2nd Annual GI ReConnect

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GI Health Foundation

Gastroparesis & Complex Motility Issues

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Disclosure Statement

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Faculty Disclosures

- **Consultant:** Aclipse, Alnylam, Ardelyx, Eli Lily, Gemelli, Neurogastryx, Pendulum, Phathom, RosVivo, Salix, Takeda, Ironwood, Evoke

Objectives

- Differentiate idiopathic gastroparesis vs functional dyspepsia
- Gastroparesis “plus” – recognizing and treating overlapping comorbidities in patients with gastroparesis

Gastroparesis vs. Functional Dyspepsia

Gastroparesis

- Abnormal gastric emptying in the absence of a mechanical obstruction
- Symptoms1:

Symptom	Idiopathic (%)	Type 1DM (%)	Type 2DM (%)
Nausea	84.3	84.6	94.9*
Vomiting	59.8	88.5*	91.5*
Bloating	57.5	56.4	62.7
Early Satiety	57.5	47.4	74.6*
Abdominal pain	76.0	60.3*	69.5
Weight loss	46.5	52.6	52.5

Functional Dyspepsia

- Bothersome postprandial fullness, early satiety, epigastric pain or epigastric burning in the absence of structural abnormalities
  - Postprandial Distress (PDS)= meal related symptoms
  - Epigastric Pain Syndrome (EPS)= pain/burning that may or may not be related to meals
- Nausea or vomiting can be present
- Symptoms present >6 months

1. Data from Parkman, H et al. *Clin Gastroenterol Hepatol*. 2011. 9(12);
2. Stanghelline V et al. *Gastroenterol*. 2016;150:1380-92.

Gastroparesis vs. Functional Dyspepsia

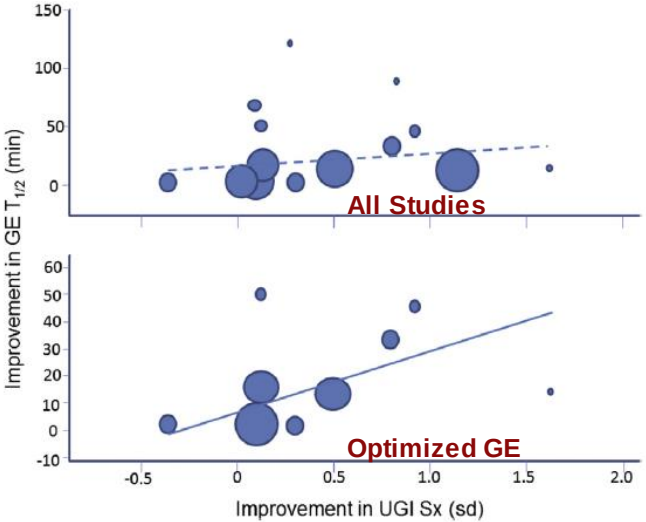
	Gastroparesis	Functional Dyspepsia
Pathophysiology	Antral hypomotility, impaired accommodation, sensory dysfunction, interstitial cells of Cajal loss	Sensory dysfunction, impaired accommodation, antral hypomotility, mucosal inflammation
Predominant symptoms	• Nausea, vomiting & postprandial abdominal pain • Weight loss	• Abdominal pain/burning (postprandial or unrelated to meals), early satiety
Symptom duration	Any	Onset >6 months with symptoms 3 days/wk
Diagnostic criteria	Delayed Gastric emptying (scintigraphy, Spirulina breath test, C^{13} breath test, wireless capsule motility	Rome IV criteria
Gastric Emptying Findings	Delayed	• Delayed =1/3 • Normal =2/3 • Rapid <5%
PPI response	+/- May further delay GE	Helps symptoms (RR =0.75)
TCA therapy	None	Helps

Adapted Moshiree B et al. *Gastrointest Endosc Clin N Am*. 2019 Jan;29(1):1-14.

Association Between Delayed Gastric Emptying and Upper Gastrointestinal Symptoms: A Systematic Review and Meta-Analysis

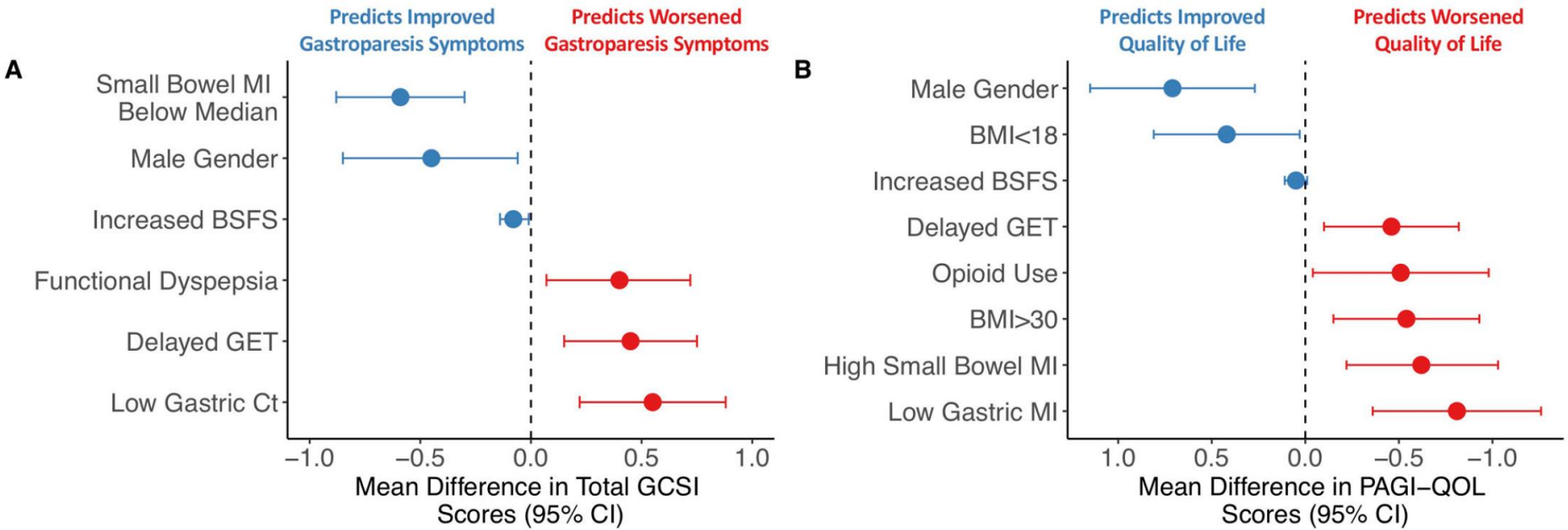
- ***Optimized*** gastric emptying correlates with upper GI symptoms and change in symptoms with prokinetics

