




Update on Rational Symptom-Based Treatment of Gastroparesis/Gastropathy

Oley Foundation Symposium on "Managing Gastroparesis Day!"
June 23, 2021
Hiroshi Mashimo MD PhD



Main Take-Home Points

- Besides diabetes, poor glucose control, medications, abdominal surgeries, pregnancy, etc. – may lead to disorder of gastric emptying (too slow or too fast), stomach discomfort, nausea/vomit, bloating
- Measures of gastric emptying (timing/severity) poorly correlate with symptoms and overlaps with functional dyspepsia
- Mainstay of medical therapy is symptom-based:
 - Promotilides
 - Anti-nausea
 - Pain reduction
- Address coincident issues: bacterial overgrowth/dysbiosis, malnutrition/food aversion, neuroinflammation, anxiety/depression
- Non-medical treatments include:
 - Herbs/acupuncture (Complementary Medicine)
 - Electrical stimulators vs. pacers
 - ? G-POEMs, Jejunostomy/venting G tube

Importance of Gastropathy in Diabetes Care

- Doctors generally screen for renal, ophthalmic, podiatry, cardiac and neurological problems in diabetic patients, but gastrointestinal (GI) problems are commonly under-recognized because patients do not volunteer information or are not directly asked by doctors
- Symptoms that can be confused with reflux disease, ulcers, gallstone, pancreas, irritable bowel, etc.
- Can manifest by poor oral glycemic control
- Review medications: anticholinergics, antihistamines, antidepressants, narcotics; diabetes medicines such as amylin analogs and GLP-1 may worsen
- 19-76% patients in a diabetes clinic reported significant GI symptoms, most commonly:
 - Early satiety
 - Reflux (e.g., heartburn)
 - Abdominal pain
 - Nausea/vomiting
 - Diarrhea
 - Constipation

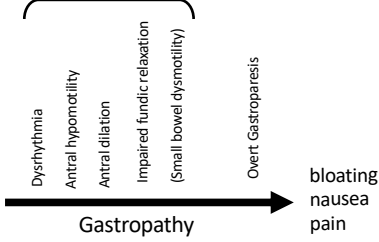
} suggestive of gastropathy

Zhao, X., Mashimo, H. *Curr. Treatment Options in Gastroenterol.* 2015; 13(4):452-472.

stomach paralysis Gastroparesis: Definition

delayed gastric emptying in the absence of a fixed mechanical obstruction of the pylorus or duodenum

Spectrum of Gastric Dysmotility in Diabetics



Gastropathy in Diabetics: potential other causes besides autonomic neuropathy

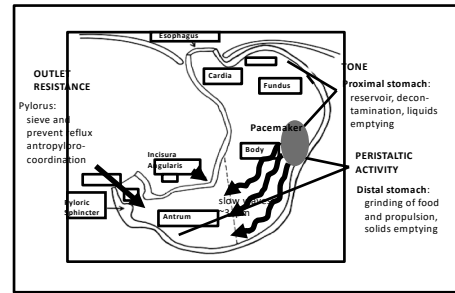
- Metabolic and endocrine:** DKA, pregnancy, hypothyroidism, electrolyte imbalance, renal failure, neoplastic (breast/small cell/pancreas)
- Medications:** anticholinergics, narcotics, β -adrenergics, Ca^{2+} -channel blockers, glucagon, levodopa, loperamide, THC, alcohol, tobacco, etc.
- Postsurgery:** vagal nerve injury, partial gastrectomy, fundoplication, Whipple
- Infectious:** acute viral gastroenteritis, EBV, varicella, parvovirus-like, Chagas, C. botulinum
- Gastritis:** atrophic, pernicious anemia
- Rheumatologic:** scleroderma, SLE, polymyositis/dermatomyositis
- Pseudo-obstruction:** idiopathic, secondary (amyloidosis, MD, paraneoplastic)
- Electrical dysrhythmia:** tachy, brady, or gastroduodenal dyssynchrony
- Central nervous system:** tumor, bulbar poliomyelitis, depression, CVA, head trauma, labyrinthine disorders, seizures, abdominal migraine
- Peripheral nervous system:** Parkinson's, Guillain-Barre, MS, dysautonomia
- Idiopathic**

