



Gastroparesis 2017-There is effective therapy and prevention is at hand

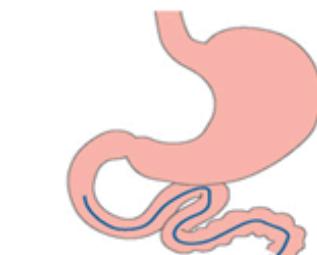
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Director of Center for Neurogastroenterology and GI Motility
Department of Internal Medicine
Texas Tech University, El Paso, TX

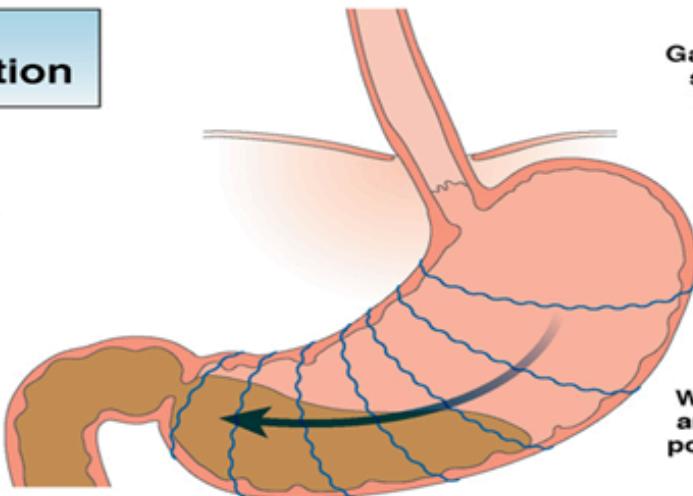
Background

- Gastroparesis, is defined as delayed gastric emptying with associated symptoms in the absence of mechanical obstruction.
- The cardinal symptoms are upper abdominal pain, postprandial fullness, bloating, early satiety nausea, and with more severe illness, vomiting.
- In advanced cases there is weight loss, malnutrition, dehydration, electrolyte imbalance, hypo/hyper-glycemic fluctuations, bezoar formation and aspiration pneumonia.
- It affects up to 10 million individuals in the United States (3%); with 70% female; median age: 50 years.

Normal gastric function



Role of small bowel motility in accepting triturated gastric contents



Motilin

Cholecystokinin

Ghrelin

GI peptides modulate post-prandial gastric nutrient emptying

Gastric motility controlled by slow gastric waves which originate from interstitial cells of Cajal (ICC) and entrain gastric smooth muscle cells

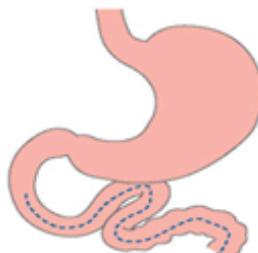
Electrical activity begins at junction of fundus and body (3 cycles/min)



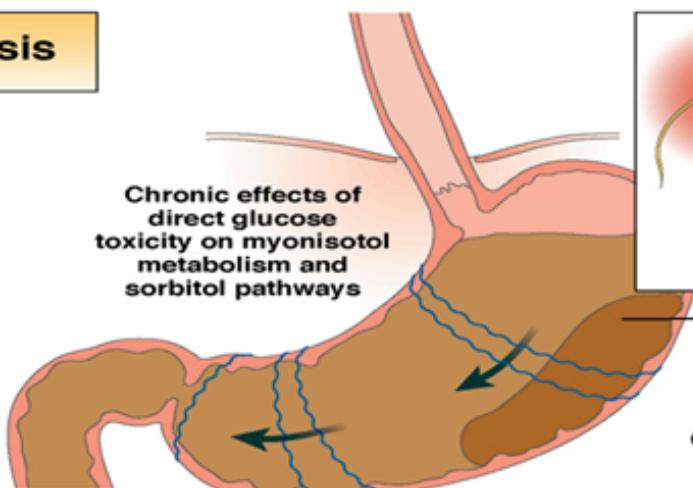
Waves are conducted circumferentially and distally toward pylorus with action potentials* signaling electro-mechanical coupling (muscle contraction)

The enteric nervous system integrates neuro-hormonal control and coordination of muscle contractility, relaxation, and sphincter function

Gastroparesis



Impaired small bowel motility and bacterial overgrowth

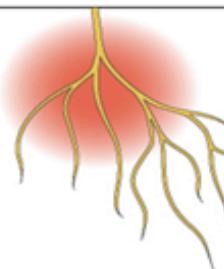


Chronic effects of direct glucose toxicity on myoinositol metabolism and sorbitol pathways

Motilin

Ghrelin

Imbalance of post-prandial hormone release



Vagus nerve neuropathy:

- Fewer antral contractions
- Decreased gastric tone
- Impaired antroduodenal incordination
- Antral hypomotility
- Pyloric dysfunction leading to delayed emptying

Retained food (bezoar)

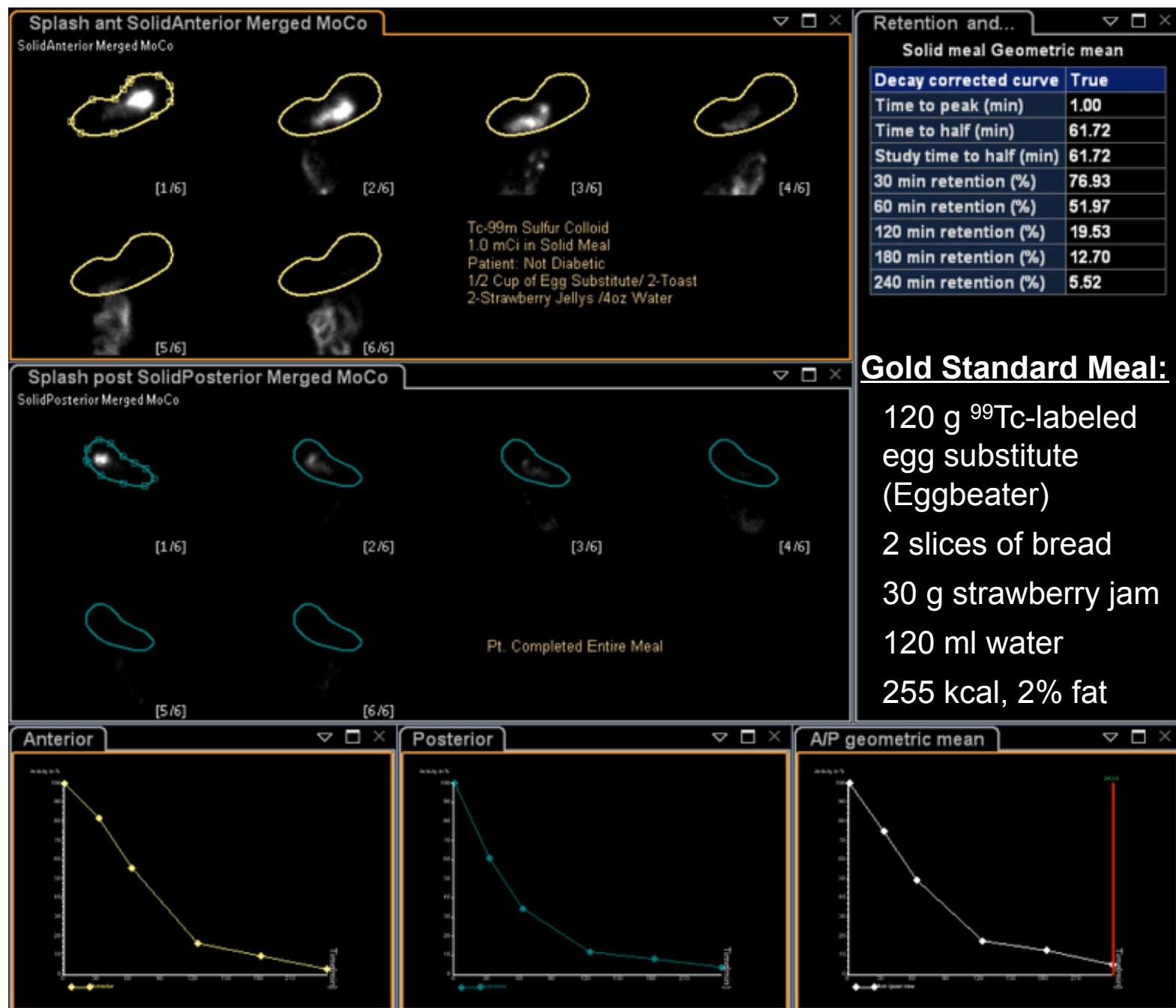
Depletion and disruption of ICC network

Gastric electric dysrhythmias (tachygastria and erratic conductivity)