OR (95%CI); I^2	Nausea	Vomiting	Abdominal pain	Bloating	Early Satiety	Composite
All Groups	1.5 (1.3-1.7); 11%	1.5 (1.1-2.0); 63%	1.2 (1.0-1.6); 63%	1.5 (1.1-2.0); 73%	1.7 (1.3-2.3); 56%	2.8 (1.5-5.2); 61%
Optimal GE	**1.6 (1.4-1.8);** 0%	**2.0 (1.6-2.7);** 14%	**1.5 (1.0-2.2);** 70%	1.6 (1.1-2.5); 82%	**1.8 (1.2-2.6);** 75%	7.7 (0.7-82.3); 84%
Suboptimal GE	1.2 (0.9-1.6); 15%	1.2 (0.8-1.6); 47%	1.0 (0.7-1.5); 46%	1.4 (0.9-2.1); 45%	1.7 (1.2-2.4); 0%	2.3 (1.2-4.4); 34%



Priya Vijayvargiya,[1] Sina Jameie-Oskooei,[1] Michael Camilleri,[1] Victor Chedid,[1] Patricia J Erwin,[2] Mohammad Hassan Murad[3]; Vijayvargiya P et al. *Gut*. 2019;68:804-813.

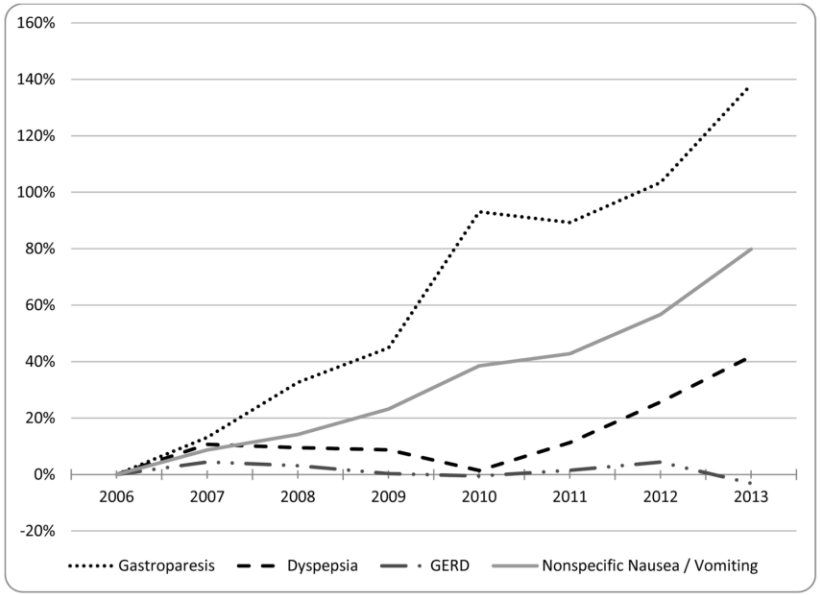
Functional Dyspepsia & Delayed Gastric Emptying Predicts Worse Symptoms & QOL

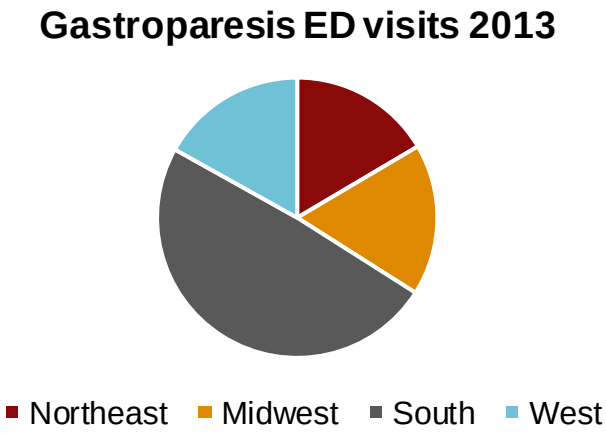


Lee A et al. *Clin Gastroenterol Hepatol*. 2022;20(3):e407-e428.

Increasing Gastroparesis ED Utilization Compared to Functional Dyspepsia

- Gastroparesis related ED visits increased 138% over 7 years
- The south had the highest rate of ED utilization





Hirsch W et al. *J Clin Gastroenterol*. 2019;53:109-113.

Age, Male Sex, Diabetes and Delayed Gastric Emptying Independent Risk Factors for Increased Mortality

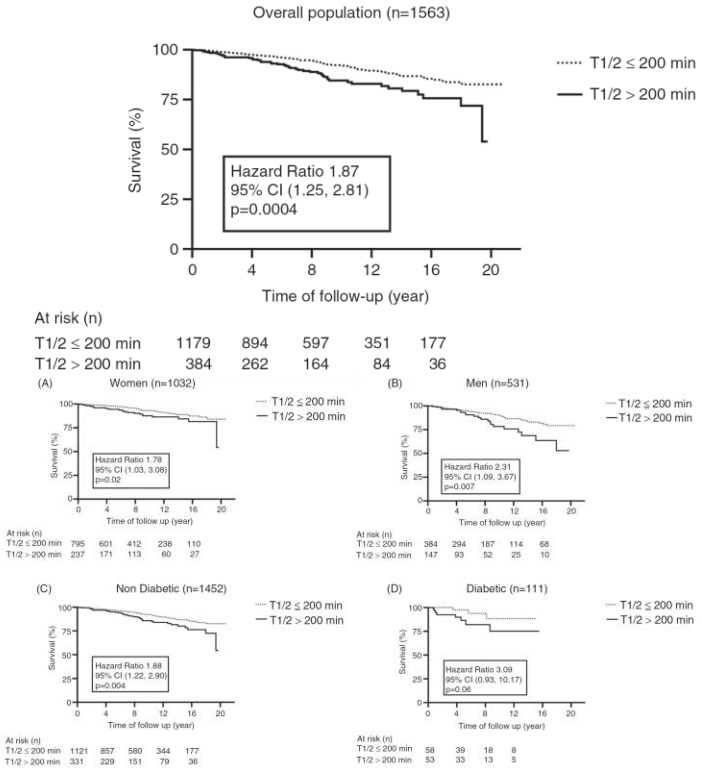


TABLE 2 Mortality rate according to the second gastric emptying test performed during the follow-up

