AIBD REGIONALS

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THE AMERICAN COLLEGE OF GASTROENTEROLOGY

OUR MISSION CONTINUES.

JOIN US FOR ONE OF THE FOLLOWING EVENTS TO EXPAND YOUR IBD EDUCATION

BOSTON | June 27, 2020 [VIRTUAL]
CHICAGO | July 25, 2020 [VIRTUAL]
LOS ANGELES | August 22, 2020 [VIRTUAL]
CHAPEL HILL | September 12, 2020
HOUSTON | September 26, 2020

ACG members receive a 15% Discount with Code: **ACG15**
Register at: aibdregionals.com

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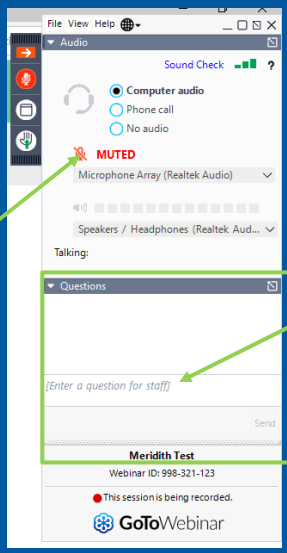
Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.



Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

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How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2020 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2021 for this activity.

ACG will submit MOC points on the first of each month. Please allow 3-5 business days for your MOC credit to appear on your ABIM account.

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MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.

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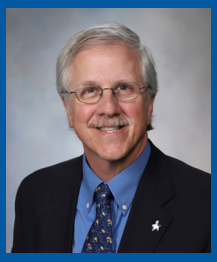
ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!



Week 13: Health Maintenance for the Patient with IBD
Francis A. Farraye, MD, MSc, FACG
June 18, 2020 at Noon EDT

Week 14: EOE and EGID: Pearls and Pitfalls
Kathy A. Peterson, MD, Msci
June 25, 2020 at Noon EDT

Visit **gi.org/ACGVGR** to Register

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ACG/American Neurogastroenterology and Motility Society

Restarting Your Motility Practice During COVID-19

Webinar
Monday, June 15, 2020
8:00 to 9:30 pm Eastern Daylight Time

Presenters
- Mark B. Pochapin, MD, FACG
- Jason Baker, PhD
- C. Prakash Gyawali, MD, MRCP, FACG
- Baharak Moshiree, MD, FACG
- William D. Chey, MD, FACG
- Satish S.C. Rao, MD, PhD, FACG
- Abraham R. Khan, MD, FACG

Moderator: John E. Pandolfino, MD, MSCI, FACG

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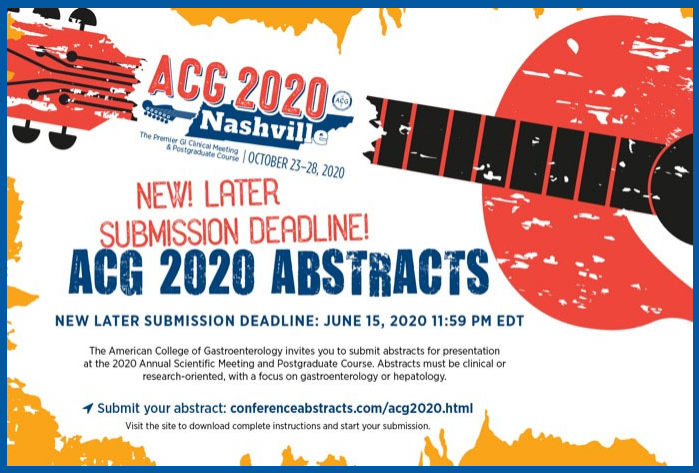
DEADLINE NEXT WEEK!

ACG 2020 ABSTRACT SUBMISSION DEADLINE EXTENDED 2 WEEKS!



NEW!! DEADLINE: JUNE 15, 2020
11:59pm Eastern

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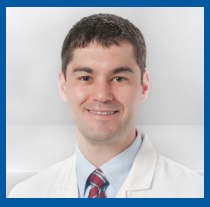
Disclosures:



Moderator:
Scott L. Gabbard, MD
No Conflicts of Interest.

Speaker:
Henry P. Parkman, MD, FACG
Takeda - consultant, research grant
NIH Gastroparesis Research Consortium - research grant

Off Label Usage:
Will briefly discuss several new or off label treatments for gastroparesis including domperidone, TAK-906, relamorlin, prucalopride.

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Gastroparesis:

Then, Now, The Future

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

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Topics

Symptoms

Diagnosis

Treatments

Medical Treatments: dietary modifications, glucose control, antiemetic agents, prokinetic agents, symptom modulators

Medically refractory gastroparesis;

Upcoming treatments for gastroparesis

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Clinical Burden of Gastroparesis for Patients 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 diabetic than idiopathic.

Parkman et al. NGM 2017

Early Satiety and Postprandial Fullness

Severity is associated with body weight, quality of life, gastric emptying.

Parkman et al. NGM 2016

Abdominal pain

Moderate-severe abdominal pain is prevalent in gastroparesis (66%), impairs quality of life, associated with idiopathic etiology, not gastric emptying.

Pain is the predominant symptom in one-fifth of gastroparetics.

Pain has largely been ignored in gastroparesis; its cause is unknown.

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

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Symptoms and Quality of Life in Gastroparesis
The IFFGD Survey of 1,393 patients

Decreased quality of life (SF-36) physical health composite (33.1±10.3)
mental health composite (36.0±12.1)
normal for healthy population 50±10

Physical health QOL summary score was negatively correlated with

nausea (r=-0.37)

early satiety (r=-0.37)

upper abdominal pain (r=-0.37)

loss of appetite (r=-0.33)

retching (r=-0.33)

postprandial fullness (r=-0.32)

vomiting (r=-0.30, p<0.01).

Yu, et al. DDS 2017

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Patient Outcomes in Gastroparesis

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Patients with gastroparesis (diabetic or idiopathic) in NIH GpCRC Gp Registry 1.

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

Chronic nature of gastroparesis. The disease burden remains high.

Positive predictors for improvement	**OR**	**p**
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 for improvement		
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;149:1762

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Patient Reported Outcome (PRO) for Gastroparesis:

Table 1: ANMS Gastroparesis Cardinal Symptom Index Daily Diary (ANMS GCSI-DD)

Participant Number:_____ **Date:**_____ **Time:**_____

Instructions: These questions ask about symptoms you may have each day. Please complete the daily diary at about the same time every evening.

For each symptom listed below, please mark with an X the box that best describes the worst severity of each symptom during the past 24 hours. Please be sure to answer each question.

	None	Mild	Moderate	Severe	Very Severe
1. Nausea (feeling sick to your stomach as if you were going to vomit or throw up)	☐	☐	☐	☐	☐
2. Not able to finish a normal-sized meal (for a healthy person)	☐	☐	☐	☐	☐
3. Feeling excessively full after meals.	☐	☐	☐	☐	☐
4. Upper abdominal pain (above the navel).	☐	☐	☐	☐	☐

The next question asks you to record the number of times either vomiting occurred in the last 24 hours. For vomiting, please record the number of vomits (throwing up with food or liquid coming out) that occurred in the last 24 hours. Record zero, if you have not vomited during the past 24 hours. If you vomited, write down the number of all vomits. If you vomited once, record one. If you vomited three times during the day, record three.

