Gastroparesis

- Recent advances in the pathophysiology and treatment -

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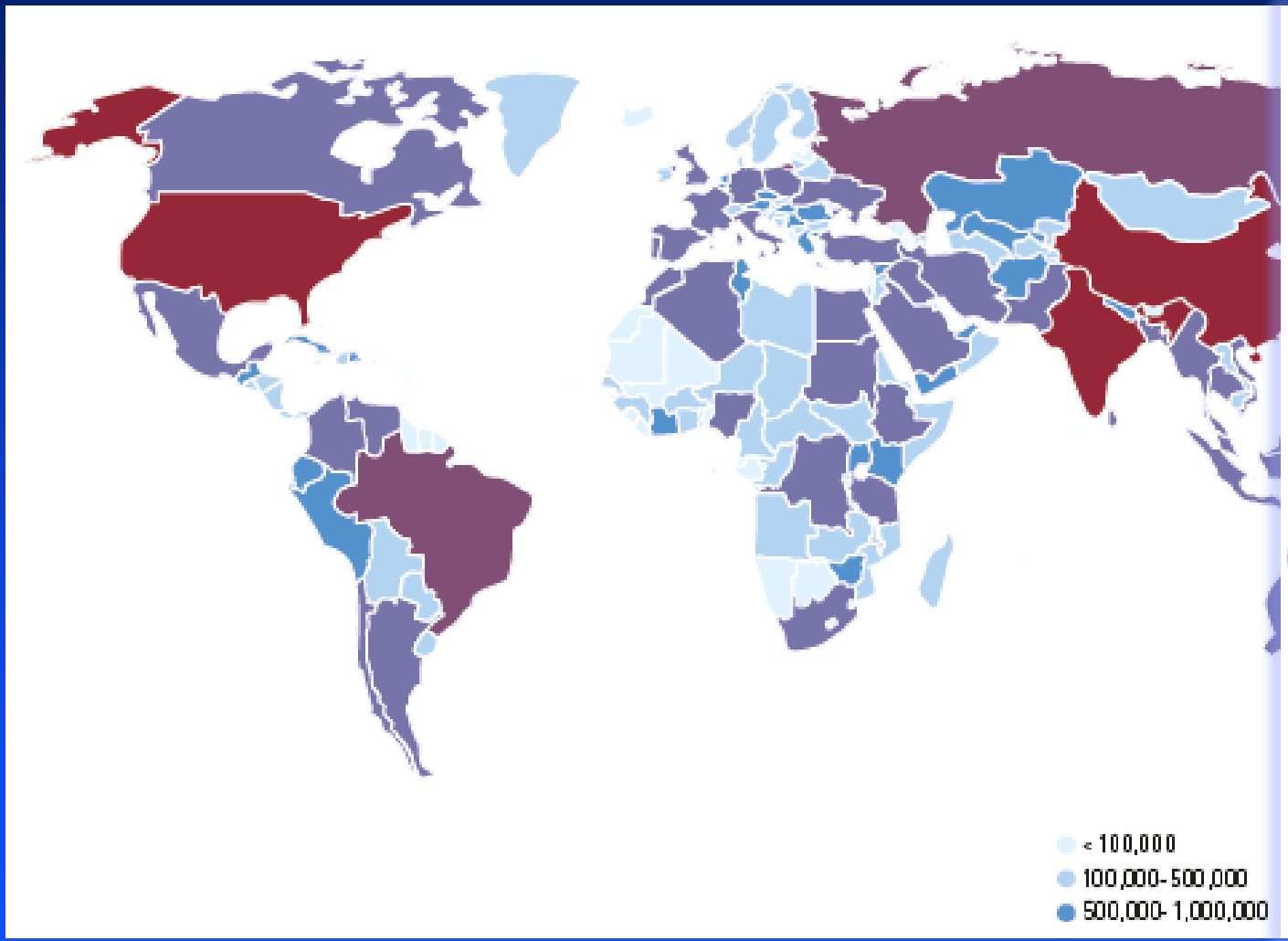
Etiology

- Idiopathic -- 40%
- Diabetes mellitus -- 30%
- Postsurgical (Gastrectomy/fundoplication)
- Connective tissue disease
- Hypothyroidism
- Malignancy
- Provocation drugs
- End-stage renal disease