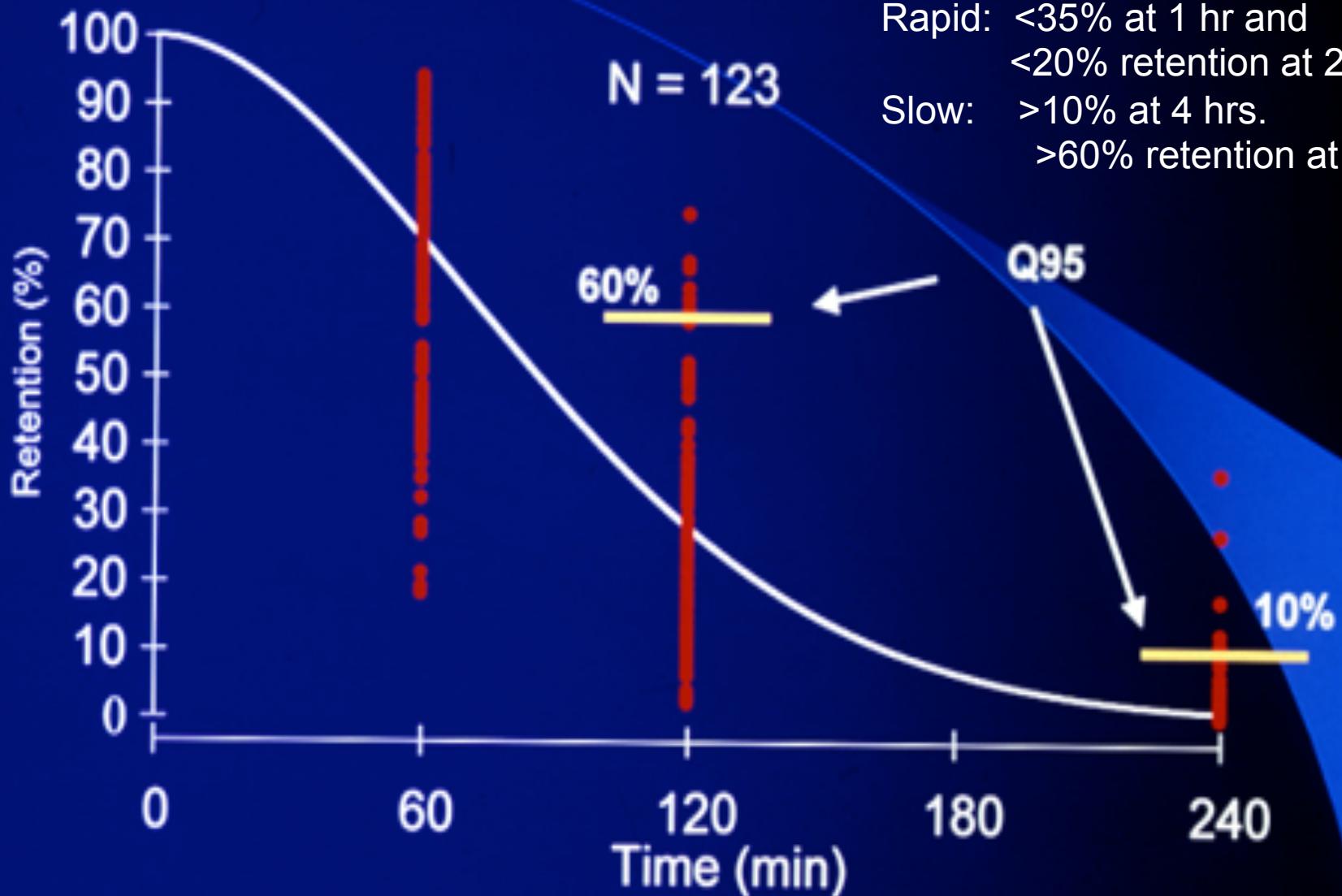


Loss of electro-mechanical coupling and impairment of gastric contractions

Normal 4-hour standardized Scintigraphic Gastric Emptying



Analysis of Gastric Emptying



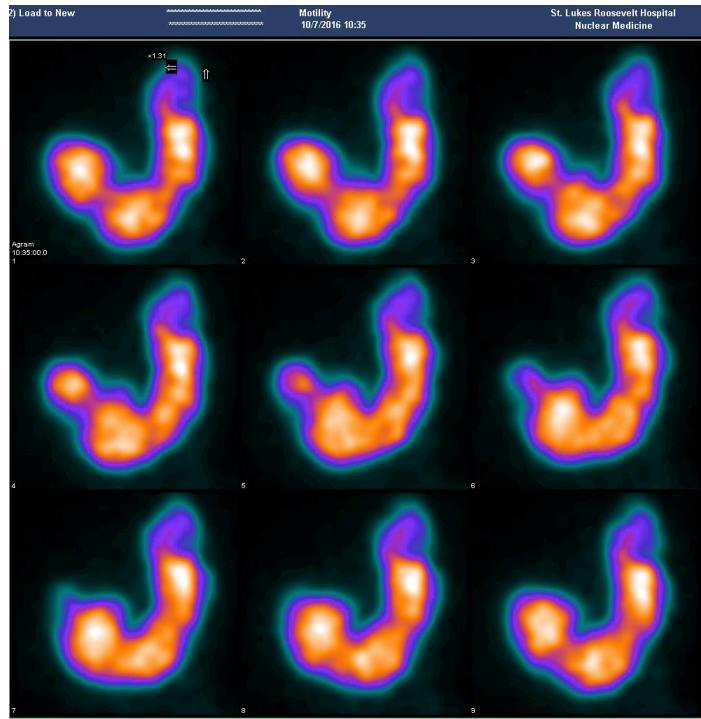
Definitions:

Rapid: <35% at 1 hr and
<20% retention at 2 hrs.

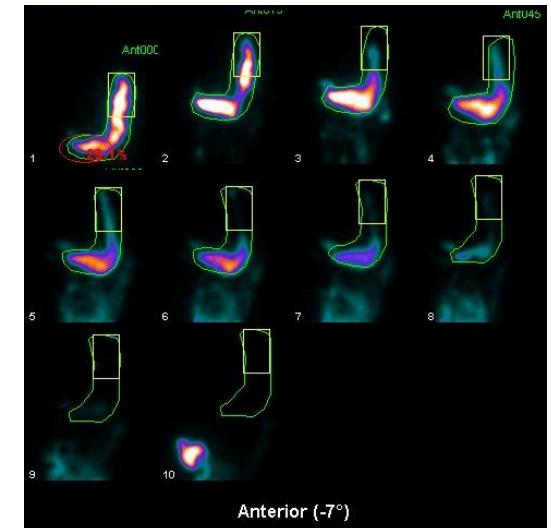
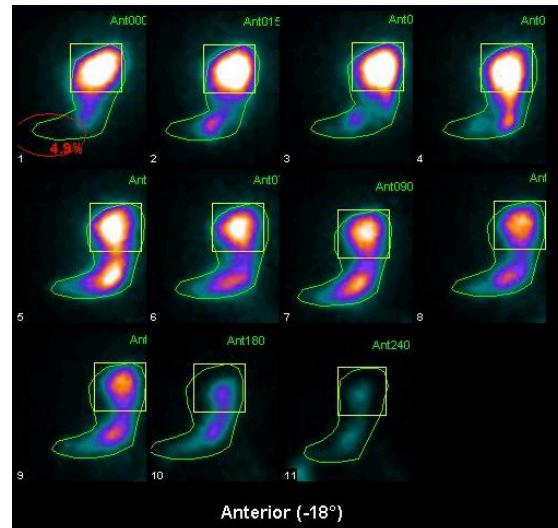
Slow: >10% at 4 hrs.
>60% retention at 2 hrs.