5. During the past 24 hours, how many episodes of vomiting did you have? ____

	None	Mild	Moderate	Severe	Very Severe
6. In thinking about your gastroparesis disorder, what was the overall severity of your gastroparesis symptoms today (during the past 24 hours)?	☐	☐	☐	☐	☐

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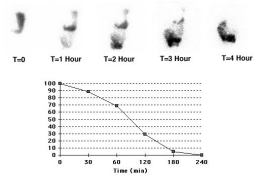
Evaluating Gastric Emptying

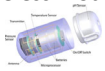
Scintigraphy:

Standardized protocol exists
- 4 hour EggBeaters Protocol

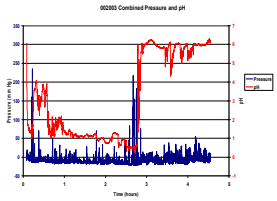
Variable methodology clinically
- meal
- imaging times



Wireless Motility Capsule:

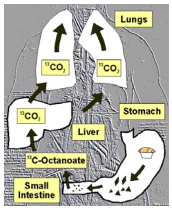


Office Test, easily standardized
Gastric emptying/contractility
Empties with phase III MMC
Measures Whole Gut Transit



GE Breath Test:

Office Based Test, easily standardized
Used in US in research studies
Now approved by FDA for clinical use
Ready to use



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Upper Gastrointestinal Symptoms Associated with Gastric Emptying:

A Systematic Review and Meta-Analysis

Meta-regression identifies differences between optimal and suboptimal GE methods:

Any GE method (breath test or scintigraphy) – optimal vs suboptimal testing methodology		
OR (95% CI): I^2	**Optimal GE studies**	**Suboptimal GE studies**
Nausea	**1.6 (1.4 – 1.8) * ; *0%***	1.2 (0.9 – 1.6) * ; *15%*
Vomiting	**2.0 (1.6 – 2.7)* ; *14%***	1.2 (0.8 – 1.6)*; *47%*
Abdominal Pain	**1.5 (1.0 – 2.2); *70%***	1.0 (0.7 – 1.5); *46%*
Bloating	**1.6 (1.1 – 2.5); *82%***	1.4 (0.9 – 2.1); *45%*
Early Satiety/ Fullness	**1.8 (1.2 – 2.6); *75%***	**1.7 (1.2 – 2.4); *0%***
Composite Sx	7.7 (0.7 – 82.3) ; *84%*	**2.3 (1.2 – 4.4); *34%***

- **Significant associations between GE and nausea, vomiting, abdominal pain and early satiety/fullness for patients who presented with upper gastrointestinal symptoms in studies using optimal gastric emptying test methods.**
- Gastric emptying is an important tool to assess upper gastrointestinal symptoms.

Vijayvargiya P, Jameie-Oskooei S, Camilleri M, Chedid V, Erwin PJ, Murad MH. Gut. 2019 May;68(5):804-813.

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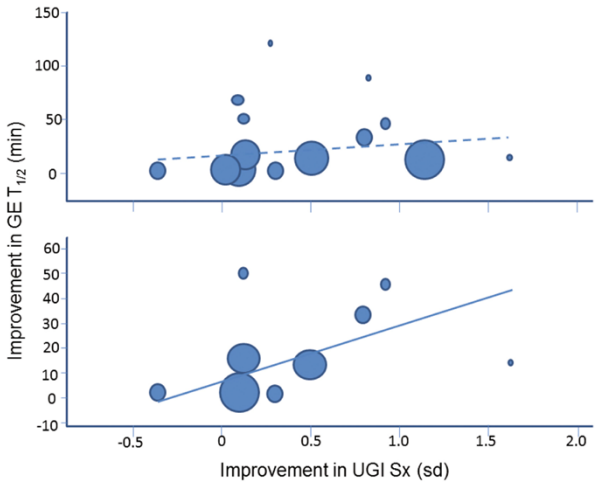
Effects of Promotility Agents on Gastric Emptying and Symptoms: A Systematic Review and Meta-analysis



Vijayvargiya P, Camilleri M, Chedid V, Mandawat A, Erwin PJ, Murad MH. Gastroenterology. 2019 May;156(6):1650-1660.

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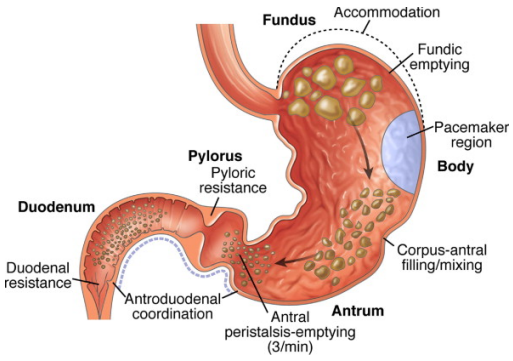
Regional gastric physiology/function



Gastric emptying reflects the coordinated function of the fundus, corpus, antrum, pylorus, and duodenum.

Important events for gastric emptying:
1. fundic relaxation, accommodation,

2. antral contractions for trituration,

3. pyloric sphincter opening,

4. Antral-pyloric-duodenal coordination

Parkman HP, Jones MP. Gastroenterology 2009;136:1526-43.

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COVID-19 and Gastroparesis - 1

Coronavirus Disease 2019 (COVID-19), a disease caused by infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), commonly presents with symptoms including **fever, cough, and shortness of breath**.

Some patients have tested positive for SARS-CoV-2 after developing **gastrointestinal (GI) symptoms** either solely or in conjunction with pulmonary symptoms. This may be due to SARS-CoV-2 **infection of the GI tract** or a systemic effect from the respiratory viral infection.

In patients with chronic GI illnesses, such as gastroparesis, COVID-19 may present as a **flare of their underlying GI condition** as viruses have historically been implicated in exacerbations of chronic GI disorders, including gastroparesis.

Some patients with no underlying GI conditions have been diagnosed with COVID-19 after presenting predominantly with nausea, vomiting and diarrhea. They may be at risk for developing **post-viral gastroparesis**, which is an important and poorly understood potential chronic inflammation-based cause of "idiopathic gastroparesis".

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COVID-19 and Gastroparesis - 2

Mostly telemedicine with patients

Keep symptomatic patients out of hospital or outpatient visit

Giving a variety of antiemetic medications

Two cases of flares of gastroparesis related to COVID-19:

T2DM on metoclopramide; ran out of medications. Nausea, vomiting; more severe flare than normal. Treated for gastroparesis flare in ED with her usual medications. Returned several days later and hospitalized for GI symptoms. Developed fever in the hospital. Chest CT – category 2. Nasopharyngeal swab positive for SARS-CoV-2.

T1DM with gastric stimulator, pyloroplasty, j tube. Several hospitalizations for increasing nausea and vomiting, leading to DKA and renal insufficiency. Treated for diabetic gastroparesis. Subsequently had antibody tests for SARS-CoV-2: positive, and flare in retrospect thought to be COVID-19.