Important Emerging Key Concepts

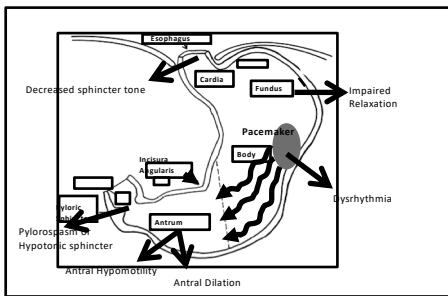
- Stomach is not a simple bag
 - Different areas have different function
 - Solid food emptied differently from liquids
- Relation of muscle and nerves to allow coordinated emptying
- Inflammation and altered sensory

understanding important for rational treatments

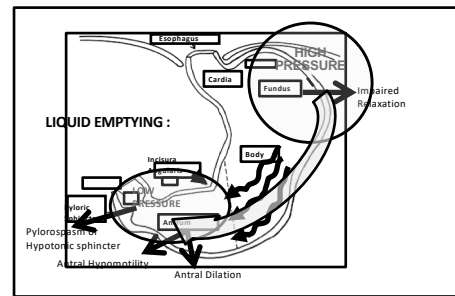
Functional Parts of the Stomach



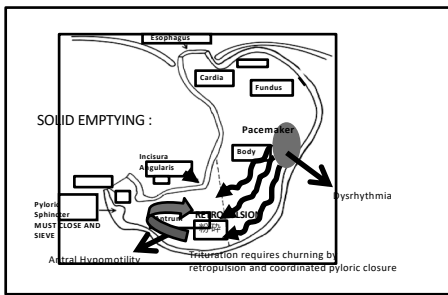
Distinct Regional Dysfunction in Diabetes



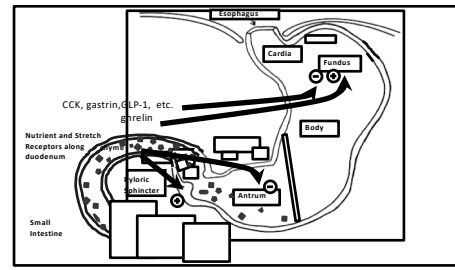
Liquids and Solids Empty Differently !

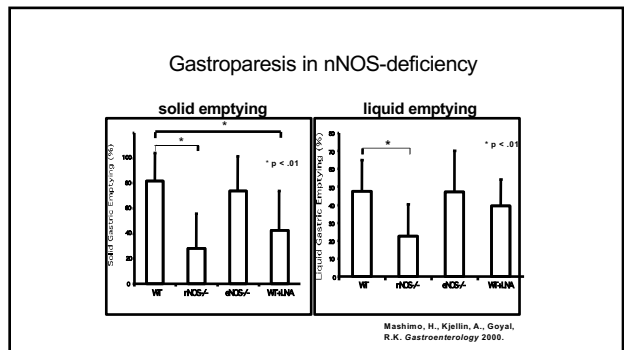
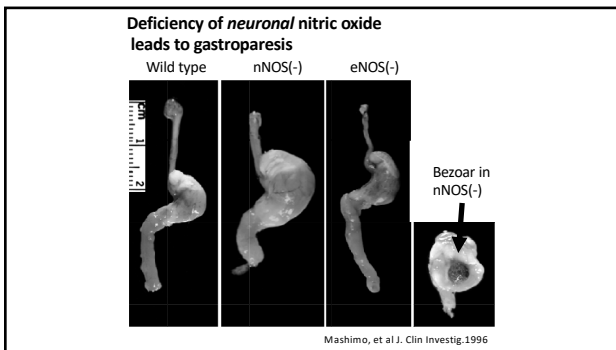
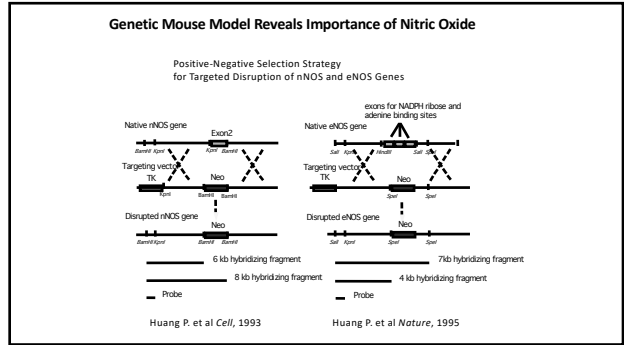
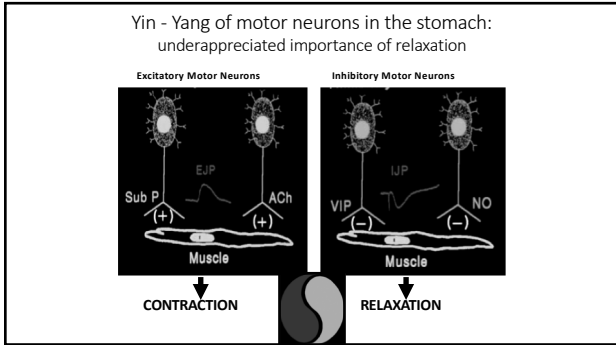


Liquids and Solids Empty Differently !