Future Directions for Gastric Scintigraphy

Antral Dynamic Scintigraphy



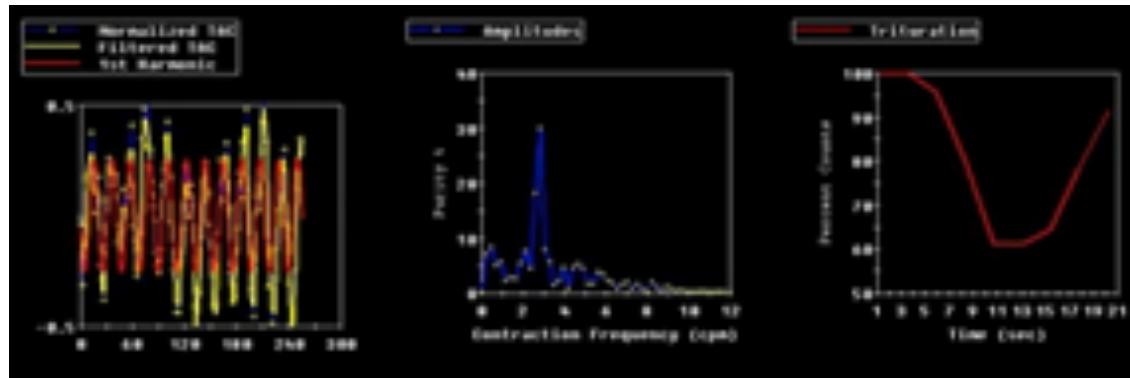
Fundic Emptying/ Accommodation



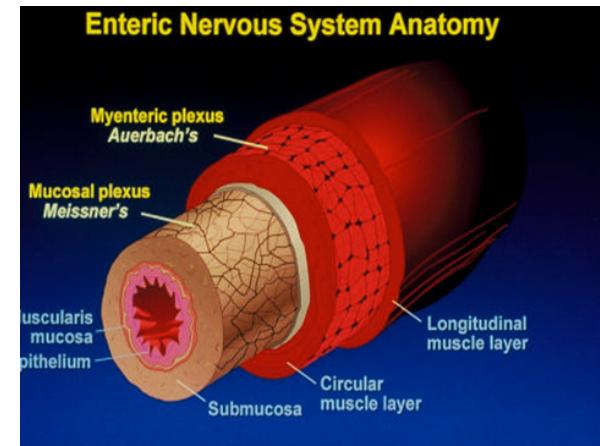
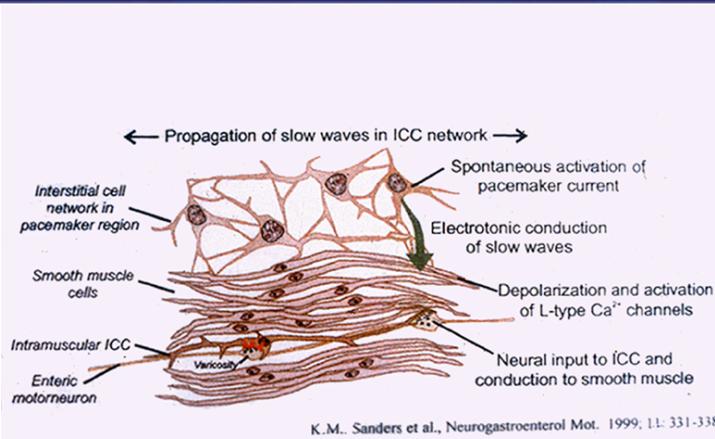
Delayed Fundic Emptying

Rapid Fundic Emptying

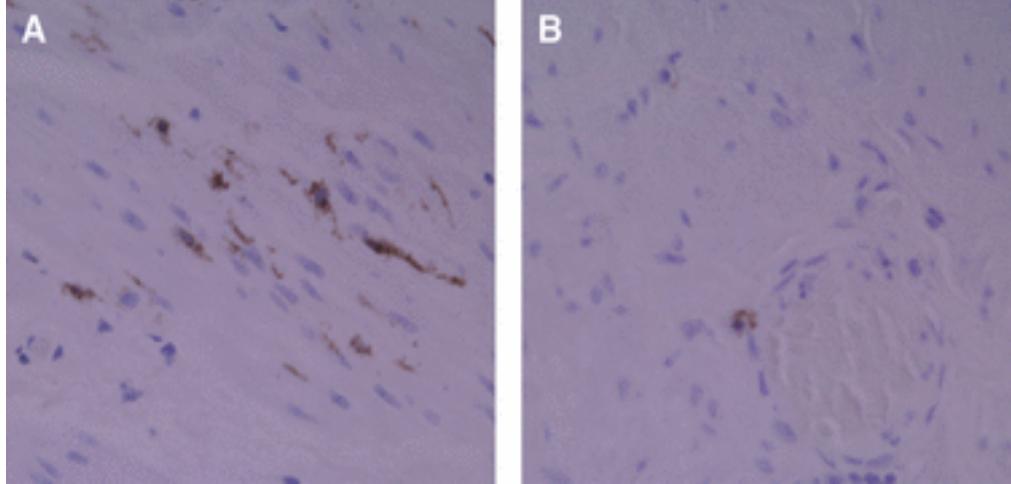
Slow GE- Normal Antral Motility



Approximately, 40% of patients refractory to medical therapy and requiring GES therapy have depletion of ICC in the antrum or gastric body.



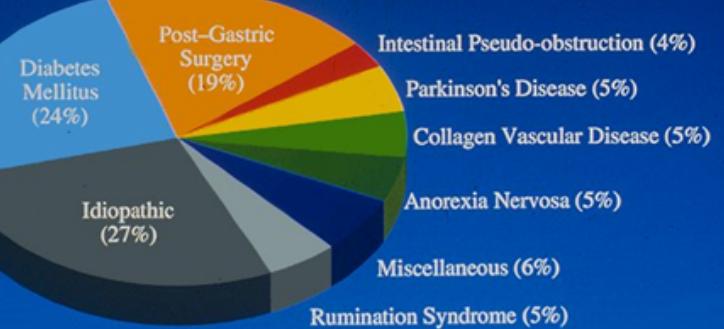
C-Kit Staining of antral smooth muscle for ICC



Normal (>10 ICC/HPF)