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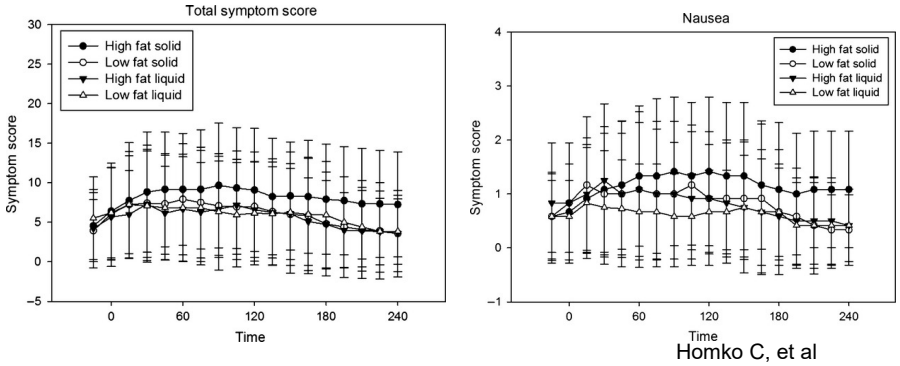
Effect of dietary fat and food consistency on gastroparesis symptoms in patients with gastroparesis

High-fat solid meal increased symptoms among Gp patients;
low-fat liquid meal had least effect on symptoms.

With respect to nausea, low-fat meals were better tolerated than high-fat meals,
and liquid meals were better tolerated than solid meals.

Support recommendations that low-fat and increased liquid content meals
are best tolerated in patients with symptomatic gastroparesis.



Homko C, et al
NGM 2015;27:501-508.

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Small particle size diet reduces GI symptoms in patients with diabetic gastroparesis: a randomized controlled trial

56 insulin treated DM and gastroparesis, randomized

Small particle diet, compared with the control diet, reduced
nausea/vomiting (P=0.01)
postprandial fullness (P=0.02)
bloating (P=0.006)
regurgitation/heartburn (P=0.02)
not abdominal pain

A small particle diet improves the key symptoms of gastroparesis in patients with diabetes mellitus.

Olausson EA, Störsrud S, et al.
Am J Gastro 2014;109:375-85.

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Continuous Glucose Monitoring (CGM) and Insulin Pump Therapy in Diabetic Gastroparesis (GLUMIT-DG)

Diabetic gastroparesis are advised to lower blood sugars to reduce symptoms; unproven.

45 diabetic Gp, poorly controlled (A1c>8%); 29% type 1, 21±11 yr diabetes duration.

Intensive insulin regimens: Insulin pumps with continuous glucose monitoring (CGM).

Baseline A1c levels (9.4±1.4 %) decreased by 1.1% at 24 weeks (P=0.0002).

Gastroparesis Outcomes:	Baseline	Change at week 12	Change at week 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)
Liquid nutrient tolerance	420±258	15±117 (p=0.47)	59±176 (p=0.05)

Symptom and nutrient tolerance benefits maintained for 24 weeks of therapy.

Feasibility for improving both diabetes control and lowering gastroparesis symptoms. Calles-Escandón, et al. Plos One 2018

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Commonly Used Prokinetic Agents

	Pros	Cons
Metoclopramide	Approved for gastroparesis Acts as prokinetic and antiemetic both may act for efficacy Available po, IV, SQ	Side Effects Acute: dystonic reaction Subacute: depression/anxiety Chronic: tremors, TD
Erythromycin	Potent gastrokinetic agent	Side Effects: Acute: N/V Chronic: ?cardiac Tachyphylaxis (loss of effect)
Domperidone	Acts as prokinetic and antiemetic Less side effects than metoclopramide	Not approved in the USA Available with FDA IND Side effects: cardiac

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Metoclopramide to Treat Diabetic Gastroparesis

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

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Clinical response and side effects of metoclopramide: associations with clinical, demographic, and pharmacogenetic parameters.

100 patients treated with metoclopramide. DNA isolated from salivary samples;

20 single nucleotide polymorphisms (SNPs) were genotyped in 8 candidate genes

CYP1A2 and CYP2D6 coding for drug-metabolizing enzymes,

ABCB1 (MDR1) gene coding for drug transporter P-gp,

genes coding for targets of metoclopramide DRD2/3 coding for dopamine receptors, KCNH2 (hERG), coding for a pore-forming (a) subunit of voltage-gated rectifying potassium channel Kv 11.1, the gene HTR4 for serotonin receptor and the gene family ADRA1 for a1-adrenergic receptors.

Side effects to metoclopramide were more common in nondiabetic patients with normal gastric emptying.

Side effects associated with polymorphisms in CYP2D6, KCNH2, and 5-HT4 receptor HTR4 genes

Clinical response associated with polymorphisms in KCNH2 and ADRA1D genes.

Clinical parameters and pharmacogenetic testing may be useful in identifying patients before treatment with metoclopramide to enhance efficacy and minimize side effects.

JCG 2012;46(6):494-503

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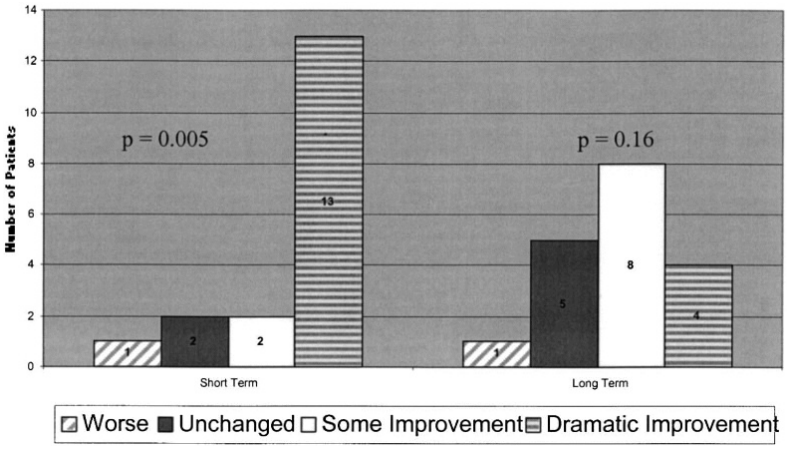
Erythromycin in the Short-Term and Long-Term Control of Dyspepsia Symptoms in Gastroparesis

25 patients with gastroparesis

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



Dhir, Richter. JCG 2004;38:237

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Domperidone to Treat Symptoms of Gastroparesis: Benefits and Side Effects from a Large Single Center Cohort

115 patients treated with domperidone

88 idiopathic, 16 diabetic, and 9 postsurgical Gp.

Side effects were reported by 44 patients (most common – headache, tachycardia/palpitations, diarrhea); **14 patients stopped treatment**.

101 patients were seen at follow-up taking domperidone (2.4±2.7 months, average dose 36±13 mg/day).