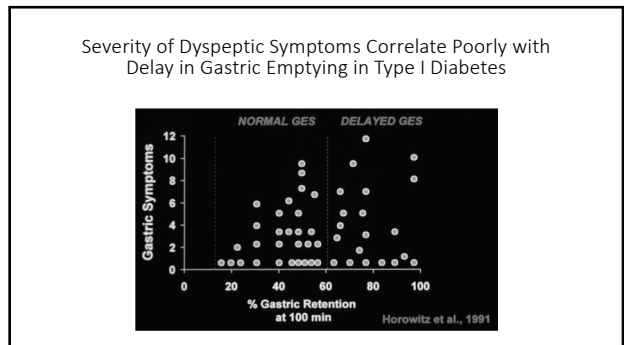
Feedback from Nutrients in Intestine Delays Gastric Emptying Through Vagally Mediated Hormonal Inhibitory and Excitatory Reflex





Selective decrease in inhibitory pathway in major gastrointestinal motility disorders:

Examples:
 Diabetic gastropathy
 Achalasia
 Pyloric stenosis
 Pseudo-obstruction
 Chronic constipation
 Hirschsprungs Disease



suggestive symptoms and potential pathogenesis

- Early satiety/anorexia/food avoidance
- Bloating/postprandial fullness
- Heartburn
- Epigastric pain
- Nausea
- Postprandial vomiting
- Weight loss

} Defective accommodation reflex

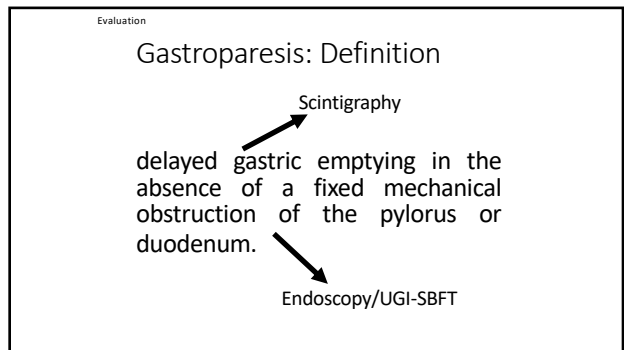
} Visceral hypersensitivity (sensory neuropathy)

} Delayed emptying

History	Etiological Implications (Ddx)
Timing	
minutes after meals	psychoneurotic, bulemic, channel ulcer, early dumping
hours after meals	obstruction, idiopathic
before breakfast	pregnancy, uremia, alcoholism, increased ICP
Duration	
hours to days	acute infect., drug/toxins, acute inflammation, pregnancy
weeks to months	obstruction, idiopathic, brain tumors, psychogenic
Quality of vomitus	
partially digested	idiopathic, obstruction
undigested	esophageal obstruction, diverticulum
bile present	patent gastric outlet
feculent odor	gastroparesis with stasis, intestinal obstruction, fistula
blood present	cancer, inflammation
Amenorrhea	pregnancy
Headache	brain tumor
Previous surgery	postvagotomy, dumping syndrome, obstruction