Gastroparesis

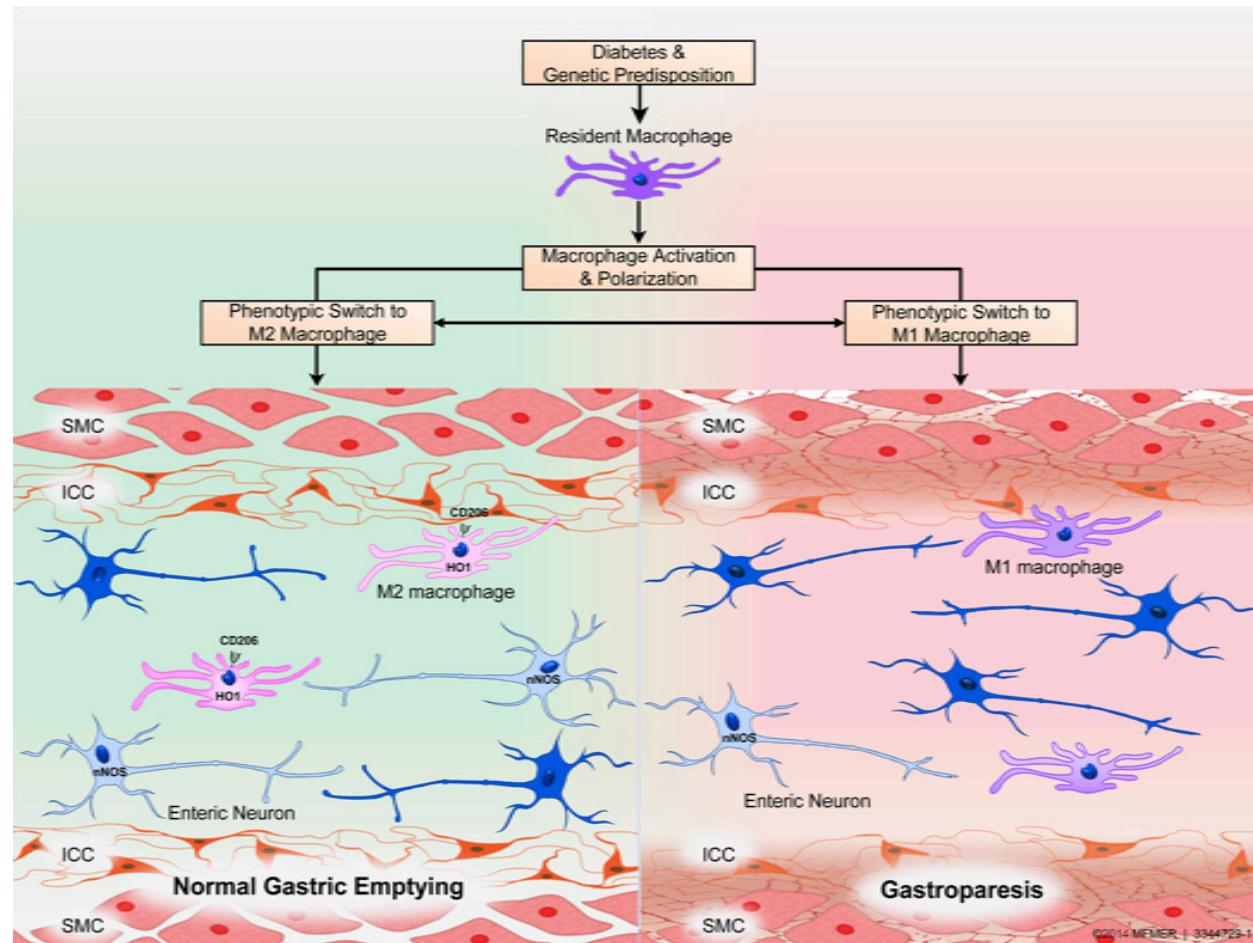
Etiologies of Gastroparesis



Bashashati M, McCallum RW. Is Interstitial Cells of Cajal–opathy Present in Gastroparesis? J Neurogastroenterol Motil. 2015 Oct;21(4):486-93.

Molecular Theory Underlying Gastroparesis:

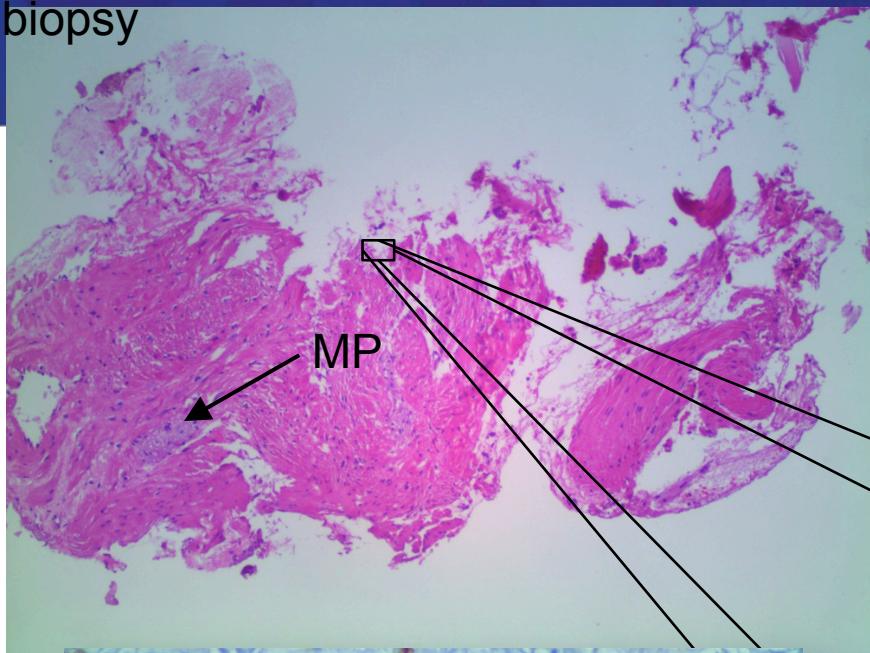
Diabetic and idiopathic gastroparesis is associated with loss of CD206-positive macrophages in the gastric antrum



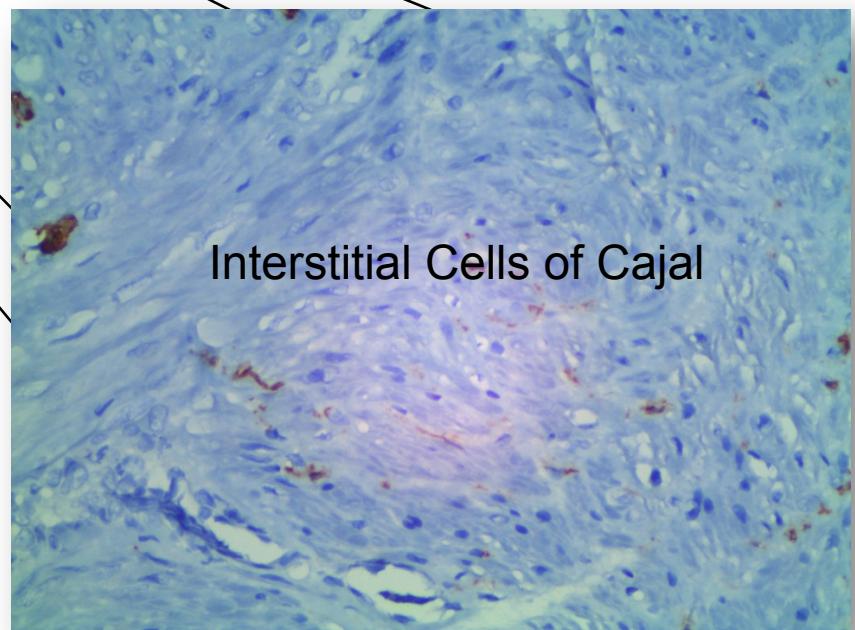
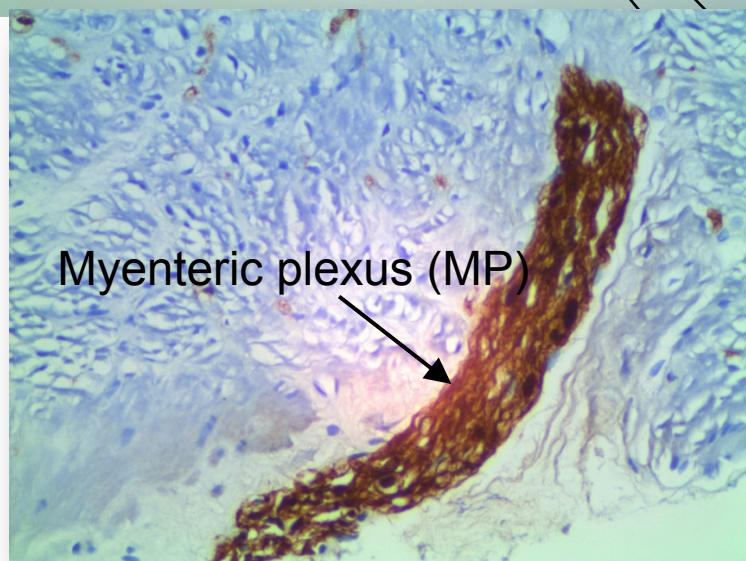
Neurogastroenterol Motil. 2015 Jan;27(1):7-18.

Neurogastroenterol Motil. 2017 Jan 9. doi: 10.1111/nmo.13018

The Future- Nonsurgical approach to obtain antral smooth muscle tissue: e.g. EUS guided biopsy



EUS Guided Biopsy of Antral Smooth Muscle



Future Directions for ICC-opathy

- EUS guided biopsies of the antral muscularis propria in patients presenting with unexplained dyspepsia, nausea & vomiting, suspected gastroparesis and postprandial distress syndromes.
- Establishing the diagnosis and developing treatment strategies based on EUS guided biopsy data.

Treatment of Gastroparesis

- **Restoration of hydration, electrolytes and nutrition**
 - Liquid soft diet, low fat – low fiber
 - Caloric liquid supplements
- **Treat nausea – antiemetics**
- **Restore coordinated gastric and small bowel motility with prokinetic agents**
- **Glycemic control**
- **Pain control**
- **Psychological measures**
- **Botulinium toxin pyloric injections**
- **Feeding tubes – endoscopic or oral**
- **Surgery**
 - A) Jejunal feeding tube, full thickness gastric biopsy
 - B) Placement of gastric electrical stimulation (GES) system
 - C) Pyloroplasty
 - D) Gastric resection – total gastrectomy

Treatment (cont.)