CPGAS averaged 2.7±2.7 ($p<0.01$) with 69 patients reporting symptom improvement and **45 patients at least moderately improved with CPGAS≥4.**

Symptom improvements were seen especially with postprandial fullness, nausea, vomiting.

Domperidone improved patients : 69/115 (60%) intention to treat

69/101 (69%) per protocol

Schey et al. DDS 2017

(45% at least moderate improvement)

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TAK-906, a dopamine 2,3 receptor antagonist, in diabetic or idiopathic gastroparesis

Randomized, placebo-controlled, dose ranging (5 mg, 25 mg, 100 mg) study of oral TAK-906 BID on Days 1-8 and QD on Day 9 (n = 12-14/arm).

Exhibits D2/3 antagonism, with elevation of prolactin levels.

Well tolerated without occurrence of safety issues.

No change in GE was observed with any TAK-906 dose or metoclopramide.

Increased volume ingested during nutrient drink test at 25 mg,

Decrease in **postprandial fullness and nausea** symptom scores.

Responses to TAK-906 were similar in IG and DG.

Overall, 25 mg appears to be the lowest, most effective dose.

To be tested in future studies of GP.

Dukes G, et al
ANMS 2019 Meeting Presentation

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Prucalopride for Symptoms and Gastric Emptying in Idiopathic Gastroparesis

Single center, double-blind, randomized, placebo controlled, crossover study

4 weeks of prucalopride 2 mg po qd versus placebo

28 idiopathic gastroparesis patients. GEBT T1/2, GCSI (0-5)

	Baseline	Prucalopride	Placebo
Gastric emptying (T1/2; min)	128±19	86±13*	141±17
Fullness/satiety	3.2±0.3	2.2±0.2*	3.3±0.3
Nausea/vomiting	1.6±0.2	1.0±0.3*	1.8±0.3
Bloating/distension	2.5±0.3	1.5±0.3*	3.1±0.3
Pain/discomfort	2.9±0.3	1.8±0.3*	2.3±0.3

No correlation between improvement in GE and symptoms

In idiopathic gastroparesis, 4 weeks prucalopride improved gastric emptying, symptoms compared to placebo and to baseline.

Carbone, Rotondo, Tack.
AJG 2019;114:1265.

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Other "Prokinetics"

Bethanechol, a muscarinic cholinergic agonist

- Does not enhance gastric emptying
- Occasionally used to increase contractility along with a prokinetic agent

Pyridostigmine, a cholinesterase inhibitor

- Efficacy in chronic constipation
- Used off label in gastroparesis and CIIP

Gudsoorkar, Quigley
AJG 2019;115:5-8

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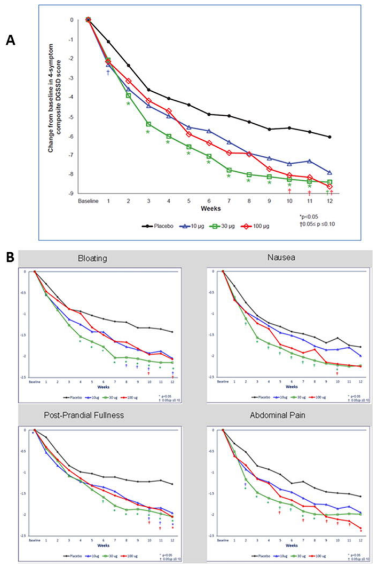
Efficacy and Safety of Relamorelin in Diabetics With Symptoms of Gastroparesis: A Randomized, Placebo-Controlled Study

- Relamorelin, selective, prokinetic ghrelin receptor agonist.
- 12-wk, 2B study - diabetic patients, mod -severe Gp Sx.
- 393 patients with DG (38% male; 10% T1DM; age, 58.2 yrs; HbA1c level, 7.6%, [range, 5.2-11.0]). Patients: ^{13}C-spirulina GE breath test $T_{1/2}$ values of 79 minutes or more (90% delayed), recent vomiting, GCSI-DD≥2.6
- Patients randomly assigned to placebo (n=104) or relamorelin (10 µg [n=98], 30 µg [n=109], or 100 µg [n=82] twice daily) for 12 weeks
- Patients given relamorelin had a 75% reduction in vomiting frequency compared with baseline (p=NS).
- All 4 symptoms of DG (composite or individual symptoms) were significantly reduced over the 12-week study period in all 3 relamorelin groups compared to placebo
- Relamorelin accelerated GE from baseline compared with placebo (by 12%).
- Dose-related worsening of glycemic control was noted in 14.5%
- **Relamorelin reduced core symptoms of DG and overall composite score compared to placebo, accelerated GE, was generally safe and well tolerated.**



Camilleri M, McCallum RW, Tack J, et al. Gastroenterology 2017;153:1240.

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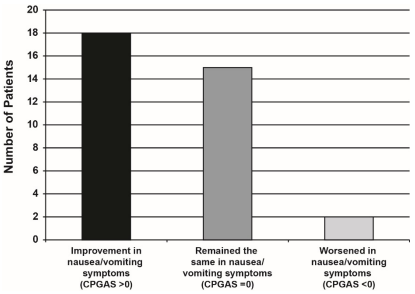
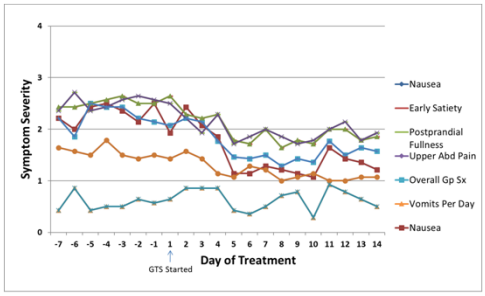
Granisetron (5-HT3 Receptor Antagonist) Transdermal System Improves Refractory Nausea and Vomiting in Gastroparesis





Simmons et al. 2015
Heckert et al. 2017
Revicki et al. 2018

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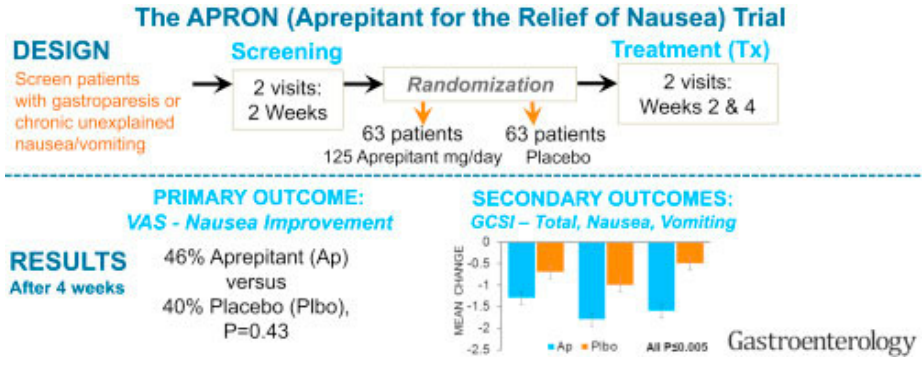
Aprepitant Effects on Nausea and Other Symptoms in Patients With Gastroparesis and Related Disorders

Randomized, multicenter, double-masked 4-week trial of the neurokinin-1 receptor antagonist aprepitant (Emend) to reduce symptoms in patients with chronic nausea and vomiting caused by gastroparesis or gastroparesis-like syndrome.



