

Peppermint + Caraway Oil VERSUS…	Efficacy of Symptom Reduction	# of RCTs
PLACEBO	Peppermint + Caraway Oil >> Placebo	3
ENTERIC FORMULATION	Equivalent	1
CISAPRIDE	Equivalent	1

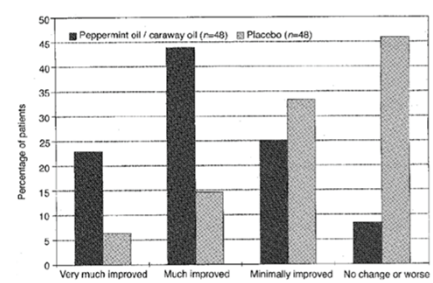
Holtmann G et al. *Phytomedicine* 2003;10 Suppl 4:56-7.

Peppermint + Caraway Oil for FD



May B et al. *Aliment Pharmacol Ther* 2000;14:1671-1677.

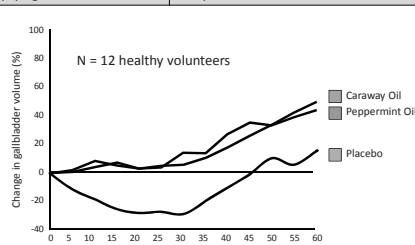
Peppermint + Caraway Oil for FD



May B et al. *Aliment Pharmacol Ther* 2000;14:1671-1677.

Mechanism of Peppermint + Caraway Oil

Mechanism	Effect Compared to Placebo
Antral Filling Time	No difference
Gastric Emptying Time	No difference
Gallbladder emptying	Complete Inhibition



Goerg KJ et al. *Aliment Pharmacol Ther* 2003;17:445-451.

Ginger

WEAK EVIDENCE

Ginger

- Indications: Nausea, vomiting
- Dose: 500-1000mg, 2-3 times daily
- Can use dry ginger or ginger tea
- Dry ginger more potent than fresh -> pro-kinetic activity concentrate on drying
- Side effects - heartburn, diarrhea, mouth and throat irritation
- Drug interactions: Possible with Coumadin, Plavix, Lovenox, Heparin and laxatives

RCTs of Ginger

Indication	Conclusions
Functional Dyspepsia N = 11	**No impact on symptoms**
Irritable Bowel Syndrome N = 45	**No impact on symptoms**
Post-operative nausea N = 288	POOLED absolute risk reduction NOT significant
Motion sickness N = 80	Superior to placebo (only after 4 hrs)
Morning sickness N = 30	Superior to placebo
Chemotherapy-induced N = 41	Superior to placebo

Ernst E et al. *British Journal of Anaesthesia* 2000;84(3):367-71.
Hu ML et al. *World J Gastroenterol* 2011;17(1):105-110.
Van Tilburg MAL et al. *Complement Ther Med* 2014;22(1):17-20.

Artichoke Leaf Extract

"Digestive aid which aims to reduce bloating, abdominal pain and cramps as well as reducing both diarrhea and constipation through normalization of GI motility."

WEAK EVIDENCE

Artichoke Leaf Extract Clinical Trials

Indication	Evidence
Functional Dyspepsia	6-week double-blind RCT, N = 247 Greater symptom improvement and global QOL scores
Irritable Bowel Syndrome	Two non-blinded, non-randomized cohort studies with no placebo, N = 488 *One of which was a post-marketing study…* Significant reductions in overall IBS symptoms

Holtmann G et al. *Aliment Pharmacol Ther* 2003;18:1099-1105.
Grundmann O et al. *World J Gastroenterol* 2014;20(2):346-362.
Bundy R et al. *The Journal of Alternative and Complementary Medicine* 2004;10(4):667-669.
Walker AF et al. *Phytother Res* 2001;15(1):58-61.