Number of people with diabetes (20-79 years), 2013



382 million people have diabetes

By 2035 this will rise to 592 MILLION

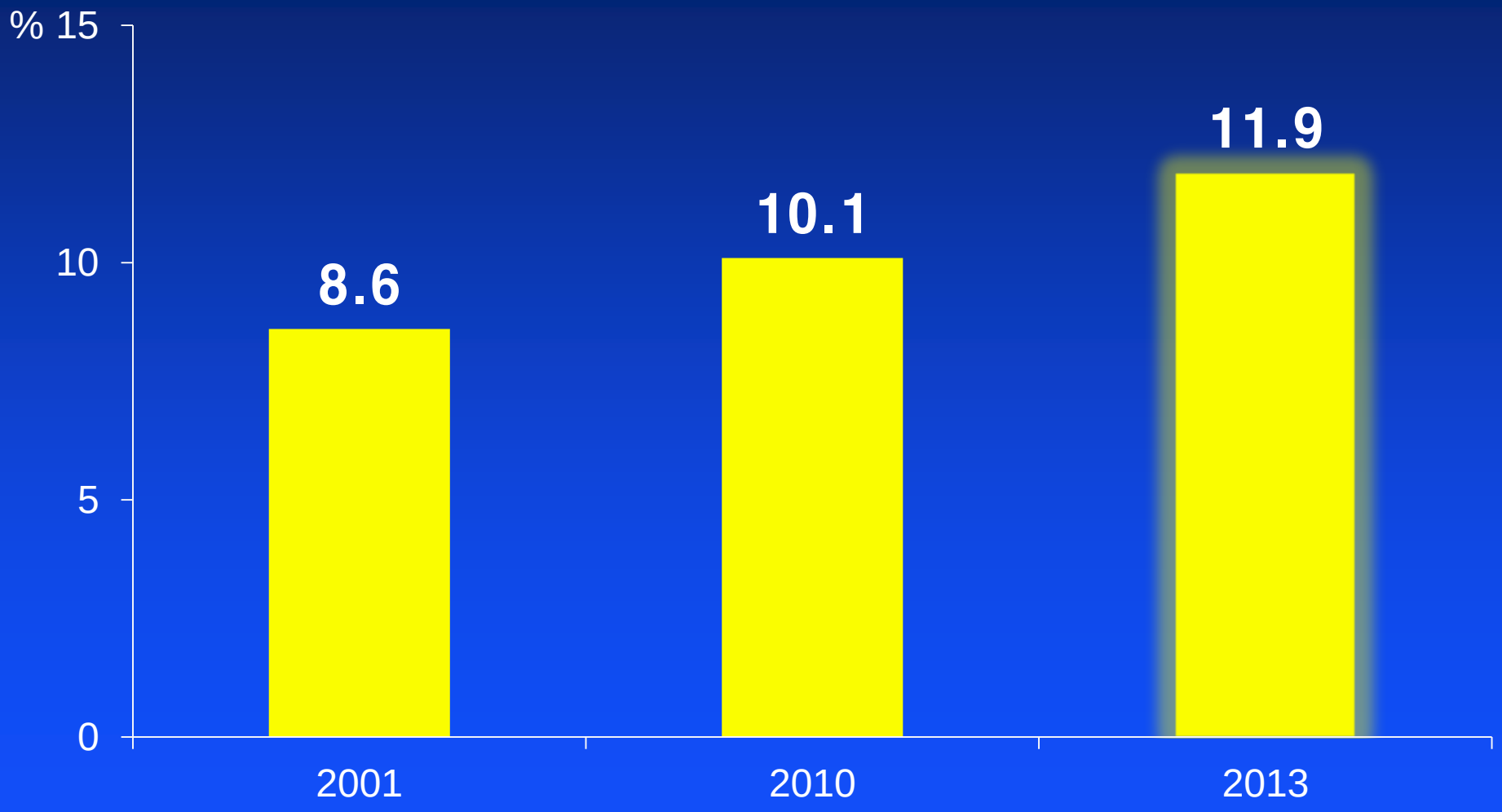
The number of people with type 2 diabetes is increasing in every country

The greatest number of people with diabetes are between 40 and 59 years of age

175 million people with diabetes are **undiagnosed**

International Diabetes Federation: Diabetes Atlas 6th ed. 2013

Prevalence of DM in Korea



(>30 yo)

Prevalence of GI symptoms in DM in Korea

Table 2. Prevalence of upper gastrointestinal symptoms in patients with non-insulin dependent diabetic mellitus