Pasricha et al. Gastroenterology 2018;154:65

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Phase II Study Results for Tradipitant in Patients with Gastroparesis

Tradipitant is an NK-1R antagonist licensed by Vanda Pharmaceuticals
Idiopathic and diabetic gastroparesis
Tradipitant 85 mg BID
well tolerated

ITT Population (n=141)

	Tradipitant n=73	Placebo n=68	p-value
Primary End Point			
DD-Nausea	-1.25	-0.73	0.0099
Secondary End Points			
DD-% Nausea Free Days	28.8	15.0	0.0160
GCSI	-0.93	-0.58	0.0223

Now in Phase III studies for DG and IG with primary endpoint decrease in nausea severity

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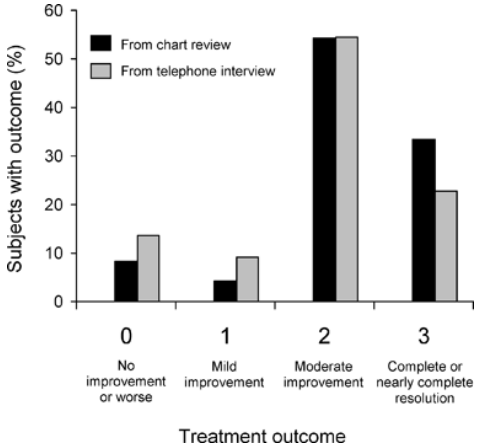
Tricyclic Antidepressants for Chronic Vomiting in Diabetic Patients

24 diabetic patients treated with TCAs 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.

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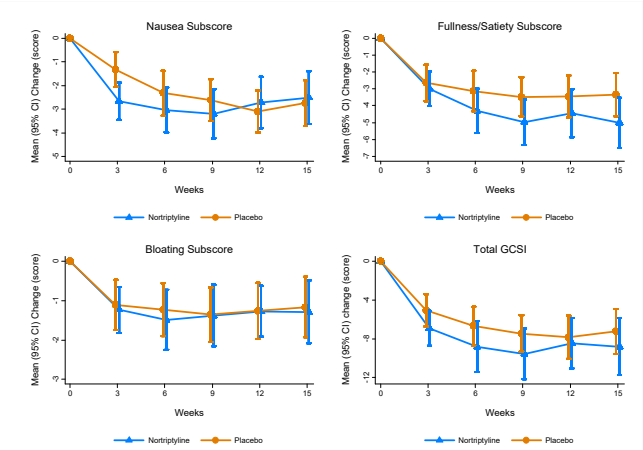
Nortriptyline for Idiopathic Gastroparesis



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.

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

Parkman, et al. *JAMA* 2013

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Mirtazapine for Symptom Control in Refractory Gastroparesis:

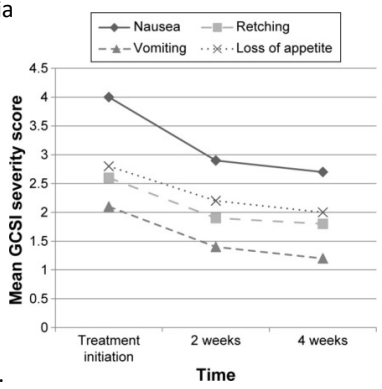
Mirtazapine reduces symptoms in functional dyspepsia weight loss, early satiation, and overall quality of life.

Aim: Assess efficacy of mirtazapine in gastroparesis.

Adults with gastroparesis and refractory symptoms.
Rx with mirtazapine 15mg po qhs (open label study).

30 patients; 24 (80%) completed 4 weeks of therapy.

14/30 (46.7%) patients experienced adverse effects, particularly drowsiness and lethargy/fatigue.
6 (20%) stopped therapy due to these adverse effects.



Mirtazapine improved nausea & vomiting in gastroparesis after 2 and 4 weeks of treatment.
Side effects led to treatment self-cessation in 20%.
Mirtazapine might be useful in select patients.

Malamood, Kataria, Schey, et al. DDDT 2017

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Buspirone, a fundus-relaxing drug, in Patients with Functional Dyspepsia

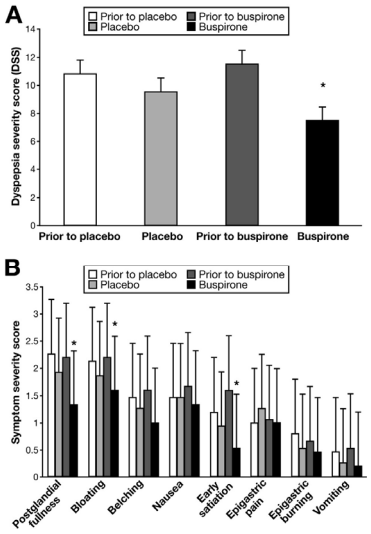
universe.gi.org

Randomized, double-blind, placebo-controlled, crossover study 17 patients (13 women)

5HT-1a receptor agonist

Buspirone 10 mg TID qac reduced overall severity of symptoms of dyspepsia and individual symptoms of early satiation, postprandial fullness, and bloating. Buspirone did not alter gastric emptying of solids or sensitivity to gastric distention, but it increased gastric accommodation, and delayed gastric emptying of liquids. Adverse events were similar for buspirone and placebo.

In FD, 4 weeks of buspirone improved symptoms and gastric accommodation, whereas gastric emptying of liquids was delayed.



Tack et al. CGH 2015

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Marijuana Use in Patients with Symptoms of Gastroparesis.

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Orexigenic, antinauseant and pain-relieving properties of MJ attract patients with Gp.

59 of 505 (11.7%) patients with symptoms of Gp reported use of marijuana.

MJ users: higher nausea/vomiting (2.7 vs 2.1), higher upper abdominal pain (3.5 vs 2.9)

Most patients using marijuana had chronic symptoms (80%); minority cyclic Sx (20%).

Marijuana uses: 51% had been using MJ > 2 years, 47% of patients using this once or more per day, 81% rated their benefit from marijuana as better or much better.

Comparatively 4.4% were using dronabinol (marinol)

55% using this for 1-6 months, with 77% rating their benefit as better or much better.

Marijuana users increased anxiety, panic indices.

A significant minority (12%) of patients with symptoms of Gp use marijuana.

Patients with severe nausea and abdominal pain more likely to use marijuana, consistent with its perceived benefits.

The synthetic analog, dronabinol, used by small minority, comparable in efficacy to MJ.

Physicians should inquire about use of MJ and other cannabinoids by their patients.

Parkman et al. DDS 2019

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Where are we with Prokinetic treatments?