Escalating the intensity of therapy

- Mild gastroparesis
 - Not daily symptoms, no hospitalizations, no impact on work and family functioning
 - Recommend diet, glucose control, antiemetics prn, review of medications and metabolic state
- Moderate gastroparesis
 - Daily symptoms, not continuous, occasional hospitalization, interfering with work and family functioning
 - Recommend, diet, prokinetics, one or more antiemetics and glucose control, also question addressing pain and psychological aspects
- Severe gastroparesis
 - Daily, continuous symptoms, multiple ED/hospitalizations, not able to work and function
 - Recommend, combining prokinetics, multiple antiemetics, nutrition support, Enterra, research trials and surgical options

Medical Management of Gastroparesis

- **Standard of treatment includes:**

Antiemetics

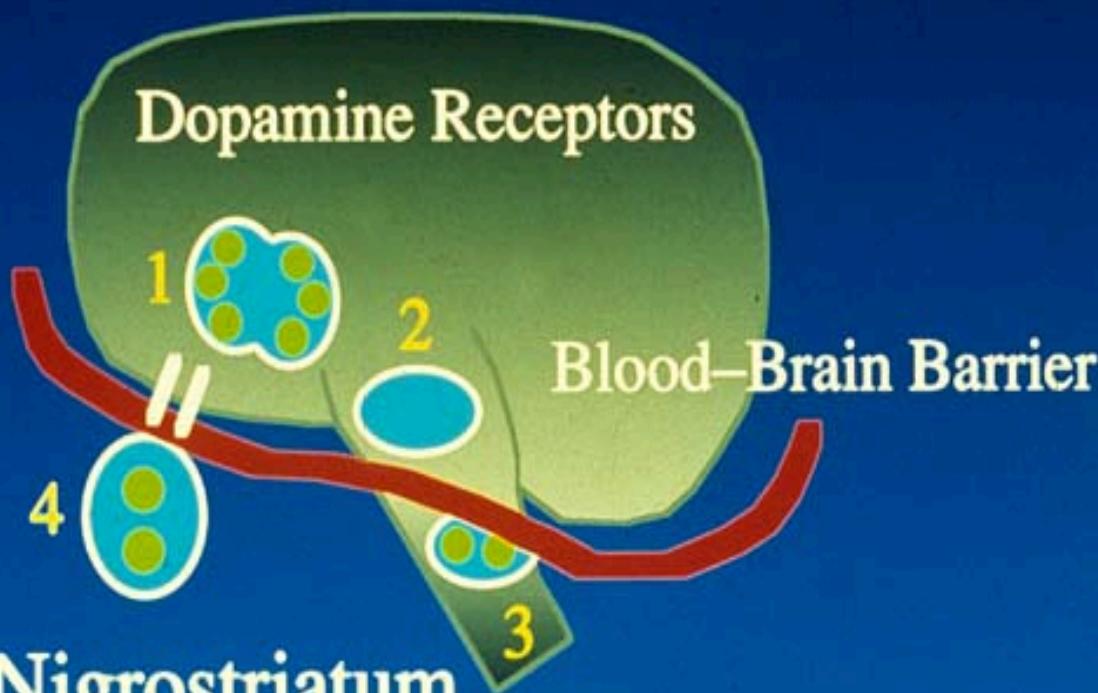
Compazine (Prochlorperazine)
Phenergan® (Promethazine)
Zofran® (Ondansentron)
Emend (Aprepitant)
Scopolamine patch
Marinol

Prokinetics

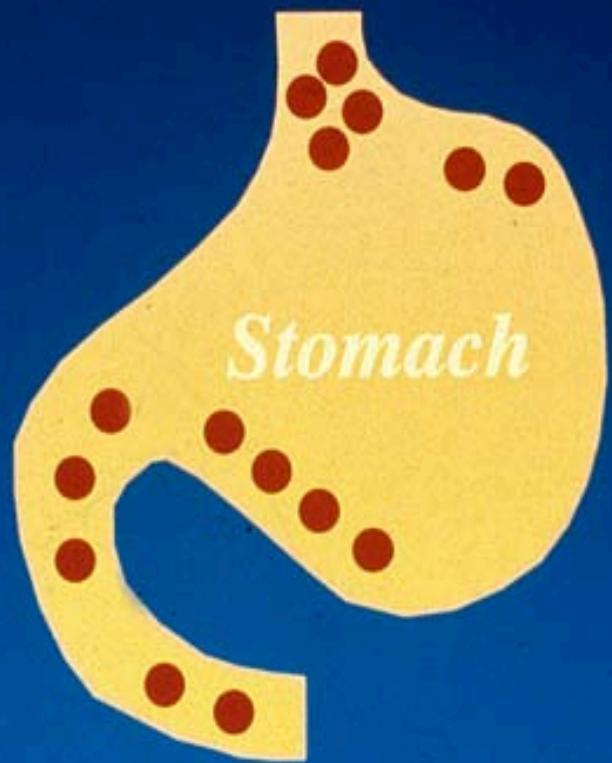
Erythromycin
Reglan® (Metoclopramide)
Motilium® (Domperidone)

Brain-Gut modifiers: TCA (Amitriptyline,Nortriptyline) & Remeron (Metazrapine)

Anti-Emetic Prokinetic Effects of Dopamine Antagonists



1. Nigrostriatum
2. Vomiting Center
3. Chemoreceptor-Trigger-Zone (CRTZ)
4. Pituitary

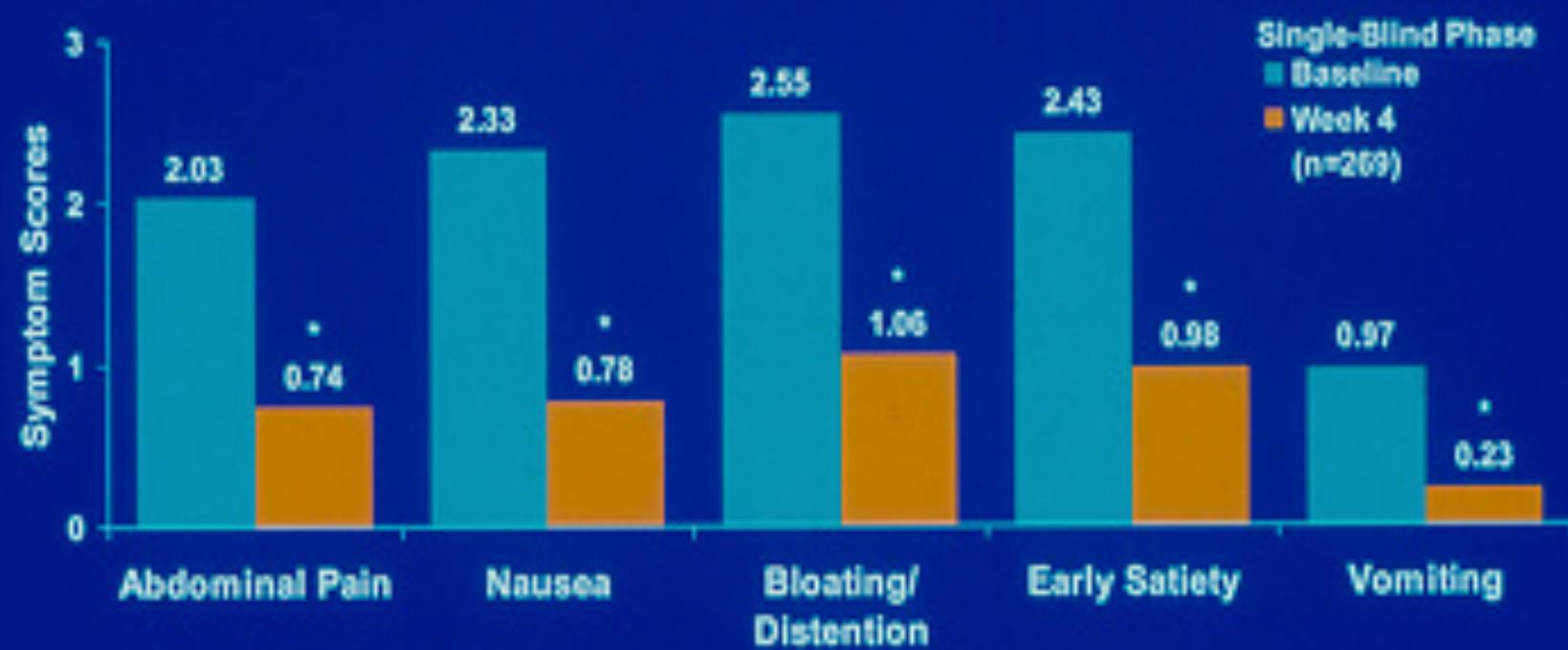


Recommendation Regarding Initiating Reglan Therapy from Medico-legal Standpoint

- **Discuss with patient, available family members & with a nurse present all the side effects expected with Reglan.**
 - a) Emphasize initial first day namely “muscle spasm” type immediate reactions (1-5% range)
 - b) The early onset side effects (within first week) namely anxiety – akinesia, insomnia or excessive sleep and fatigue (20% range)
 - c) Long term side effects namely depression, Parkinsonism, prolactin related & rare tardive dyskinesia (1-5% range)

Overall side effects could be in to excess of 30%
- **Document all this discussion in the office chart and medical record or in a specifically designed informed consent which patient and/or nurse also sign.**

Multicenter Domperidone Trial: Significant Reduction in Symptom Scores in Phase I



*P<0.001

Data on file, Janssen Pharmaceutica Inc.