Other Herbal Medicines for IBS

Herbal Med	Study Design	Efficacy
Padma Lax	Randomized, double-blind, placebo-controlled pilot study N = 61	Less constipation, abdominal pain, & flatulence compared to placebo ($p < 0.05$) after 3 mo
Carminatives	Randomized, double-blind, placebo-controlled pilot study N = 121	Significant decrease in IBS-SSS: 50 (curcumin/fennel essential oil) vs. 26 (placebo) ($p < 0.001$)
Tong Xie Yao Fang	12 poorly conducted studies	Diverse end points, adjustments to combination based on IBS symptom presentation
Tumeric	Randomized, double-blind, placebo-controlled study N = 106 Partially blinded, randomized, two-dose, pilot study N = 207	No therapeutic benefit over placebo Reduction in IBS prevalence in both treatment groups (1 or 2 tabs) compared to baseline ($p < 0.001$) after 2 mo

Grundmann O et al. *World J Gastroenterol* 2014;20(2):346-362.
Portincasa P et al. *J Gastrointestin Liver Dis* 2016;25(2):151-157.
Bundy R et al. *J of Alternative and Complementary Med* 2004;10(6):1015-1018.
Brinkhaus B et al. *Scandinavian J of Gastroenterology* 2005;40:936-943.

WEAK EVIDENCE

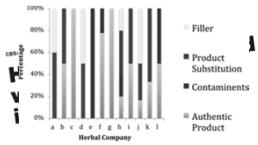
Other Herbal Medicines for FD

Herbal Med	Study Design	Efficacy
Xiaoyao San (MXS)	Meta-analysis with 14 "weak" trials	Total effective rate of symptom improvement: 82.6% to 93.7% Symptoms furthermore reduced by a combination of MXS and prokinetic drugs compared to prokinetic drugs alone
Xinwei decoction	Randomized, double-blind (?), placebo-controlled study N = 73	Significantly decreased FD symptom & depression/anxiety scales, compared to both domperidone and placebo ($p < 0.01$).
Chois mastic gum	Randomized, double-blind, placebo-controlled study N = 148	Significantly lower symptoms scores compared to placebo after 3 weeks ($p < 0.05$).

Qin F et al. *J of Gastroenterol Hepatol* 2009;24(8):1320-5.
Dabos KJ et al. *J of Ethanopharmacology* 2010;127:205-209.
Zhao L et al. *Amer J of Chinese Medicine* 2005;33(2):249-257.

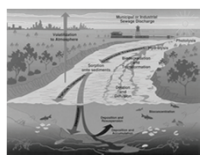
WEAK EVIDENCE

Concerns About Herbal Medicines



Misinformation

Poorly Conducted Studies



Poor/Inconsistent Quality

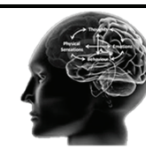
Safety Concerns

Holtmann G et al. *Clinical Gastroenterology and Hepatology* 2015;13:422-432.
http://theconversation.com/herbal-medicines-adulterated-contaminated-or-just-plain-missing-its-an-international-scandal-6060

CAM Therapies for FGIDs

Herbal Medicines

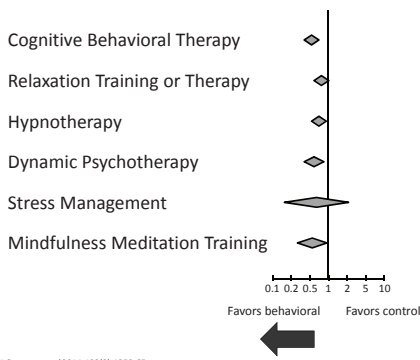
Mechanical Interventions



Behavioral Therapies

Diet & Lifestyle Modifications

Behavioral Therapies for IBS



Ford AC et al. *Am J Gastroenterol* 2014;109(9):1350-65.

Behavioral Therapies for FD

Therapy	Study Design	Efficacy
Relaxation Training	Self-help program versus recording symptoms (control) N = 103	Week 12: pain intensity and frequency reduced in treatment compared to control group ($p < 0.01$) Year 1: No significant difference between groups Drop-out rates: 38% (self-help) and 49% (control)
Cognitive Behavioral Therapy	CBT versus no tx N = 100	Year 1: improvement in epigastric, nausea, heartburn, constipation, and diarrhea ($p < 0.05$)
Psychodynamic-Interpersonal Psychotherapy	Psychotherapy versus supportive care (counseling sessions) N = 95	7 sessions: greater improvement in total FD symptoms in psychotherapy compared to supportive care ($p = 0.02$) Year 1: no difference
Hypnotherapy	Hypnotherapy versus supportive care + placebo (control) or ranitidine BID (medical) N = 126	Week 16: symptom scores lower in hypnotherapy compared to both the control ($p = 0.01$) and medical group ($p = 0.06$) Week 56: hypnotherapy group felt better, were less likely to visit their clinicians, and were less likely to start medications for their FD ($p < 0.001$)

Lacy BE et al. *Aliment Pharmacol Ther* 2012;36(1):3-15.