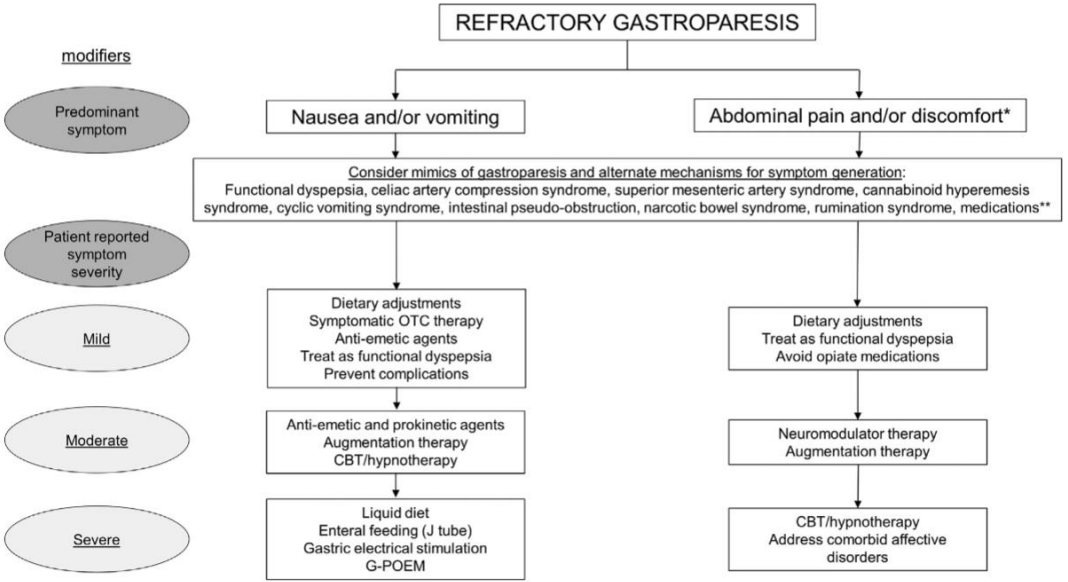
	n	5 years	10 years
Delayed-normalised	46	2.2%	2.2%
Delayed-delayed	35	4.5%	9.1%
Normal-normal	85	1.3%	1.6%
Normal-delayed	13	6.7%	6.7%
P value		0.60	0.40

Variable	HR	95% CI	*P*
Age	1.06	1.05-1.08	<0.0001
Men	1.84	1.26-2.69	0.002
T1/2 > 200	1.63	1.09-2.42	0.02
Diabetes	1.96	1.04-3.71	0.002
BMI	0.97	0.93-1.01	0.14

Gourcerol G et al. *Aliment Pharmacol Ther*. 2022;55:867-875.

Treatment Approach to Medically Refractory Gastroparesis

- "***Medically refractory gastroparesis*** can be defined as **persistent symptoms** in the context of objectively confirmed gastric emptying delay, despite the use of **dietary adjustment** and **metoclopramide** as a first-line therapeutic agent"



First Line Therapy

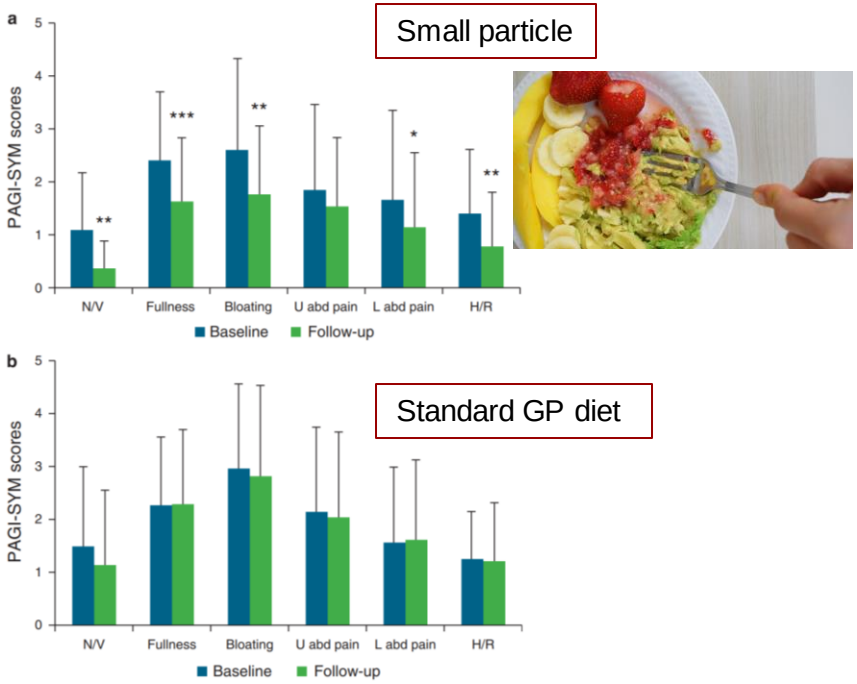
1. Exclude meds that delay gastric emptying
2. Small particle diet x 4 wks
3. Metaclopramide 10 mg TID before meals and QHS x 4 wks

Lacy B et al. *Clin Gastroenterol Hepatol*. 2022;20:491-500.

Small Particle Diet vs. GP Diet

- Small particle vs. standard gastroparesis diet x 20 weeks
  - Low fat (25-30%) & Low fiber (15 g/d)
  - 3 meals; 3 snacks
- Small particle = “easy to mash with a fork”

Poorly Digestible	Medium Digestible	Easily Digestible
Raw vegetables	Cooked carrots	Pureed vegetables
Corn	Cooked broccoli crown	Asparagus tips
Avocado	Pears without skin	Mashed avocado
Oranges, blueberries	Raspberries, Strawberries	Pureed fruits
Almonds	Scrambled eggs	Almond/Peanut butter
Meats	Sliced deli meats	Minced meats
Shrimp/ raw salmon	Cooked fish	Fish pate



Olausson E et al. *Am J Gastroenterol*. 2014;109:375-385.