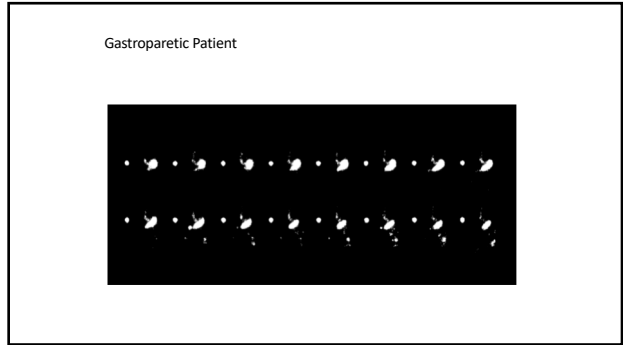
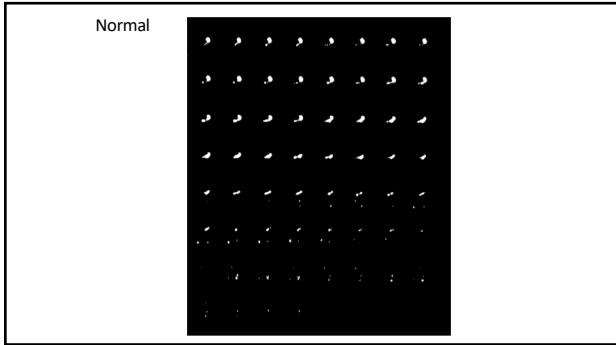
History can suggest gastroparesis, but has limited usefulness in establishing etiology

EVALUATION

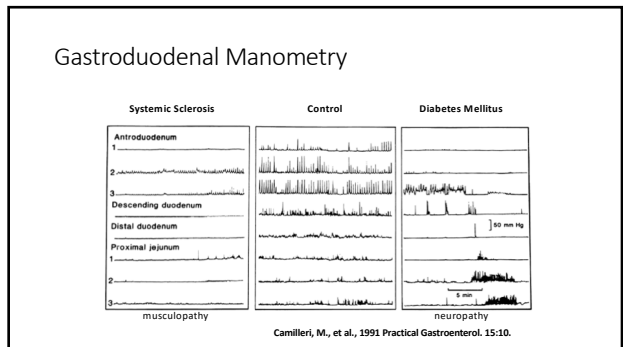
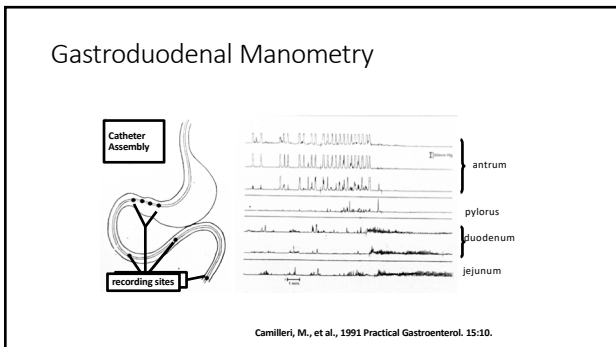
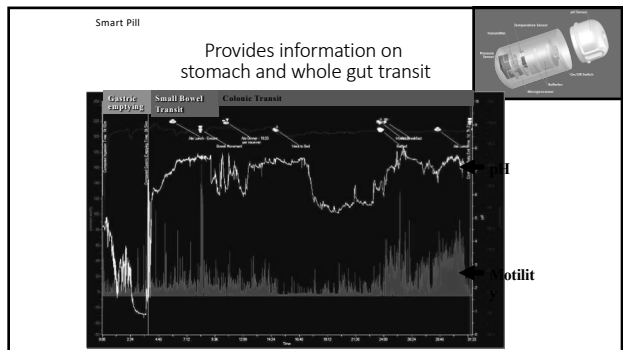


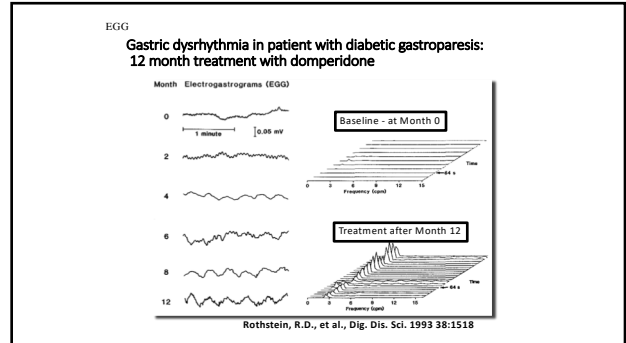
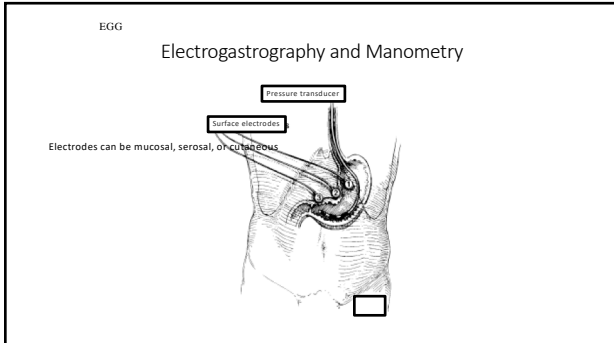
- ### EVALUATING GASTRIC DYSMOTILITY
- REVIEW MEDICATIONS!
 - Endoscopy/UGI-SBFT
 - rule out mucosal disease and obstruction
 - Gastric Emptying Tests
 - Gastro-duodenal Manometry
-
- Electrogastrography
 - Barostat
 - PP for vagal integrity
 - Smart Pill