D2 and D3 receptor antagonists

Domperidone via FDA IND

European concerns for cardiac side effects, limiting to 7 d

Metoclopramide nasal spray. Promising phase III study

3 new agents with less cardiac/neurologic SE about to start studies

5-HT4 receptor agonists

Prucalopride approved for chronic constipation

2 new agents without cardiac toxicity in pipeline; 1 finishing phase 2b

Motilin receptor agonists

2 agents; 1 equivocal results (low dose improved sx; high dose improved GE)

Ghrelin receptor agonists

TZP-101, 102. Studies stopped

Relamorelin for DG

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Refractory Gastroparesis

- Jejunostomy tube for feeding into small intestine
  - bypassing gastroparetic stomach.
  - Generally, give patients trial of NJ feedings to check if tolerating
- Gastrostomy tube for venting of stomach
- G-J tubes can decompress stomach and provide enteral nutrition

- Gastric electric stimulation: high frequency stimulation
  suppressing symptoms, particularly nausea, vomiting

- Pyloromyotomy/pyloroplasty
  - Re-emergence of this treatment; laparoscopically, endoscopically

- Parenteral Nutrition via central line (PICC)
  - If long term, problems with infection, thrombosis

- ?Gastric bypass (gastrojejunostomy) or gastric sleeve

- Gastrectomy (last resort) near-total
  completion, for post surgical gastroparesis

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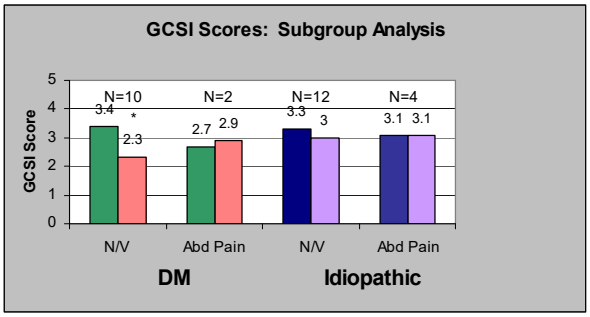
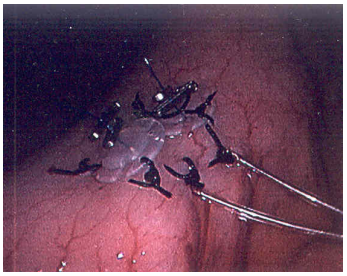
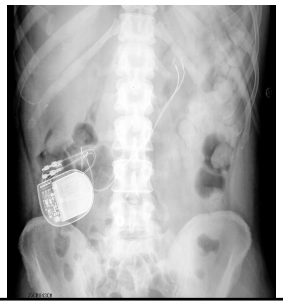
Clinical Improvement with Enterra Gastric Electric Stimulation Treatment for Refractory Gastroparesis
The Temple Experience (2004-2006)

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.

Marenki, et al.

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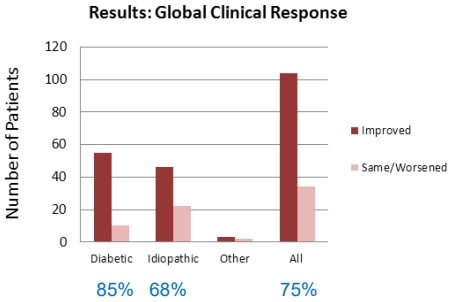
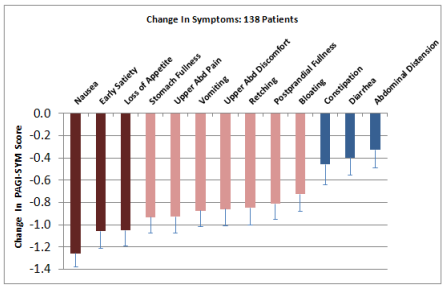
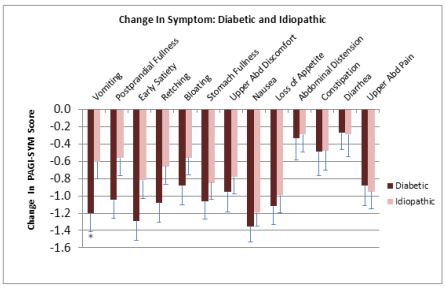
Gastric Electric Stimulation for Refractory Gastroparesis: A Prospective Analysis of 151 Patients at a Single Center







Heckert, et al. DDS 2015

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Effectiveness of Gastric Electrical Stimulation in Gastroparesis: Results From the Gastroparesis Research Consortium

Assessed the effects of gastric electric stimulation (GES) using change in GCSI total score and nausea/vomiting subscales between baseline and 48 weeks. **Propensity score methods** to control for imbalances in patient characteristics between comparison groups: 81 GES, 238 controls.

This multicenter study of gastroparesis patients found

Improvements in gastroparesis symptoms among GES patients.

Accounting for imbalances in patient characteristics (using propensity matching of GES to non-GES patients, only **nausea** remained significant.

Patients with **greater symptoms** at baseline improved more with GES.

Abell et al. NGM 2018

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Gastric Electrical Stimulation Reduces Refractory Vomiting in a Randomized Crossover Trial. The French Study

Large, multicenter, randomized, double-blind crossover trial to study the efficacy of GES in refractory vomiting, with or without gastroparesis.

172 patients (133 with gastroparesis) with chronic (>12 months) of refractory vomiting (idiopathic, type 1 or 2 diabetes, or postsurgical). GES device was implanted and left unactivated until patients were randomly assigned, in a double-blind manner, to groups that received 4 months of stimulation or no stimulation (control); 149 patients then crossed over to other group for 4 months.

During both phases of the crossover study, vomiting improved with the device on (median score, 2) than the control group (median score, 1; P <0.001), in diabetic and nondiabetic patients. Vomiting scores improved when the device was ON in patients with delayed (P<0.01) or normal gastric emptying (=0.05). Gastric emptying was not accelerated during the ON period compared with the OFF period.

In a randomized crossover study, GES reduced the frequency of refractory vomiting in patients with and without diabetes, although it did not accelerate gastric emptying or increase of quality of life.

Ducrotte P, Coffin B, et al. Gastroenterology 2020;158:506.

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Non-invasive vagal nerve stimulation improves symptoms and gastric emptying in patients with idiopathic gastroparesis

Open-label pilot study to assess the benefit of non-invasive externally held cervical vagal nerve stimulation in patients with mild to moderate idiopathic gastroparesis.

Patients self-administered the gammaCore vagal nerve stimulator for 4 wks.

There was an improvement in total symptom scores (2.56±0.76 to 1.87±1.05; P=0.01), with 6/15 (40%) participants meeting primary endpoint. Responders had more severe gastric delay at baseline and clinical improvement correlated with duration of therapy. Therapy was associated with a reduction in gastric emptying ($T_{1/2}$ 155 vs 129 minutes; p=0.053).

Short-term non-invasive vagal nerve stimulation led to improved cardinal symptoms and accelerated gastric emptying in a subset of patients with idiopathic gastroparesis.

Gottfried-Blackmore A, Adler EP, et al. Neurogastroenterol Motil. 2020;32:e13769.