Metoclopramide Remains the **ONLY** FDA-Approved Drug for Gastroparesis

Metoclopramide is the only FDA approved drug for gastroparesis since 1979

- 4 Double-Blind Placebo-Controlled RCT (predominantly DG)
  - Improved symptoms
  - Accelerated gastric emptying
- 2 Double-Blind Comparator RCT (metoclopramide vs. domperidone or erythromycin)
  - Similar in symptom improvement and acceleration of gastric emptying

Use of metoclopramide decreased following Black Box warning (February 2009)

Table 1. Medical treatment for gastroparesis before and after the metoclopramide black box warning

Medication	Before black box *N* (%)	After black box *N* (%)	Odds ratio	95% confidence interval	*P* value
Metoclopramide	37 (69.8%)	31 (23.7%)	0.13	0.07–0.27	$P < 0.0001$
Domperidone	6 (11.3%)	47 (35.9%)	4.38	1.74–11.02	$P = 0.0006$
Gastroparesis diet	2 (11.3%)	57 (43.5%)	19.64	4.58–84.14	$P < 0.0001$

Camilleri M et al. *Am J Gastroenterol*. 2013;108:18-37; Ehrenpreis E et al. *Am J Gastroenterol.* 2013;108:866-872.

Metoclopramide Revisited

Intranasal Metoclopramide for Diabetic GP

- Metoclopramide TID AC and QHS x 6 wks

Treatment	*N*	Baseline mean	Mean change from baseline	Difference from oral 10 mg Mean (95% C.I.)	*p*-value
Oral 10 mg	16	22.8	−13.9	–	–
Nasal 10 mg	30	23.4	−17.7	−3.8 (−7.1, −0.5)	0.026
Nasal 20 mg	30	21.3	−18.4	−4.6 (−7.9, −1.2)	0.008

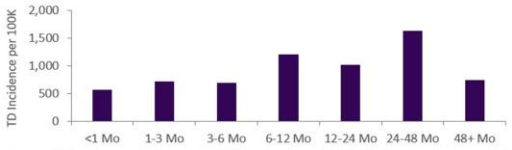
*Baseline TSS and Study Center adjusted mean change.

- FDA approved dosing in 15 mg per spray (not to exceed QID, limited to 8 weeks)

Risk of tardive dyskinesia

- Prior rates of TD reported 1-15%
- Incidence of TD in gastroparesis
  - General population: 9.4 per 100,000 (0.01%)
  - Metoclopramide without GP: 33.4 per 100,000 (0.03%)
  - Gastroparesis: 76.6 per 100,000 (0.08%)
  - Gastroparesis plus metoclopramide: 98.6 per 100,000 (0.10%)
- Risk of TD increased with age, female sex, renal dysfunction, mental health disorder, DRBA (dopamine receptor blocking agent) use, diabetes and longer duration of use

	General population		Metoclopramide prescribed patients		Gastroparesis patients		Gastroparesis patients prescribed metoclopramide	
	Incidence per 100K	Ratio (95% CI)	Incidence per 100K	Ratio (95% CI)	Incidence per 100K	Ratio (95% CI)	Incidence per 100K	Ratio (95% CI)
Renal dysfunction								
Yes	37.5	6.8 (6.3, 7.4)	65.2	3.5 (2.6, 4.7)	113.6	2.8 (1.8, 4.3)	134.7	2.3 (1.3, 4.3)
No	5.5		18.6		40.9		57.5	
Diagnosis of mental health disorder								
Yes	35.9	15.6 (14.1, 17.3)	60.1	4.4 (3.2, 6.0)	110.7	3.4 (2.2, 5.4)	134.0	3.0 (1.5, 5.7)
No	2.3		13.7		32.4		45.2	
DRBA use								
Yes	40.4	12.2 (11.2, 13.4)	61.8	6.2 (4.2, 9.0)	106.9	2.4 (1.5, 3.6)	131.2	3.2 (1.5, 6.7)
No	3.3		10.0		45.2		40.9	
Diabetes								
Yes	28.9	5.5 (5.0, 5.9)	64.2	3.5 (2.6, 4.6)	89.6	1.9 (1.2, 3.1)	108.4	1.5 (0.8, 2.9)
No	5.3		18.5		46.7		70.2	



Parkman H et al. *Neurogastroenterol Motil*. 2014; 26, 521–528;
McCallum R et al. DDW 2022. Sa1470.

Antiemetic & Neuromodulator Therapies

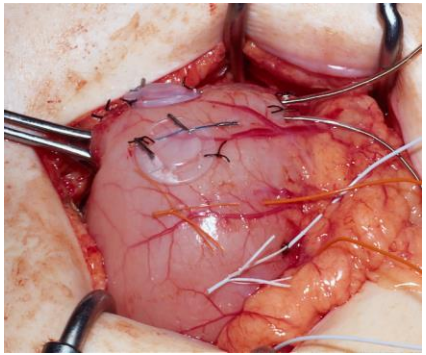
Antiemetics

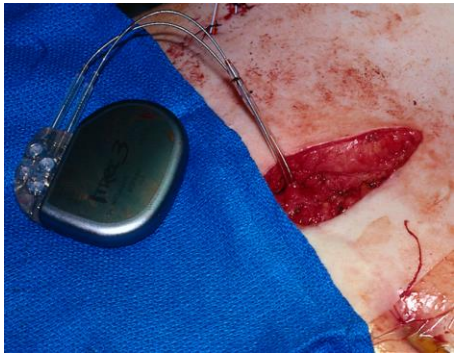
Antiemetic Class	Example
H1 antagonist	Diphenhydramine Meclizine Promethazine Cyproheptadine
Muscarinic (cholinergic) M1 antagonist	Scopolamine
D2 antagonist	Metoclopramide Domperidone Prochlorperazine Trimethobenzamide
5-HT3 antagonist	Ondansetron Granisetron Dolasetron Palonosetron (IV)
Neurokinin (NK1) antagonist	Aprepitant Fosaprepitant (IV)
Cannabinoid (CB1) agonist	Dronabinol
Benzodiazepine	Lorazepam Alprazolam