Conclusions From Erythromycin Literature

1. Erythromycin has strong gastric prokinetic effect
2. Small bowel motility enhanced, small bowel transit is not
3. Initiate low oral dosing of 250 mg per day - increase as needed based on side effects, efficacy and concerns for tachyphylaxis
4. Useful as adjunct or combination agent
5. Dose ranging and double-blind studies needed

Tricyclics for Nausea and Vomiting

- Main experience with Amitriptyline and Nortriptyline with median dose 50 mg/d (range 25-200mg)
- Successful in patients unresponsive to prokinetics and with delayed gastric emptying (Prakash, Clouse et al. *Dig Dis Sci*, 1998)
- Additional ameliorating effects on epigastric/abdominal pain often present in gastroparesis patients
- NIH Gastroparesis Consortium Study: Limited efficacy in idiopathic gastroparesis (JAMA 2013)
- No antiemetic clinical effects demonstrated for SSRI's

Pain control in gastroparesis

- Recognition that abdominal pain can be present and is important symptom in GP patients
- Differential diagnosis for pain: Peptic ulcer disease, acute or chronic cholecystitis, gall bladder dyskinesia, IBS, SIBO, median arcuate ligament syndrome
- NSAID's, Tylenol, Tramadol preferred
- TCA, SSRI, SNRI (cymbalta), gabapentin, pregablin etc could be considered
- Avoid narcotics !!!!!!
Role of narcotics-fentanyl patch, methadone
- Referral to pain management clinic

Feeding Tubes in Gastroparesis

- **No role for a PEG for nutrition or decompression, and limited role for PEG-PEJ (temporary trial of tolerance for jejunal feedings)**
- **TPN not appropriate with intact small bowel**
- **Jejunostomy tube – Surgical, Radiological, or Endoscopic placement – is the choice for both nutrition and medications**
- **Resorting to these measures means failed medical therapy and an indication for gastric electrical stimulation (GES)**

Future gastroparesis pipeline:

A) Antiemetics: Tradipitant- VANDA (beyond Aprepitant; antagonist of human substance P/neurokinin 1 (NK1)- phase 3 trials in progress.

B) Prokinetic agents:

- 1) Ghrelin agonists: Relamorelin- Rhythm Pharma, phase 3
- 2) 5HT-4 agonists: Velusetrag- Theravance Pharma, phase 3
- 3) Prucalopride-Shire Pharma
- 3) Dopamine 2 and 3 antagonists:
 - intranasal metoclopramide- Evoke Pharma, phase 3
 - 2 Domperidone-like agents with no cardiac toxicity:
 - TAK-906(ATC-1906): in phase 2 trials
 - Neurogastrix- agent from Europe, to be studied

Gastric Neurostimulation (Enterra® Therapy)

Indicated for the treatment of chronic, intractable nausea and vomiting secondary to diabetic or idiopathic gastroparesis under a Humanitarian Device Exemption (HDE).

System includes:

*Implantable neurostimulator:
Medtronic Model 7425G or 311

*Neuromuscular leads (2):
Medtronic Model 4351

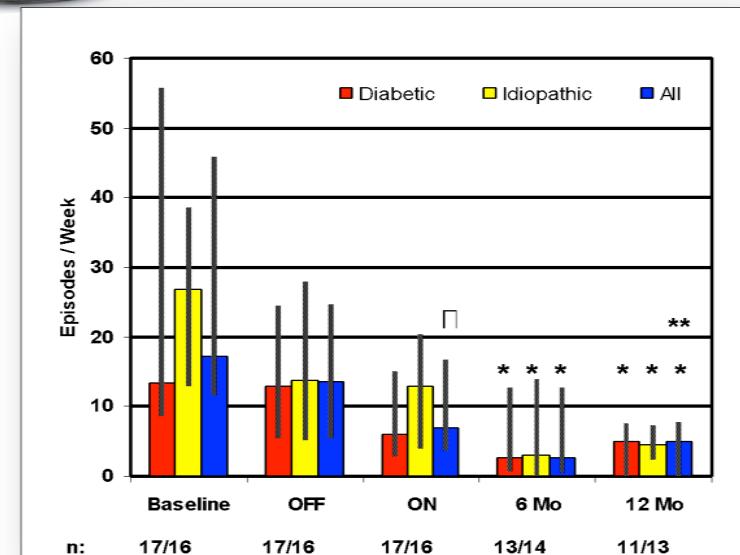
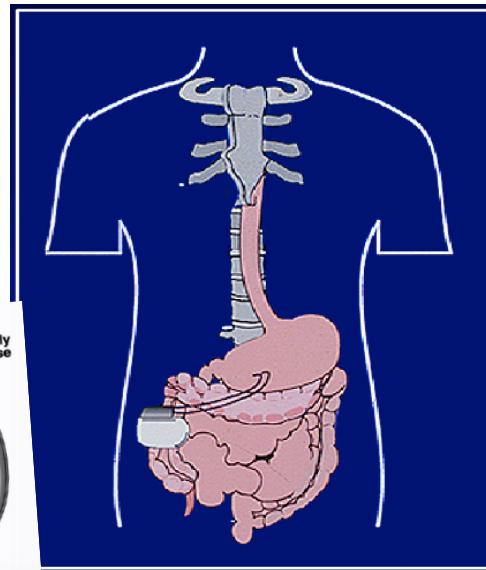
Stimulation Parameters