CAM Therapies for FGIDs

Herbal Medicines

Mechanical Interventions

Behavioral Therapies

Diet & Lifestyle Modifications

Massage and Reflexology

- **Efficacy: Unknown**
- Case reports: gut-directed massage may relieve specific symptoms such as bloating and chronic constipation (not specific for IBS).
- No significant differences in small study comparing foot reflexology massage to non-reflexology foot massage.

Grundmann O et al. *World J Gastroenterol* 2014;20(2):346-362.

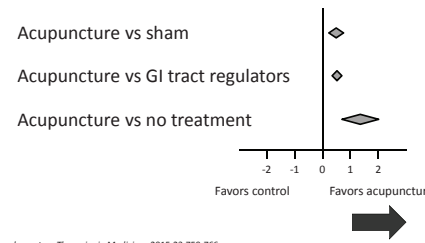
Acupuncture for IBS

- **Efficacy: Unlikely**
- At least 4 double blind, sham controlled trials
- No differences in responder rates between acupuncture & sham acupuncture
  - Adequate relief of IBS, IBS-QOL, IBS-SSS
- Real benefit: interaction between CAM provider and patient?

Chey WD et al. *Gut and Liver*. 2011;5(3):253-266.

Acupuncture for Functional Dyspepsia

- **Efficacy: Likely**
- Meta-Analysis with 20 studies, 1423 cases



Kim KN et al. *Complementary Therapies in Medicine*. 2015;23:759-766.

CAM Therapies for FGIDs

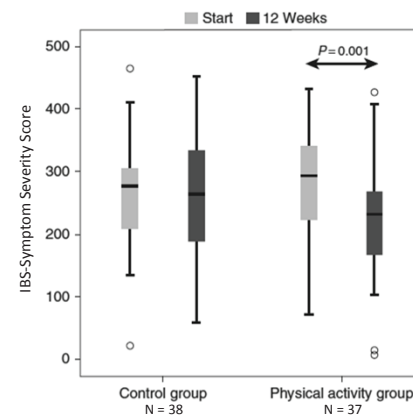
Herbal Medicines

Mechanical Interventions

Behavioral Therapies

Diet & Lifestyle Modifications

Exercise & IBS



Johannesson E et al. *Am J Gastroenterol*. 2011;106:915-922.

Yoga for IBS

- **Efficacy: Possibly**
- 6 RCTs
  - Significantly decreased bowel symptoms, IBS severity and anxiety compared to conventional treatment.
  - Significant improvements in QOL, global improvements, and physical functioning after yoga compared with no treatment.
  - Risk of bias of included studies unclear

Schumann D et al. *Clin Gastro and Hep*. 2016;ahead of print.

Yoga for FD

Irritable Bowel Syndrome CAM Toolkit

Herbal Medicines	Behavioral Therapies	Mechanical Interventions	Diet and Lifestyle Changes
STW 5	CBT		Some Exclusionary Diets
Peppermint Oil	Mindfulness Therapy		Exercise
	Hypnotherapy		Yoga?
	Psychotherapy		
	Relaxation		
	Stress Management		

Functional Dyspepsia CAM Toolkit

Herbal Medicines	Behavioral Therapies	Mechanical Interventions	Diet and Lifestyle Changes
STW 5	Relaxation Training	Acupuncture	Some Exclusionary Diets
Peppermint + Caraway Oil	CBT		
	Psychotherapy		
	Hypnotherapy		

SAVE THE DATE • AUGUST 2017

12th Postgraduate Course

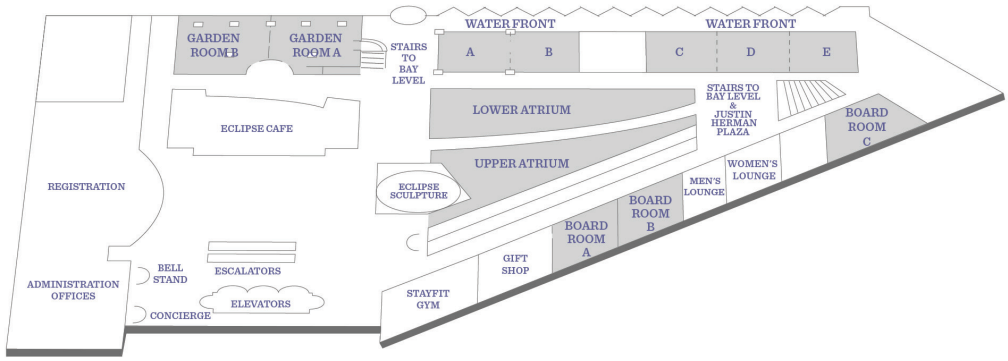
Gastrointestinal Motility & Neurogastroenterology in Clinical Practice