Neuromodulators

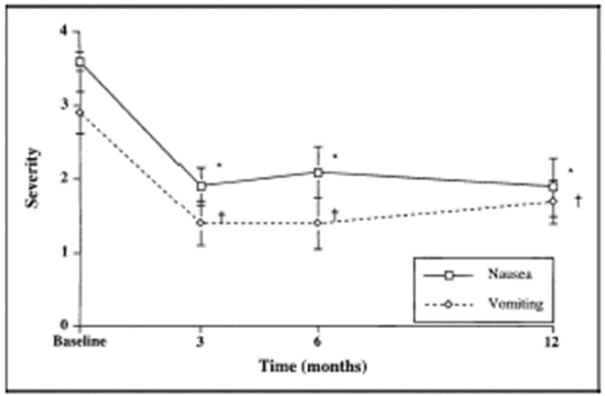
Neuromodulator Class	Example	Side Effects	Published Data
TCA - M1, H1, alpha-1, SERT, NET antagonist	Nortriptyline Amitriptyline Desipramine	Sedation, constipation, tachycardia, hypotension, QT prolongation	- Negative RCT in idiopathic GP
Tetracyclic Antidepressant - alpha-2 agonist, 5HT2, %HT3, H1 antagonist	Mirtazapine	Weight gain, constipation, sedation, abnormal LFTs	- 4 Case reports in gastroparesis - 1 Case series in gastroparesis - Accelerates gastric emptying and increases accommodation in dogs
Atypical Antipsychotic - 5HT3, D2 antagonist	Olanzapine	Weight gain, EPS, QT prolongation, constipation	- None for gastroparesis or GI disorders - Effective in prevention of CINV
GABA analog - ?MOA	Gabapentin Pregabalin	Sedation, fatigue, headaches, weight gain	- None for gastroparesis - 6 RCT and 1 case series prevention of PONV - 1 RCT and 1 case series CINV - 1 case series and 1 case report hyperemesis gravidarum
Azapirones - 5HT1, 5HT2 agonist	Buspirone	Nausea, headaches, dizziness, mood changes, seizures	- 1 randomized placebo study in FD
Benzodiazepine	Lorazepam Alprazolam	Sedation, hypotension, withdrawal symptoms	- Anticipatory nausea/vomiting in CINV - Case series abortive Rx CVS

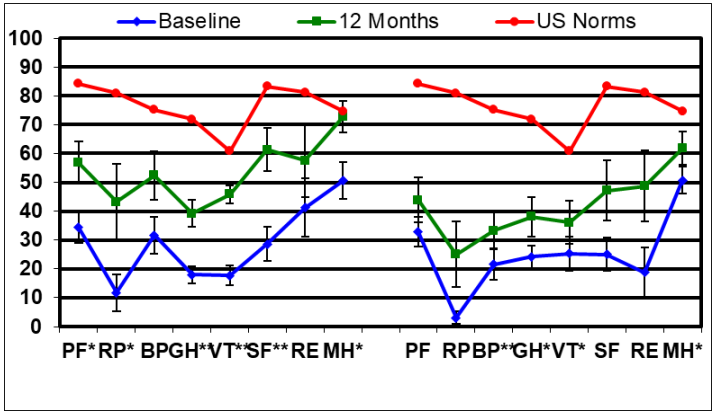
Gastric Electrical Stimulation





- Decreases symptoms of nausea & vomiting
- Improves QOL
- Symptom improvement independent of gastric emptying change





Forster et al. *Am J Surg*. 182:676, 2001.