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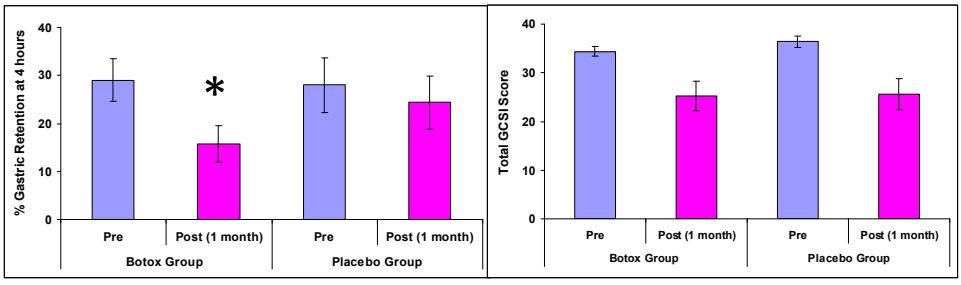
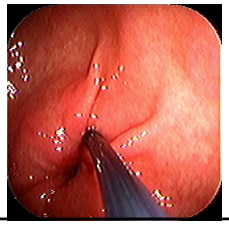
Randomized, Placebo-Controlled Trial of Botulinum Toxin A for the Treatment of Gastroparesis

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

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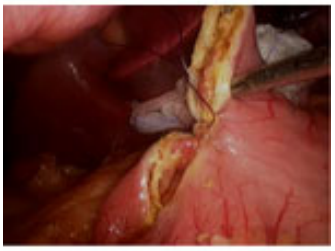
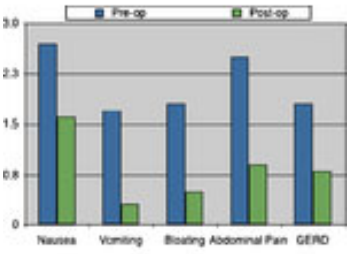
Laparoscopic pyloroplasty for gastroparesis results in sustained symptom improvement

- Review of 28 patients underwent laparoscopic pyloroplasty as Rx for gastroparesis 2007-2010.
- Laparoscopic Heineke-Mikulicz pyloroplasty performed in 26 patients. Laparoscopic assisted, flexible trans-oral endoscopic circular stapled pyloroplasty 2 pts.
- 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, GER Sx
- Improvement persisted at 3 months for nausea, vomiting, bloating, abdominal pain, GERD Sx.
- Prokinetics were significantly reduced 89% to 14%.

- Minimally invasive pyloroplasty provides excellent outcomes for patients with gastroparesis.





Hibbard ML, Dunst CM, Swanström LL. J Gastrointest Surg. 2011;15:1513-9.

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Gastric Per Oral Endoscopic Myotomy (G-POEM) for Treatment of Refractory Gastroparesis: Early experience

Initial experience performing G-POEM for refractory gastroparesis of different etiologies.

All 13 Gp patients successfully underwent G-POEM.

(1 DGp, 4 IGp, 8 PSGp:

4 esophagectomy esophageal cancer, 3 Nissen fundoplication, 1 esophagectomy achalasia.

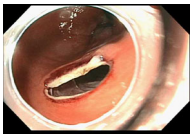
No procedure related side effects.

11 patients completing FU questionnaires; 8 improved (**73%**).

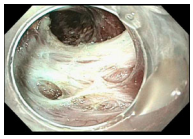
Symptom severity scores tended to improve, particularly vomiting, retching, loss of appetite.

6 patients had post GES; GES improved in 4.

G-POEM treatment of refractory gastroparesis is a feasible and safe technique. Can be successfully performed in patients with a variety of etiologies including different types of postsurgical Gp.



Submucosal Tunnel



Pyloromyotomy

Questions for G-POEM

- Who to pick for procedure
- Durability of procedure
- Placebo controlled study
- Comparative studies to other treatments

Malik, …, Stavropoulos. DDS 2018

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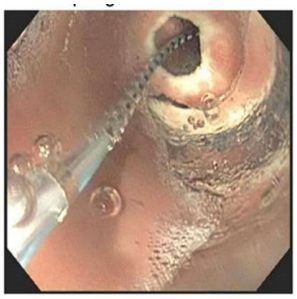
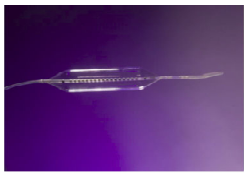
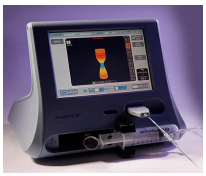
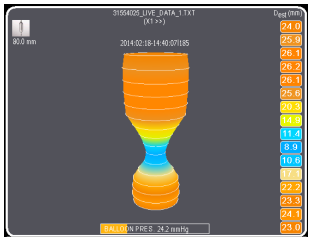
Assessing Pyloric Sphincter Pathophysiology Using Impedance Planimetry in Patients with Gastroparesis







Impedance planimetry 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

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Peroral endoscopic pyloromyotomy is efficacious and safe for refractory gastroparesis: Prospective trial with assessment of pyloric function

Prospective study on feasibility, safety, efficacy of G-POEM.

20 patients refractory gastroparesis (10 DG, 10 non-diabetic)

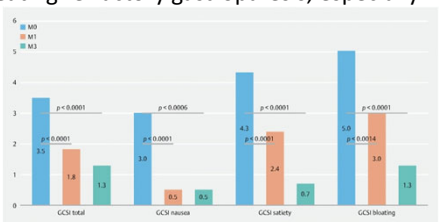
Patients treated by G-POEM after pyloric EndoFLIP.

Feasibility of the procedure was **100 %**.

G-POEM **improved symptoms** (GCSI: 1.3 vs. 3.5), quality of life, **gastric emptying** (T½: 100 vs. 345 minutes) at 3 months.

Clinical success of G-POEM using EndoFLIP inflated to 50 mL had specificity of 100 % and sensitivity of 72.2 % (*P*=0.04) at a **distensibility threshold of 9.2 mm²/mmHg**.

G-POEM was efficacious and safe for treating refractory gastroparesis, especially patients with low pyloric distensibility.



Jacques, Pagnon, et al
Endoscopy 2018

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Surgical Interventions for Refractory Gastroparesis: Gastric Stimulator, Pyloromyotomy, or Both?

Patients undergoing surgical intervention from 1/16 – 11/18 were given pre and post PAGI-SYM and CPGAS questionnaires.