Symptoms	Men (n=249)	Women (n=359)	Overall [95% confidence interval]
Globus	10 (4.0)	18 (5.0)	28 (4.6) [2.9-6.3]
Rumination	12 (4.8)	17 (4.7)	29 (4.8) [3.0-6.5]
Heartburn	16 (6.4)	27 (7.5)	43 (7.1) [5.0-9.2]
Acid regurgitation	10 (4.0)	17 (4.7)	27 (4.4) [2.8-6.1]
Nausea	10 (4.0)	31 (8.6)*	41 (6.7) [4.7-8.8]
Vomiting	3 (1.2)	7 (1.9)	10 (1.6) [0.6-2.7]
Early satiety	22 (8.8)	46 (12.8)	68 (11.2) [8.6-13.7]
Bloating	23 (9.2)	45 (12.5)	68 (11.2) [8.6-13.7]
Dyspepsia	34 (13.7)	46 (12.8)	80 (13.2) [10.5-15.8]

Data are presented as number (%).
* $p<0.05$ vs. male.

Oh JH, Choi MG et al. Korean J Intern Med 2009

Contents

- Gastroparesis?
- Prevalence
- Recent advances in pathophysiology & treatment
- Summary

What is gastroparesis?

- Symptoms
- Absence of obstruction
- Delayed gastric emptying

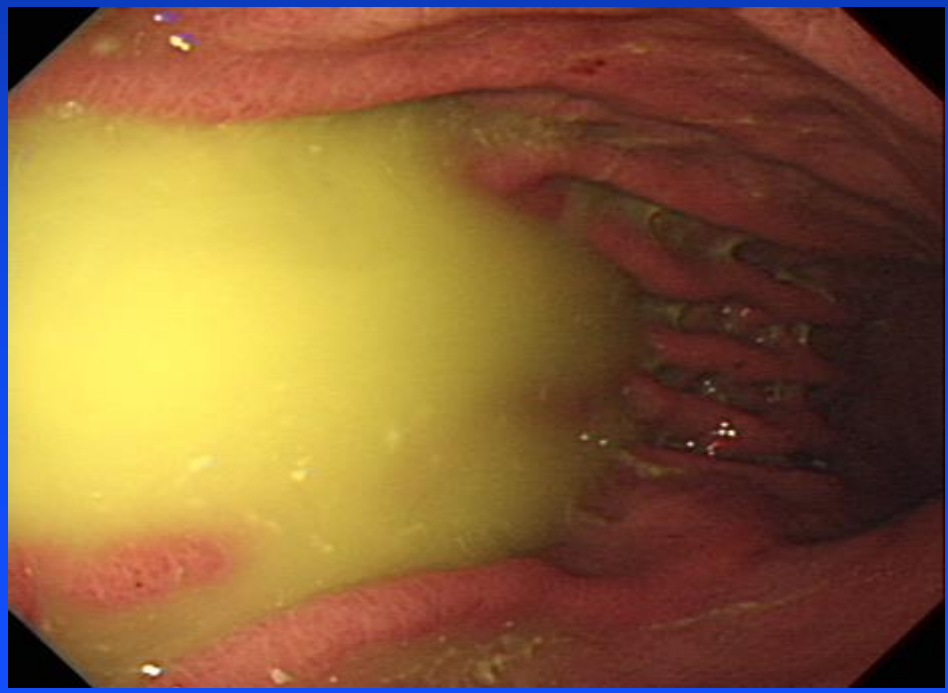
Classification

- Mild gastroparesis
- Moderate : Compensated gastroparesis
  - moderate symptoms with use of daily medications, maintain nutrition with dietary adjustments
- Severe : Gastric failure
  - refractory symptoms that are not controlled,
  - inability to maintain oral nutrition