Gastric Electrical Stimulation

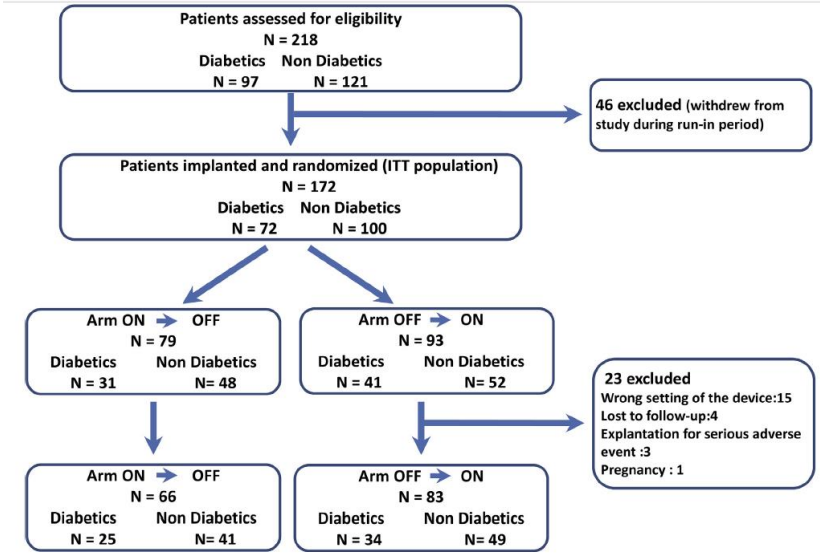


Table 1. Vomiting score

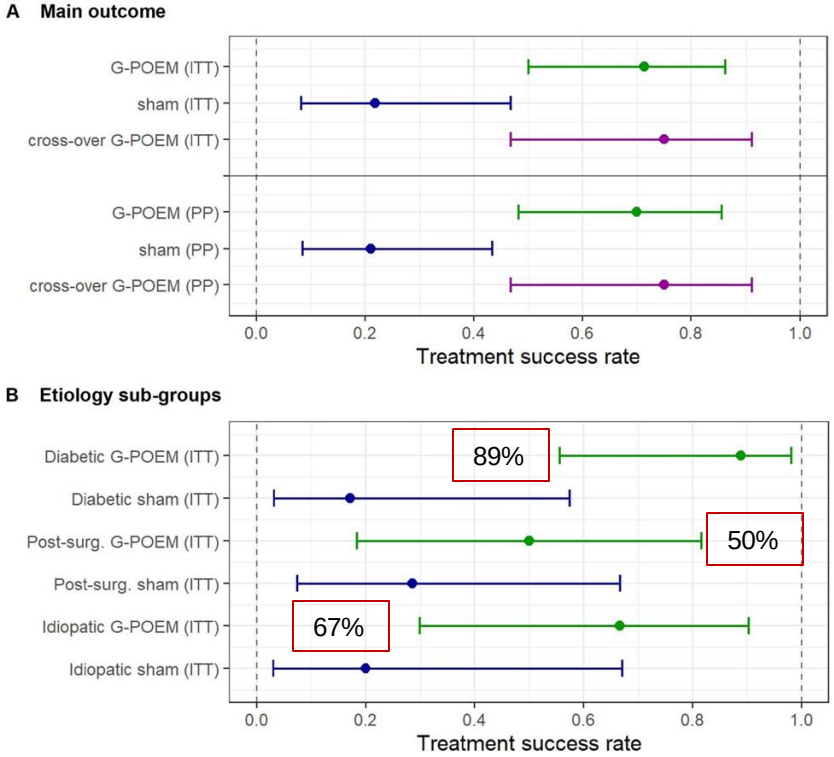
Scoring	Frequency of vomiting
0	Several vomiting episodes a week
1	No more than 1 vomiting episode a week
2	At least 1 vomiting episode a month
3	Less than 1 vomiting episode a month
4	No vomiting episode

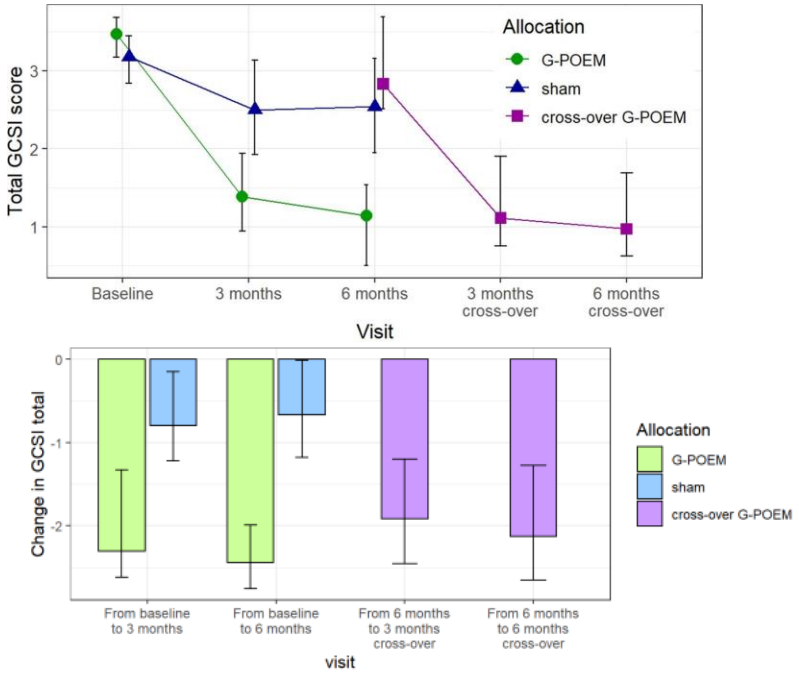
	ON	OFF	
Vomiting Score (median)	2.0	1.0	<0.001

Symptoms	ON mode	OFF mode	*P* value
Abdominal pain	1.8 ± 1.1	1.8 ± 1.1	.58
Bloating	1.8 ± 1.2	1.7 ± 1.2	.70
Quality of appetite	2.0 ± 1.2	1.7 ± 1.2	.04
Regurgitation	2.0 ± 1.2	1.9 ± 1.2	.09
Easy to eat	1.6 ± 1.1	1.4 ± 1.2	.09
Nausea	2.1 ± 1.2	1.7 ± 1.3	.003

Ducrotte P et al. *Gastroenterol*. 2020;158:506-514.

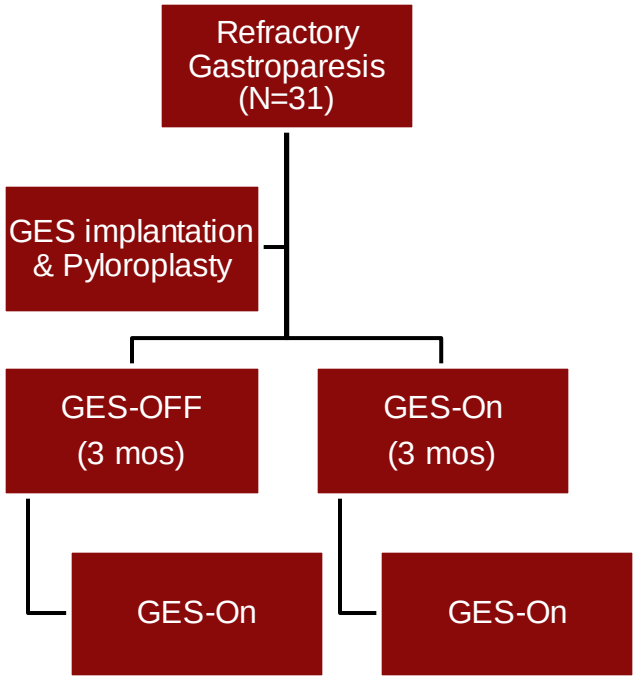
G-POEM





Martinek J et al. *Gut*. 2022:doi: 10.1136/gutjnl-2022-326904.