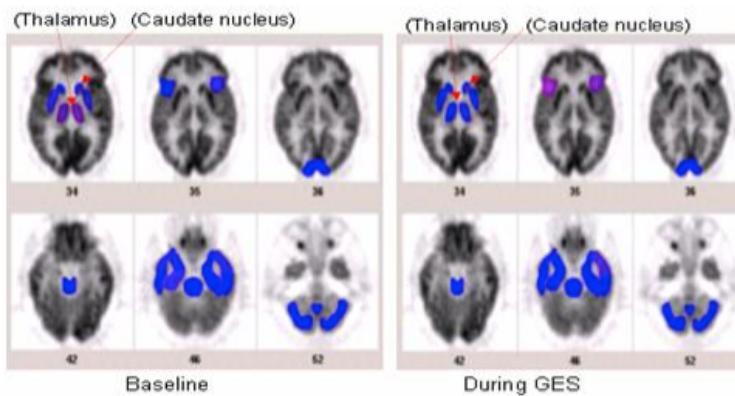
Amplitude: 5 milliamps

Pulse Width: 330 μ sec

Cycle: 12 cpm

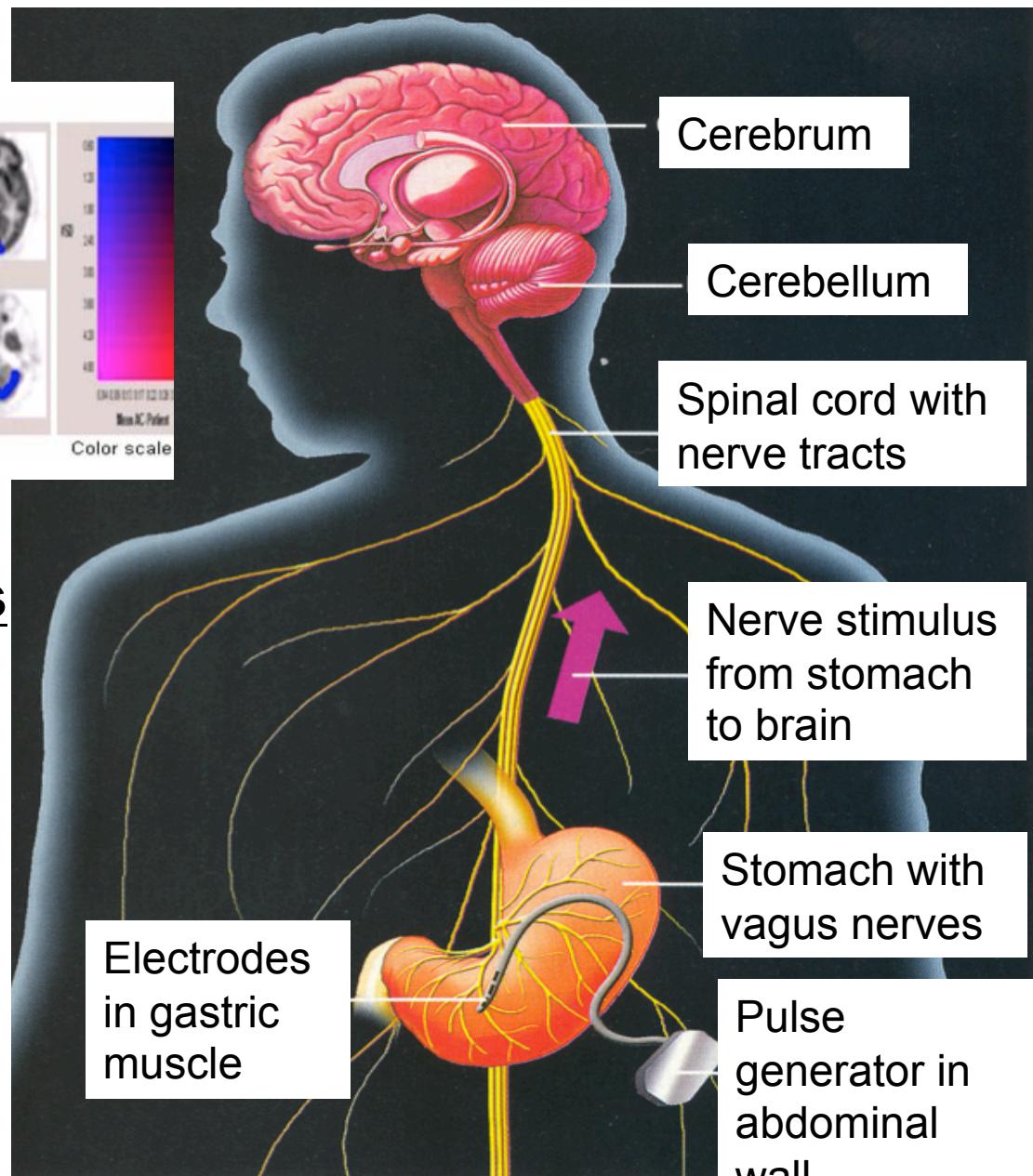
(On Time: 0.1 sec-14 Hz;
Off Time: 5.0 sec)



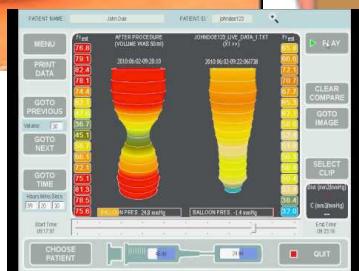
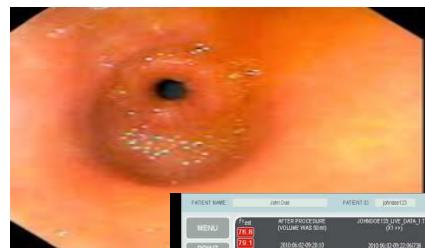
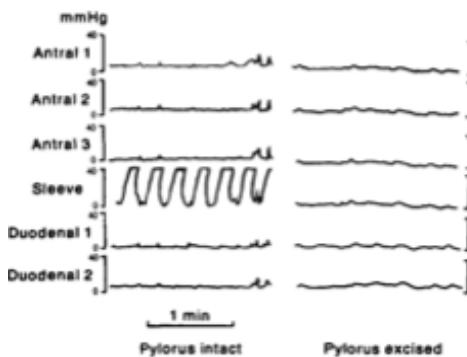


Mechanisms of Actions of Enterra System:

- 1) Centrally acting anti-emetic- Thalamic and caudate lobe areas identified by PET Scan.
- 2) Increased vagal activity- associated increased fundic relaxation and food intake.
- 3) It does not change gastric emptying or electrical dysrhythmias
- 4) Abdominal pain is not a target



The role of the pylorus –implications for both diagnosis and therapy



Pathological studies of the pylorus in GP vs. Controls

Neurogastroenterology & Motility

N G M

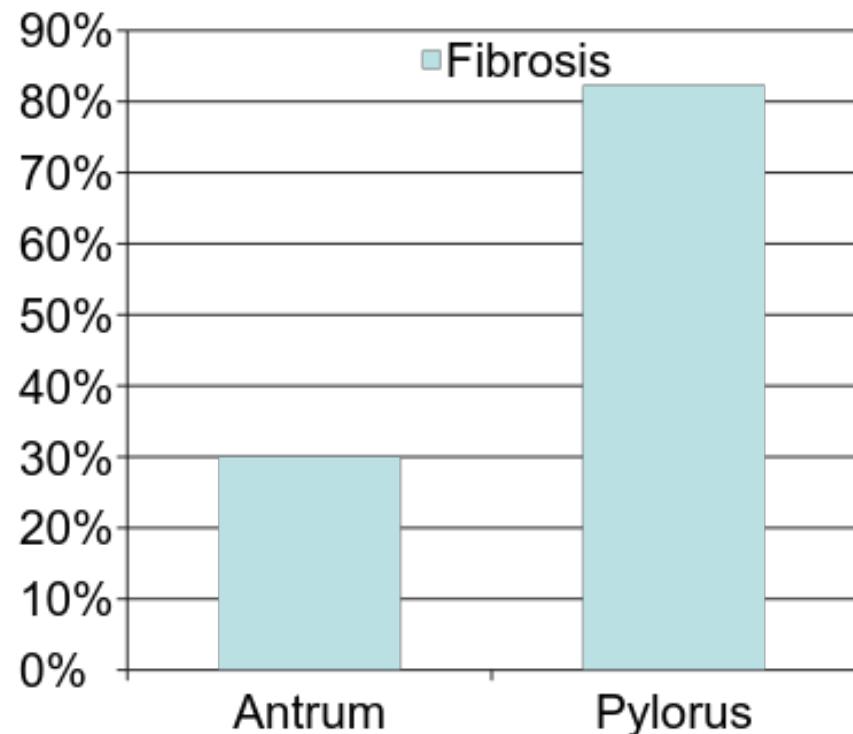
Neurogastroenterol Motil (2016) 28, 1048–1054

doi: 10.1111/nmo.1

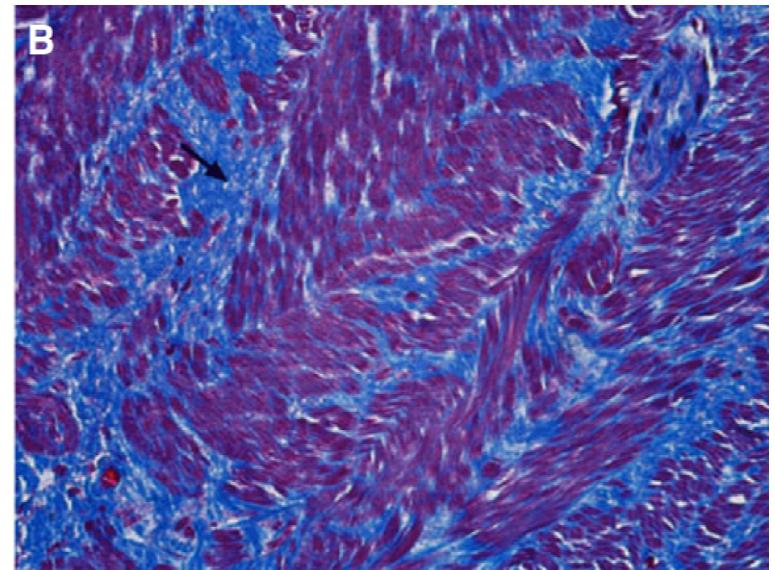
Depleted interstitial cells of Cajal and fibrosis in the
pylorus: Novel features of gastroparesis

S. MORAVEJI, *,# M. BASHASHATI, †,# S. ELHANAFI, ‡ J. SUNNY, † I. SAROSIEK, † B. DAVIS, § A. TORABI¶ &
R. W. MCCALLUM†

Collagen fibrosis is more common in the pylorus than the antrum of gastroparesis patients.