August 4–6, 2017

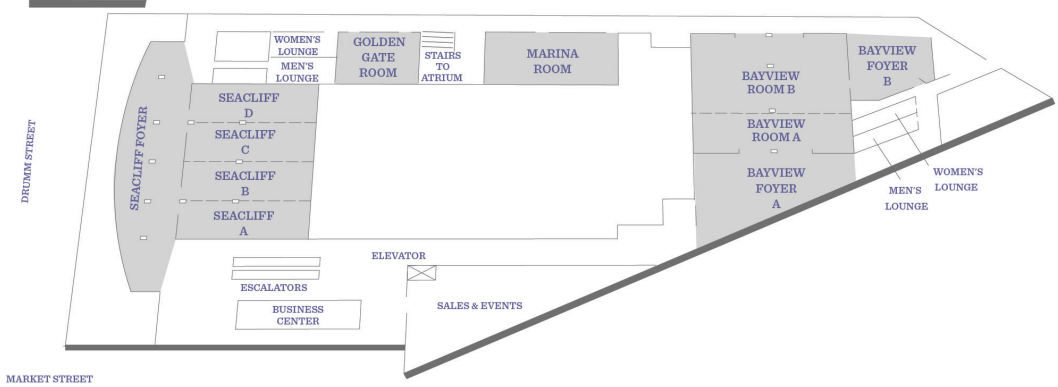
New York, NY

FNM 2016 HYATT REGENCY SAN FRANCISCO • FLOOR PLANS

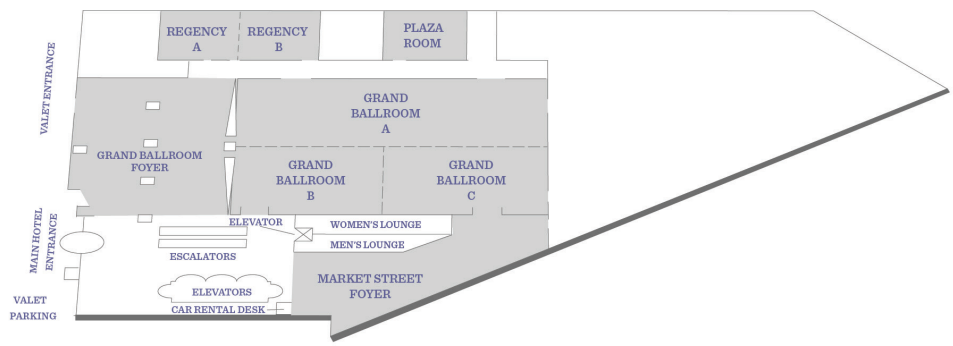
Atrium Level



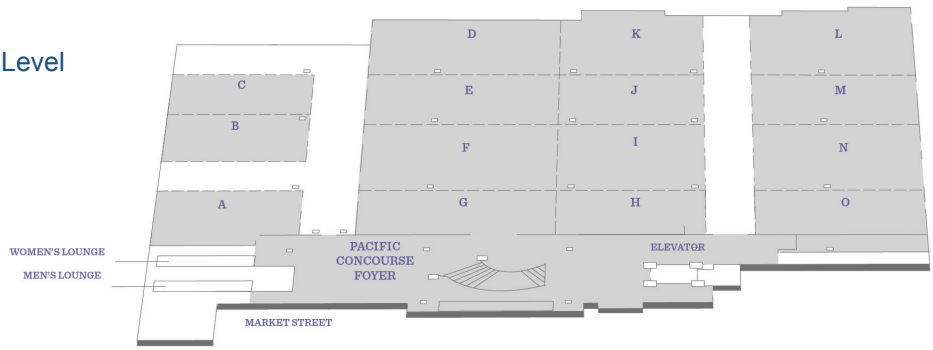
Bay Level



Street Level



Pacific Concourse Level



American Neurogastroenterology and Motility Society

www • motilitysociety • org