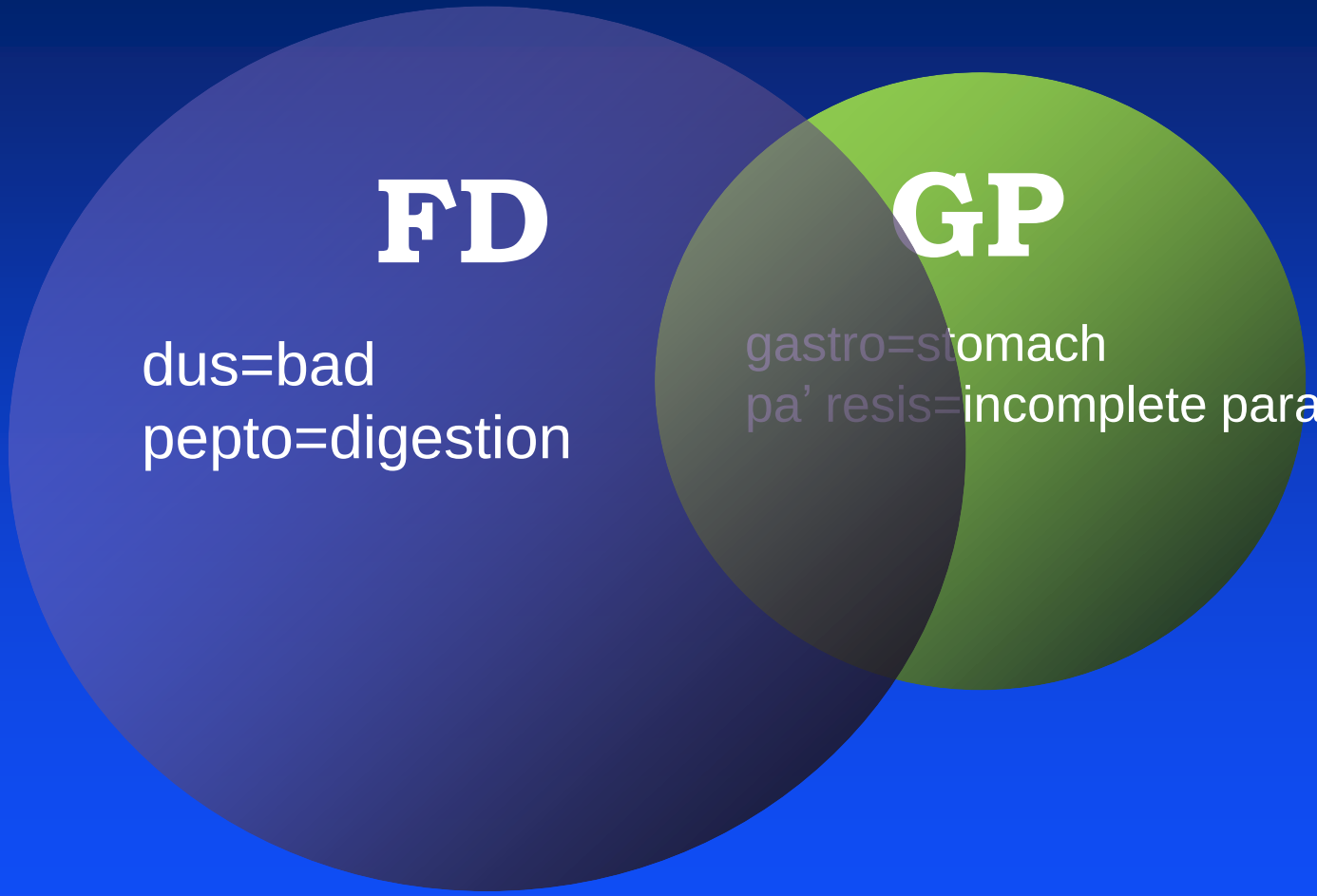
Stanghellini V. Gut. 2014

Typical symptoms?

- Nausea, vomiting
- Abdominal discomfort
- Early satiety
- Postprandial fullness
- Bloating



Gastroparesis: separate entity or just a part of FD?