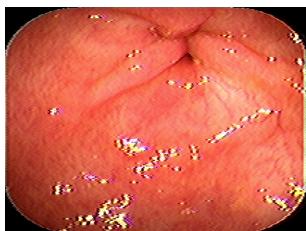


Trichrome staining of the pylorus in gastroparesis

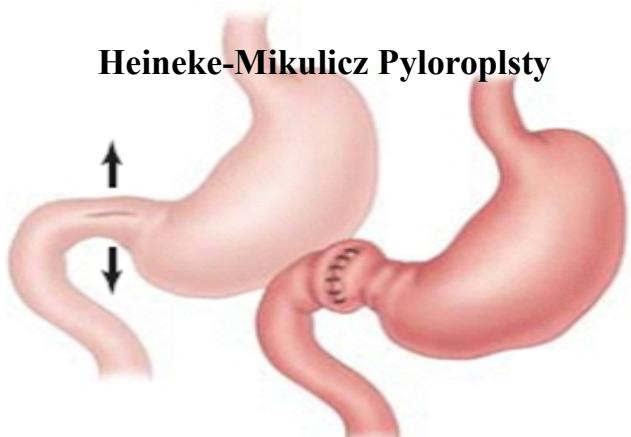


Evolving pyloric based therapies for GP

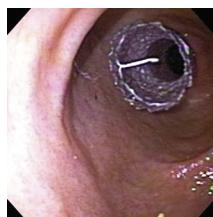
Botox Injection into Pylorus for Gastroparesis



Heineke-Mikulicz Pyloroplasty



Pyloric stenting



Endoscopic pyloromyotomy

Khashab et al. Gastric peroral endoscopic myotomy for refractory gastroparesis: first human endoscopic pyloromyotomy. (GIE)

-LAPAROSCOPIC PYLOROPLASTY WITHOUT GES IMPROVED SYMPTOMS OF GASTROPARESIS

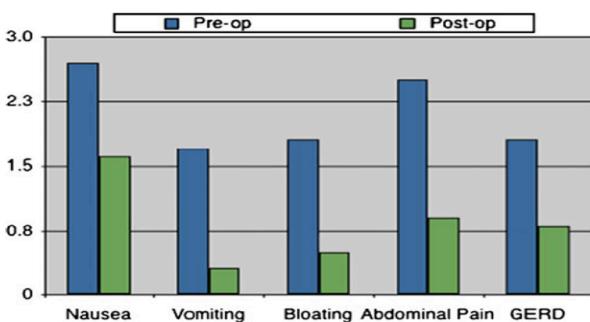


Fig. 4 Gastroparetic symptom scores before and 3 months after laparoscopic pyloroplasty

GES plus Heineke-Mikulicz Pyloroplasty



[Journal of Gastrointestinal Surgery](#)
February 2017, Volume 21, Issue 2, pp 222-227

The Long-Term Efficacy and Safety of Pyloroplasty Combined with Gastric Electrical Stimulation Therapy in Gastroparesis

Authors

Authors and affl

Brian R. Davis [✉](#), Irene Sarosiek, Mohammad

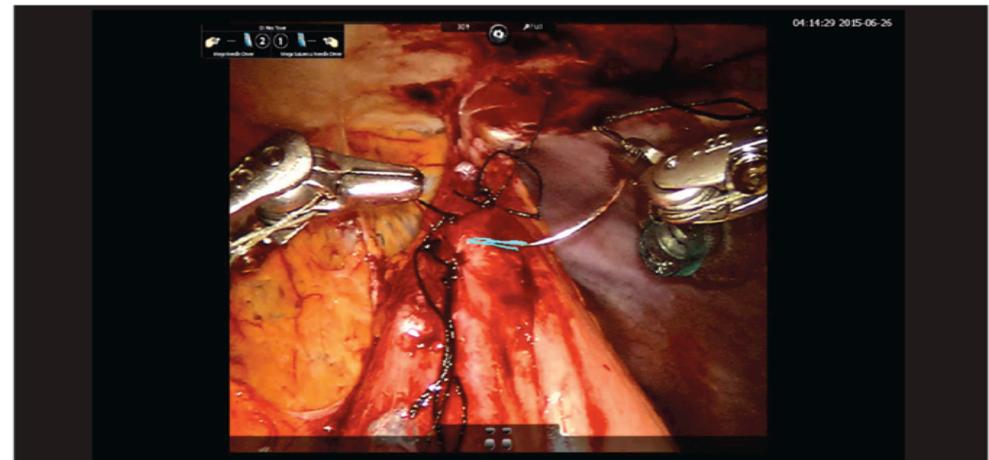


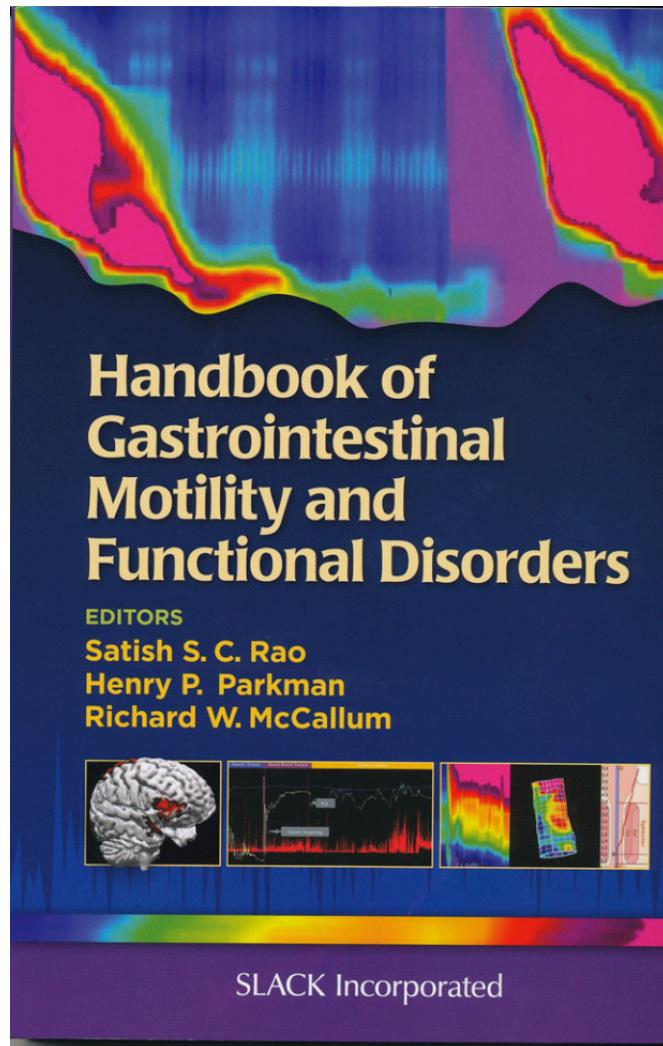
Figure 1. Robotic pyloroplasty closure is pictured demonstrating robotic wrist articulation to create a Lembert stich layer with a telestration marking to show the path of the needle.

In this prospective single-arm trial, 27 gastroparesis patients who underwent simultaneous gastric electrical stimulator implantation with Heineke-Mikulicz pyloroplasty were studied.

- *There was 71% improvement in total symptoms score.*
- *Gastric emptying was normalized in 60%.*
- *There were no post-surgical complications.*

Major advances in the diagnosis and management of Gastroparesis since 2000

- 1) Gastric emptying methodology- “the gold standard” and beyond.
- 2) Understanding electrophysiology and enteric neurons in antral smooth muscles and new non-surgical techniques to access this tissue.
- 3) We are poised for intervention to prevent gastroparesis based on histology and molecular findings: The role of ICC and macrophages are evolving.
- 4) Re-appreciation of the role of the pylorus: implications for both diagnosis and therapy.
- 5) Definitive treatment available for patients refractory to medical therapy: GES+Pyloroplasty



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