- ### Gastric Emptying Tests: Indications
- To evaluate:
- Unexplained nausea/vomiting
 - "Motility-like" non-ulcer dyspepsia (bloat, early satiety, anorexia)
 - Severe gastroesophageal reflux disease refractory to medications
 - Suspected gastroparesis in diabetics
 - Suspected dumping/stasis after gastric surgery
 - Suspected chronic intestinal pseudo-obstruction
 - Possible re-evaluation in known gastroparetic in clinical trials of promotility agents
- Not necessary if overt retention of food (on xray or endoscopy) after reliable fast
- Camilleri et al., Gastro 1995 115:747

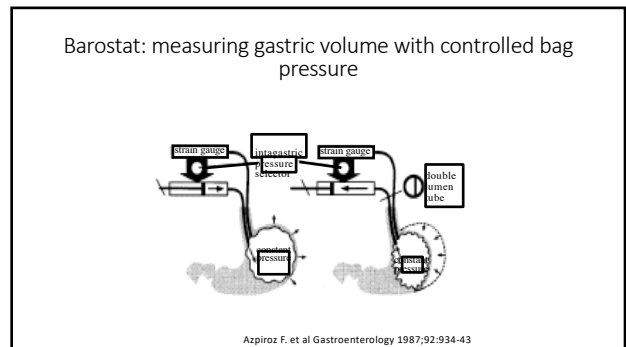


- ### Other Gastric Emptying Tests
- Gastric Emptying Breath Tests (GEBT, Advanced Breath Test Diagnostics) – C^{13} -Spirulina Breath Test – FDA-approved
 - Intubation/aspiration
 - ex. 750ml saline via ngt, check resid. after 30 min; nl <375ml
 - variable aspiration, and checks only liquid emptying
 - Radiological detection of radiopaque markers taken with meal (Poitras P., et al. 1997) or barium beefsteak meal
 - Breath tests ^{13}C -octanoic acid
 - indirect measure, noninvasive, reproducible, no radiation (stable isotope), less expensive
 - need normal intestinal absorption, liver metabolism, and lung function
 - require validation against scintigraphy
 - Acetaminophen absorption
 - noninvasive measure of liquid emptying
 - not extensively validated, need multiple blood samples, limited accuracy
 - Single-photon-emission CT (SPECT) imaging of gastric accommodation
 - SmartPill





- EGG
- ### EGG interpretation
- Evaluation of frequency and power
 - may define abnormality in a different subset of patients than those with emptying or manometry
 - positive predictive value of abnormal EGG is estimated at 60%–90%
 - suggested that dysrhythmias may be better indicators of symptoms such as nausea and early satiety than gastric emptying, and may better correlate with symptomatic responses to medications



TREATMENT

- ### Current Treatment of Gastroparesis
- Correct underlying condition
 - Review medications! control hyperglycemia!!! <- ? tid FS check
 - ?insulin pump therapy in diabetics
 - Hydration and nutrition, check dentition
 - Dietary changes
 - small frequent meals, low residue, low fat
 - Psychological measures: empathy/education, support groups, relaxation/hypnosis
 - Medical treatments
 - Botulinum toxin?
 - For failures, decompression (PEG-J) and nutrition (PEJ) only after trial of NG and NJ tubes
 - Surgery - g-POEMs? rare except outlet obstruction from PUD or carcinoma - generally disappointing
 - Gastric Electrical Stimulation/Pacing

Medications that Slow Gastric Emptying

- anticholinergic agents
- antidepressants
- beta-adrenergic agonists
- calcium channel blockers
- ganglion blocking agents
- levodopa
- nicotine
- octreotide
- opiates
- tranquilizers
- vincristine

Diabetes drugs that cause or worsen gastroparesis:

- amylin analog pramlintide (Symlin) both Type 1 and 2
Vella A. et al Neurogastro and Motil 2002 14:123.
- GLP-1 agonist
 - Short acting: exanetide (Byetta), lixisenatide (Adlyxin), semaglutide (Rybelsus)
 - Long acting: exanetide (Bydureon), liraglutide (Victoza), dulaglutide (Trulicity), semaglutide (Ozempic)
- May need to switch to DPP IV inhibitors: vildagliptin (Galvus), sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Trajenta)

For example, in clinical trials:

- Nausea was 39% for exanetide vs. 5% for sitagliptin
- Vomit was 19% for exanetide vs. 5% for sitagliptin

Berg et al. Diabetes Obes Metab 2011 13:982

Three-step Dietary Treatment

STEP 1: rehydration Day 1-2

- sip Gatorade or salty bouillon solution to ingest goal 1-1.5L over 24 hours, multiple vitamin
- avoid citrus or highly sweetened drinks

STEP 2: diet advance to soups

- soups with noodles/rice and crackers, 6 small-volume meals per day, goal 1500 cal/day and maintain/gain weight
- avoid fatty foods

STEP 3: introduction of more solid foods

- starches (require less electrocontractile work), white meat
- avoid red meat, fresh vegetables, fiber

from: Mashimo, May, Goyal in Joslin's Diabetes Mellitus (14th Ed. 2005)

Pharmacological Treatment

- prokinetics
- antiemetics
- pain control
- antibiotics (bacterial overgrowth)

- NOT octreotide (actually decreases postprandial antral motility index); however phase III augmentation of small bowel
- NOT muscarinic agonists alone (actually just discoordinated contractions)
- Sumatriptan, buspirone, sildenafil - relax fundus for dyspepsia but may delay gastric emptying
(Edmunds, M.C. et al., 1998 Alim. Pharmacol. & Therap. 12:167)

Prokinetic Therapy

Medication	Other Mechanisms	Dosage	Comments
Dopamine D₂-R antagonists			
*Metoclopramide (Reglan)	5-HT ₄ facilitate ACh release 5-HT ₃ antagonist	5-20 mg po qid iv/liq/pr/nasal	short course (4-12 wks) per FDA warning 10% CNS SEs; 1% dystonia
Domperidone	peripheral D ₂ R antagonist	10-30 mg qid	not cross BBB; FDA IND w IRB
Itopride (Ganaton)	similar to domperidone also Ache inhibitor	50mg	no known cardiac SEs available in Asia
Motilin receptor agonists			
Erythromycin	stim cholin nerves ↑ antral contrac	50-250 mg qid	strongest prokin iv; lower dose decr SEs 2x sudden death, tachyphylaxis w/in days
Azithromycin ?			
5-HT₄-R agonists			
Cisapride (Propulsid)	↑ ACh rel from ENS ↑ sim mus contractions	10-20mg qid	withdrawn 2000 compassionate use
Tegaserod (Zelnorm)	5HT ₄ antag, 5HT ₄ agonist partial agonist	6 or 12 mg tid	
Prucalopride	highly selective agonist	2mg qD	avoids cardiac toxicity
Muscarinic receptor agonist/Cholinesterase inhibitors			
Bethanechol	contractions not coordinated	25mg qid w/ prokin	sig AEs * The only medication presently FDA-indicated for gastroparesis; all others off-label use

Antiemetics

Dopamine D ₂ -R antag with prokinetic without prokinetic	metoclopramide, domperidone prochlorperazine (Compazine), trimethoprim/benzamide (Ilgan), thiethylperazine (Torecan)
Serotonin 5-HT ₃ -R antag	ondansetron (Zofran), granisetron (Kytril) dolasetron (Anzemet), tropisetron (Navoban)
Tricyclic antidepressants	desipramine, nortriptyline, amitriptyline
Muscarinic M ₁ -R antag	scopolamine, hyoscyamine, clemidium (Quarzan)
Histamine H ₁ -R antag	dimenhydrinate (Dramamine), meclizine (Antivert), promethazine (Phenergan)
Cannabinoids	tetrahydrocannabinol, CBD/CBG etc.
Benzodiazepines	lorazepam (Ativan)
Neurokinin NK ₁ -R antag	aprepitant (Emed)
Alpha2-adrenergic	clonidine (Catapax) <0.1mg patch, be careful with BP drop

Pain Control

- Pain from autonomic neuropathy? But more severe forms of diabetic neuropathy had LESS pain
- indomethacin and ketorolac may resolve slow wave abnormalities in DM and dyspeptic patients
 - caution ulcers and renal fct in DM
- TCAs at low doses
- SSRIs:
 - paroxetine accelerate small intestinal transit
 - duloxetine - combined SS/NA RI
- NaSSA - mirtazapine (Remeron)
- other drugs for neuropathic pain: gabapentin, topiramate, clonidine - but uncertain role in gastroparesis
- avoid narcotics
 - tramadol - less μ -R action
 - methadone or transderm fentanyl - less constipation
 - alvimopan - but not reverse effects of codeine on stomach
 - methyl naloxone (s.c.)