Gastric Stimulation & Pyloroplasty

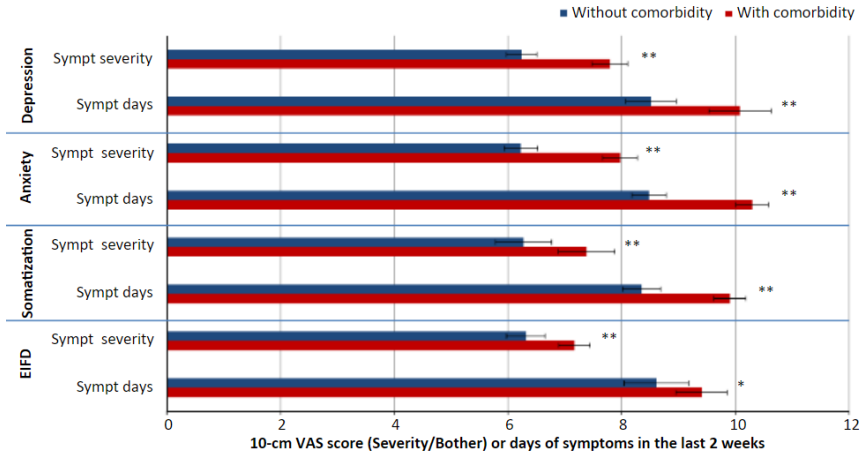


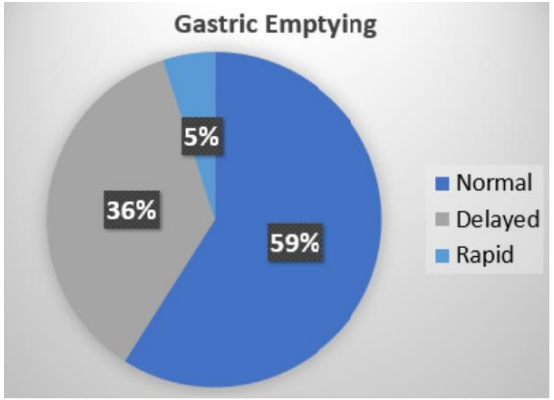
	GES-OFF			GES-On		
	Baseline	3 mos	6 mos	Baseline	3 mos	6 mos
Nausea	3.5	2.0*	1.2**	3.7	1.8*	1.6**
Vomiting	3.3	2.1	1.2**	3.3	1.1*	1.5**
Early Satiety	2.9	1.9	0.7**	3.4	1.5*	2.3
Bloating	2.8	1.8	1.0**	2.8	1.1*	1.4**
Fullness	2.7	1.5	1.0**	3.4	1.5*	2.0**
Abdominal pain	2.7	1.8	0.8**	3.1	1.1*	1.4**
Total GCSI	17.9	11.3*	5.8**	19.3	7.9*	8.8**
Mean GCSI	3.0	1.9	1.0	3.2	1.3	1.5

Sarosiek I et al. *DDW*. 2022. Oral Tu1078.

FGIDs and Gastroparesis Associated With Psychiatric and Extraintestinal Comorbidities

	Non-FGID Control (N=306)	FGID (N=606)	P value
Any Comorbidity	176 (57.5%)	469 (77.4%)	<0.001
Somatization (PHQ12 ≥10)	86 (28.1%)	282 (46.7%)	<0.001
Depression (BDI ≥14)	42 (13.7%)	208 (34.3%)	<0.001
Anxiety (BAI ≥16)	27 (8.8%)	189 (31.2%)	<0.001
Extraintestinal Functional Disorder*	109 (35.6%)	337 (55.6%)	<0.001





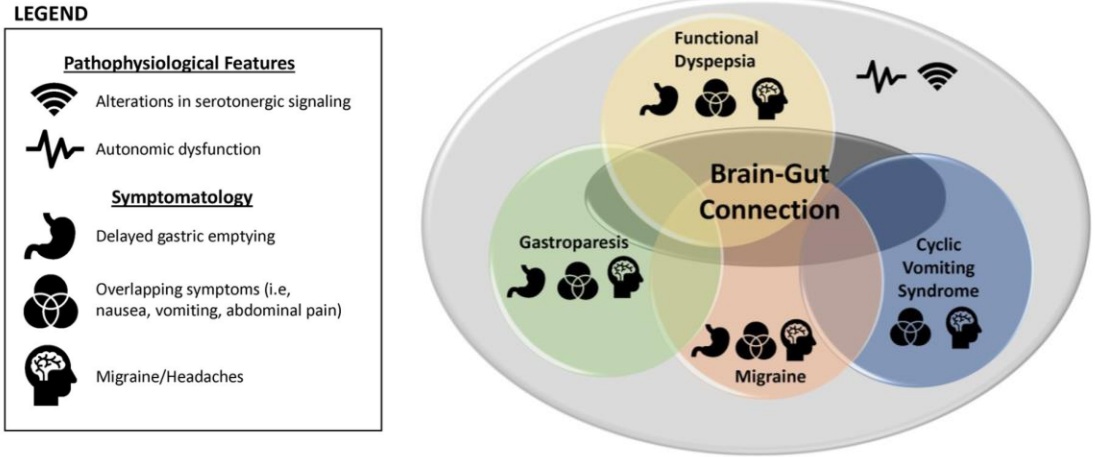
***EIFD** = chronic pelvic pain, interstitial cystitis, CFS, fibromyalgia, migraine HA, chronic HA, mitral valve prolapse, dysmenorrhea, dyspareunia, TMJ

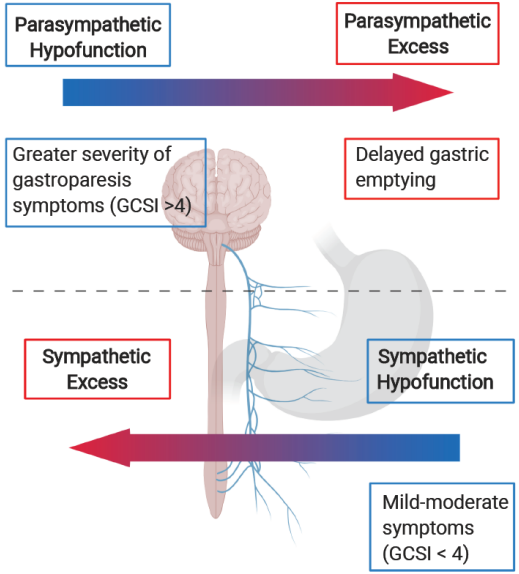
- 36% of patients with migraine have delayed gastric emptying

Nguyen L et al. DDW 2022 Sa1498; Vu J et al. *Neurogastroenterol Motil*. 2014;26:1323-1332.