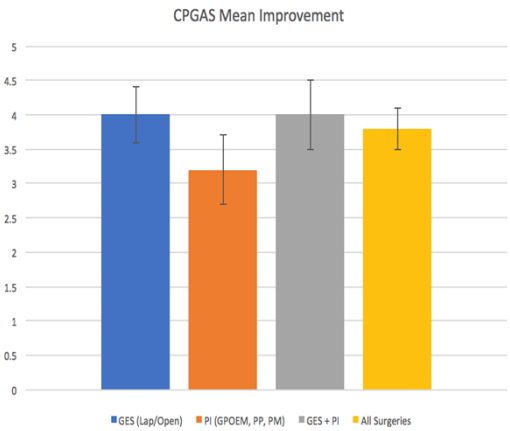
47 pts (20 GES, 13 PI, 14 GES+PI) had sufficient follow-up analysis

Overall, patients has CPGAS clinical improvement with a mean score of 3.8±0.5

GES and GES+PI had the highest improvement CPGAS score of 4.0±0.4 and 4.0±0.5, respectively

PI had lowest improvement CPGAS score of 3.2±0.5

Zoll et al. DDW 2019



Results expressed as mean symptom improvement
Bars represent SEM
Lap – Laparoscopic, Open – Open Surgery, GPOEM – Gastric Per-Oral Endoscopic Pyloromyotomy ,
PP – Pyloroplasty, PM - Pyloromyotomy

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Temple Decision Making:
GES vs G-POEM for refractory gastroparesis

Factors	Preference
Symptom characteristics	
Nausea, vomiting	GES
early satiety, postprandial fullness	G-POEM
Degree of **Gastric Retention**	G-POEM
Prior response to **botulinum toxin Rx**	G-POEM
EndoFLIP of pylorus	G-POEM
Nausea/Vomiting with marked delay	GES with pyloroplasty

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Concluding Remarks

Main symptoms of gastroparesis: nausea, vomiting, early satiety, abdominal pain; each can impair quality of life.

Gastroparesis symptoms can occur in patients with normal gastric emptying, CUNV.

Gastric emptying scintigraphy can reveal more on pathophysiology in gastroparesis than just global gastric emptying. These abnormalities may relate to symptoms.

Treatments are dietary, antiemetic treatment, prokinetic, symptom modulatory treatments.

Refractory patients considered for surgery: Gastric stimulator, pyloromyotomy. G-POEM increasingly being used, and appears promising. Patient selection for surgery needs to be considered. Treatments may target underlying pathophysiology as well as specific symptoms.

In the future, we may focus on pathology.

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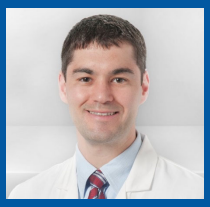
Questions?



Moderator:
Scott L. Gabbard, MD

Speaker:
Henry P. Parkman, MD, FACG

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Domperidone for Gastroparesis Symptoms

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Pragmatic outcomes research analysis of domperidone (DOM) therapy.

650 patients: 123 (19%) and 527 (81%) in DOM and control groups.

DOM group experienced moderate GP symptom improvement in 3 of 4 outcome measures: GCSI total score (delta=-0.22, p=0.005); any improvement (OR=1.63, p=0.01), improvement ≥ 1-point (OR=1.47, p=0.10), and Nausea subscore (delta=-0.32, p=0.01) compared to control group.

With multivariable patient-mix adjustment, the DOM vs. control differences was smaller: GCSI total score (delta=-0.12, p=0.15); any improvement in GCSI (OR=1.48, p=0.06), improvement in GCSI by ≥ 1-point (OR=1.25, p=0.40), and Nausea subscore (delta=-0.14, p=0.07).

Pragmatic design of our GpCRC registry showed that domperidone Rx for gastroparesis resulted in mild clinical improvement of Gp symptoms.

Sarosiek, et al.
DDW 2017

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Velusetrag Improves Gastroparesis Symptoms and Gastric Emptying in Patients with Diabetic or Idiopathic Gastroparesis in a 12-Week Phase 2B Study

232 patients with either diabetic or idiopathic gastroparesis

Velusetrag (5, 15 or 30 mg) or placebo, administered orally once daily dose.

After four weeks of dosing, patients in the 5 mg velusetrag treatment arm demonstrated significant improvements in symptom scores compared to placebo in two separate patient reported outcome (PRO) tools: the Gastroparesis Cardinal Symptom Index (GCSI) ($p = 0.03$) and the Gastroparesis Rating Scale (GRS) ($p = 0.02$).

Improvements in GRS total score maintained at 12 weeks treatment ($p=0.04$).

Compared to placebo, patients in the 5 mg treatment arm also demonstrated statistically significant improvements in gastric emptying time ($p < 0.001$) and in individual disease-specific symptom scores including postprandial fullness/early satiety, bloating and upper abdominal pain (all $p < 0.05$). Importantly, the symptom improvements seen with 5 mg of velusetrag were observed in both diabetic and idiopathic gastroparesis patients.

DDW 2017 Presentation

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Use of Cannabinoids in Patients with Symptoms of Gastroparesis

How frequently do patients with Gp symptoms resort to cannabinoids for their symptoms?

197 patients with Sx of Gp interviewed.

154 (78.2%) delayed GE: 64 idiopathic Gp, 57 diabetic Gp, 28 atypical Gp, 5 post-surgical Gp.

43 patients met Rome IV criteria for CNVS (n=38) and/or FD (34).

Figure 1: Cannabinoid use in patients with symptoms of gastroparesis

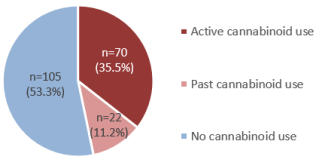


Figure 2: Perceived benefit of cannabinoids for symptoms of Gp

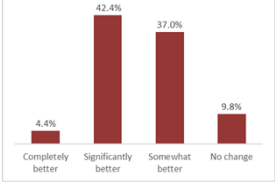
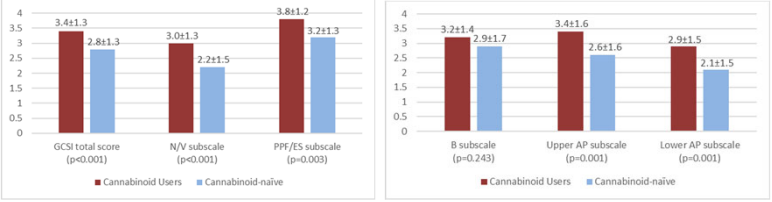


Figure 3: Gp symptom severity in cannabinoid users vs. cannabinoid naïve pts



Jehangir, Parkman
ACG Poster 2018

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Peroral endoscopic pyloromyotomy is efficacious and safe for refractory gastroparesis: prospective trial with assessment of pyloric function

Prospective study was to evaluate the feasibility, safety, and efficacy of G-POEM.

20 patients with refractory gastroparesis (10 diabetic and 10 nondiabetic) prospectively included.

Patients were treated by G-POEM after evaluation of pyloric function using EndoFLIP.

Feasibility of the procedure was 100%.

G-POEM significantly improved symptoms (GCSI: 1.3 vs. 3.5; $P < 0.001$), quality of life, and gastric emptying (T½: 100 vs. 345 minutes, $P < 0.001$; %H2: 56.0 % vs. 81.5 %, $P < 0.001$; %H4: 15.0% vs. 57.5%, $P = 0.003$) at 3 months.

The clinical success of G-POEM using the functional imaging probe inflated to 50 mL had specificity of 100% and sensitivity of 72.2 % ($P = 0.04$; 95% confidence interval 0.51 - 0.94; area under the curve 0.72) at a distensibility threshold of 9.2 mm^2/mmHg.

G-POEM was efficacious and safe for treating refractory gastroparesis, especially in patients with low pyloric distensibility.

Fontaine S, Boubaddi NE, Clement MP, et al.
Endoscopy. 2019 Jan;51(1):40-49.

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