Upcoming/Newer Drugs Potential for Gastropathy

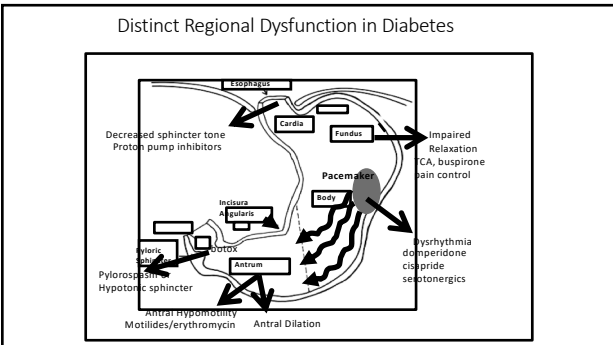
- Other 5HT agents: alosetron (re-approved for IBS-d), ARYx (ATI-7505), renzapride, mosapride, TD-5108(velusetrag)/2749
- Dopaminergic: TAK906
- CCKA antagonist: doxiglumide, loxiglumide
 - increase gastric and colonic motility, reduce visceral perception
- Motilin receptor agonist: mitemincal (GM 611-05), ABT229
 - no antibacterial properties, acid resistant
- Opioid receptor modifiers: methylaltrexone
- Neurotrophin-3 (BDNF)
- Guanyl cyclase agonist: linaclotide
- Ghrelin: Relamorelin, TZP101, pentapeptide
- Neurokinin/tachykinin analogues
- amylin antagonists

Potential Non-Drug Treatments

- Ginger - weak 5HT₃R antagonist
- Acupuncture point P6 (Neiguan point) - reduction of nausea (Koch, K.L. et al. 1997)
 - first trimester pregnancy (Evans, A.T., et al. 1993)
 - postoperative nausea and vomiting (Dundee, J.W., et al., 1989)
 - cancer chemotherapy (Dundee, J.W., et al., 1991)
- Reliefband (Woodside Biomedicals, CA)
- Gastric electrical pacing (McCallum, R.W. et al., 1998)
 - freq 10% above baseline, pulse width 300ms for entrainment
- Gastric electrical stimulation (GEMS Study Group, 1999)
 - Enterra therapy (Medtronic)
- Gene therapy?

Refractory Patients

1. Switching prokinetic and antiemetic agents
2. Combining prokinetic agents
3. Gastrostomy/jejunostomy tubes
4. Injecting botulinum toxin into the pylorus – matter of patient selection, and presently not advocated unless part of clinical trial
5. Gastric-POEM?
6. Implanting a gastric electric stimulator?



GEMS: Stimulation System

Equipment
Itrel 3 Model 7425
Intramuscular lead 4300-xx cm

Procedure	Time	Recovery
Laparotomy	1-3 hr	2-7 days
Laparoscopy	1.5-3 hr	1-4 days

Stimulation	
Rate	14 Hz
Pulse width	330 μ s
Current	5 mA
Cycle ON time	0.1 sec
Cycle OFF time	5.0 sec

SUMMARY

- Gastropathy commonly under-recognized
 - need to ask patients
 - suspect in patients with nausea/vomit, dyspepsia, early satiety, poor appetite, poor glycemic control
- Diagnose by scintigraphy, rule out mucosal disease/obstruction by endoscopy and barium small bowel follow-through
- Review culprit medications: anticholinergics, antihistamines, narcotics; amylin analogs and GLP-1 may exacerbate
- Correct underlying metabolic disorders, initiate three-step dietary progression
- Treatment: prokinetics, antiemetics, and pain control

VA BOSTON HEALTHCARE SYSTEM



Jamaica Plains



West Roxbury



Brockton

- THANK YOU -

HARVARD MEDICAL SCHOOL



BRIGHAM AND WOMEN'S HOSPITAL