Possible Pathophysiologic Links

- Overlapping altered serotonergic signaling and autonomic dysregulation
- Delayed gastric emptying associated with low resting sympathetic activity and parasympathetic excess during Valsalva or Standing challenge





Sympathetic withdrawal (low sympathetic activity in response to a sympathetic challenge) was the most common autonomic abnormality found among all patients

Aurora S, Nguyen L. *Headache*. 2021;00: 1-14; Nguyen L et al. *Neurogastroenterol Motil*. 2020.

Autoimmune Gastrointestinal Dysmotility

Features of AGID
Neural autoantibody*
Symptoms • Extraintestinal neurologic (autonomic) symptoms • Subacute onset of symptoms • Severe symptoms refractory to medical therapy
Extraintestinal Autonomic Dysfunction • Autonomic reflex screen (adrenergic & cardiovagal) • Thermoregulatory sweat test (sudomotor)
Personal or family hx (1st degree) of autoimmunity
History of recent or past neoplasia or risk factors for CA

- IVIG 0.4 g/kg weekly x6-12 weeks
- Methylprednisolone 1 g IV daily x3 then weekly x6-12 weeks
- 74% improved symptoms +/- motility or autonomic testing

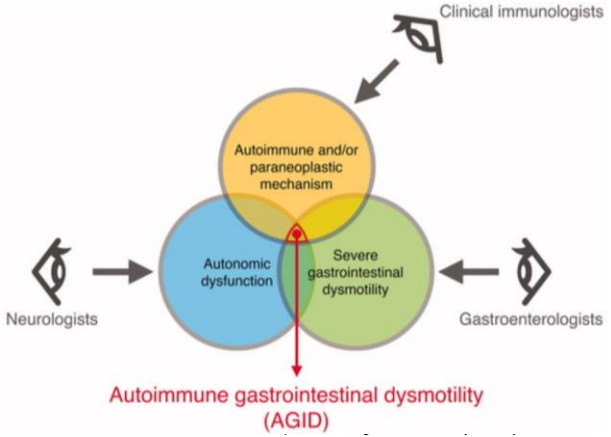
	Responders (n = 17)	Non-responders (n = 6)	p-value
Demographics			
Median age (range) at diagnosis	36 y (16–76)	53.5 y (20–72)	0.22
Clinical features			
Subacute onset	9 (53%)	1 (17%)	0.18
Personal/family Hx autoimmunity	10 (59%)	2 (33%)	0.34
Paraneoplastic AGID	3 (18%)	0 (0%)	0.54
Laboratory abnormalities			
Antinuclear antibody	7 (41%)	3 (50%)	1.0
Neural-specific autoantibody	12 (71%)	4 (67%)	1.0
Extra-intestinal autonomic testing			
Abnormalities	14 of 16 (88%)	5 of 5 (100%)	1.0
Postimmunotherapy improvement	6 of 7 (86%)	1 of 3 (33%)	0.18
Immunotherapy treatment			
Median time from onset to immunotherapy	19 months (4–123)	71 months (5–201)	0.13
IVIg (in those with single agent utilized)	10 of 15 (67%)	5 of 5 (100%)	0.27

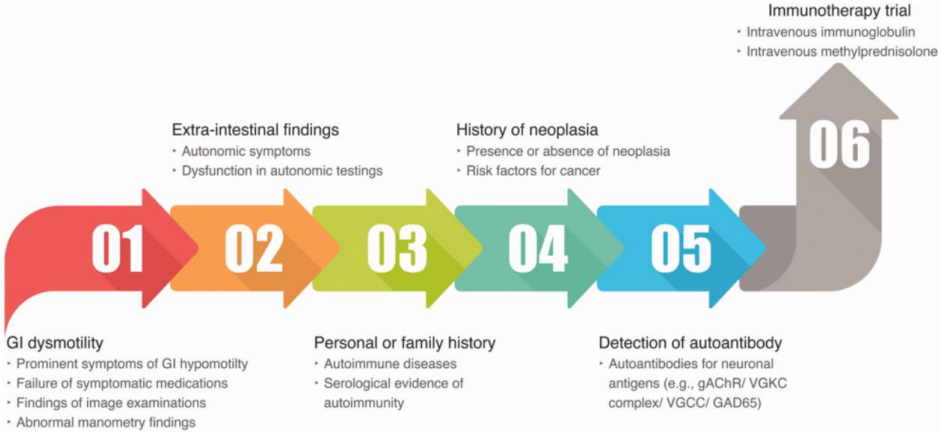
AGID, autoimmune gastrointestinal dysmotility; Hx, history; IVIg, intravenous immune globulin.

*Antineuronal ab (ANNA-1), ganglionic nicotinic AchR, voltage gated neuronal K+ channel complex, Ca2+ channel Ab (N type >PQ type), striated muscle AchR, glutamic acid decarboxylase (GAD65), peripherin.

Flanagan E et al. *Neurogastroenterol & Motil*. 2014;26:1285-1997.

Autoimmune Gastrointestinal Dysmotility





Autoantibodies (AAbs)	Gastrointestinal dysmotility	Level
(Neuronal) gAChR AAbs	Achalasia1, [5]	Esophagus
	Distal esophageal spasm [32]	Esophagus
	Gastroparesis [5,34]	Stomach
	Delayed gastric emptying [1]	Stomach
	Intestinal pseudo-obstruction [5,33]	Small intestine, colon
	Idiopathic constipation [1,30]	Colon
(Muscle) nicotinic AChR AAbs	Achalasia [1,22]	Esophagus
VGKC complex AAbs	Achalasia [1]	Esophagus
	Slow small intestine and colonic transit [1]	Small intestine, colon
	Slow transit constipation [1]	Colon
P/Q type VGCC AAbs	Achalasia [1]	Esophagus
	Delayed gastric emptying [31]	Stomach
N type VGCC AAbs	Achalasia [22]	Esophagus
	Gastroparesis [6]	Stomach
GAD65 AAbs	Achalasia [22]	Esophagus
	Slow transit constipation [30]	Colon

Nakane S et al. *Immunological Medicine*. 2021;44:74-85.

Summary

- Treat gastroparesis based on predominant symptoms
- Augmentation therapy often needed for moderate-severe GP symptoms
- Screen for extraintestinal symptoms and comorbidities
- Consider autoimmune gastrointestinal dysmotility in patients with a subacute onset of symptoms, autonomic dysfunction & autoimmunity