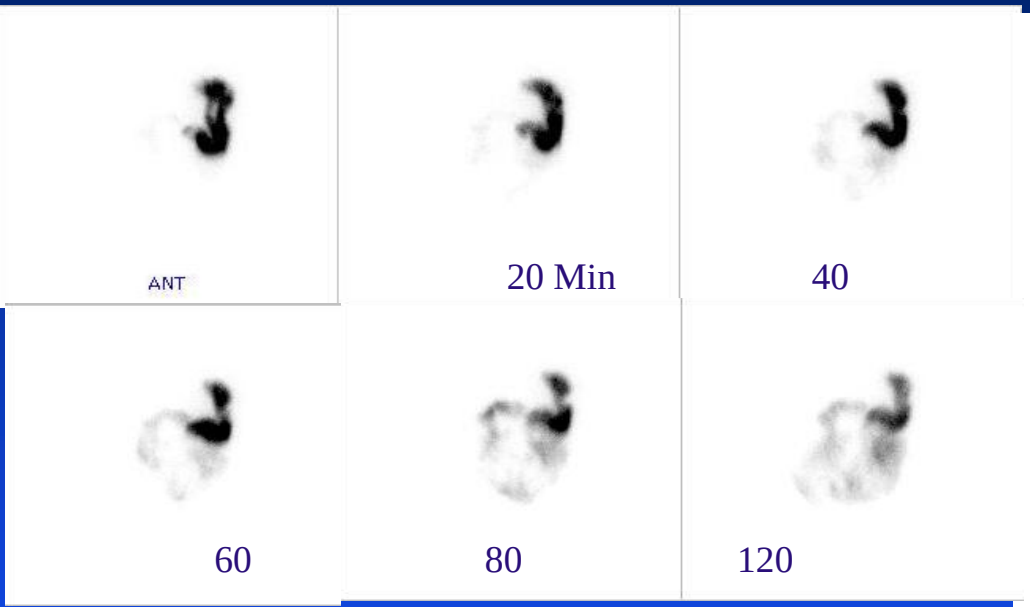
FD: Functional dyspepsia,
GP: Gastroparesis

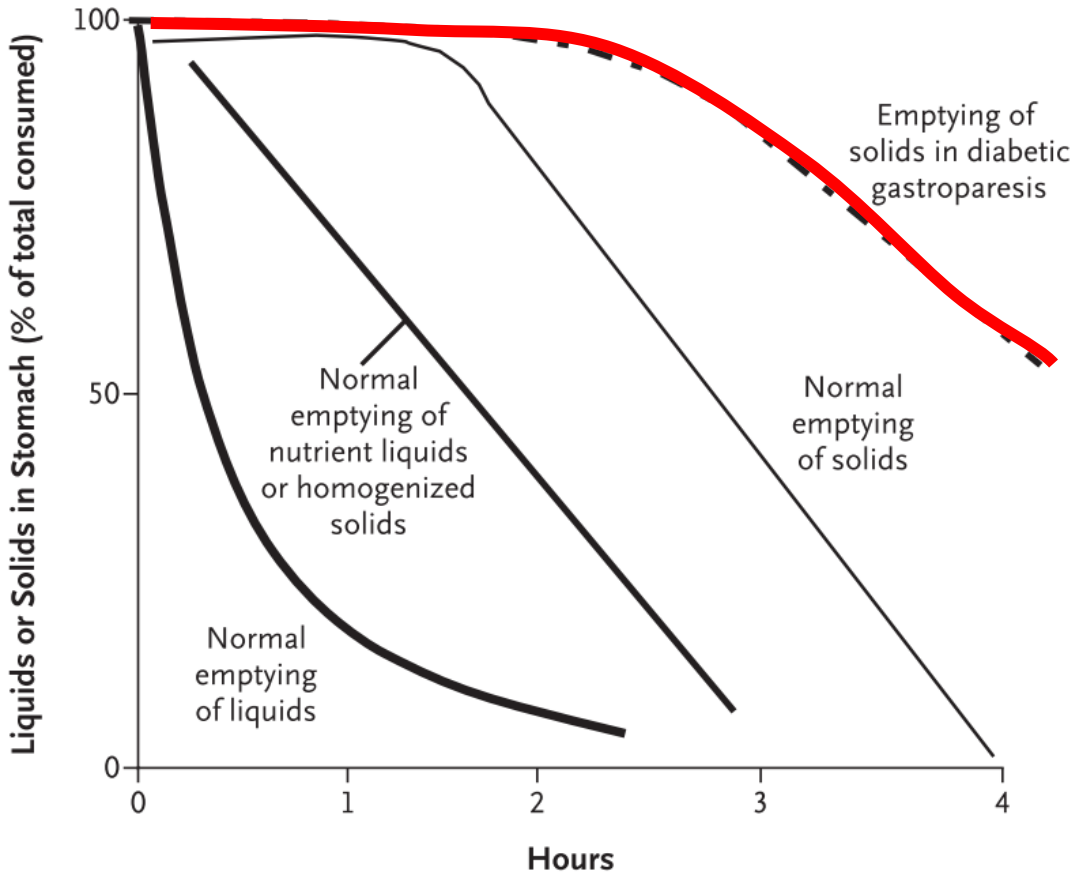
Stanghellini V. Gut. 2014

Diagnosis

- Scintigraphy
- Wireless motility capsule (WMC)
- Breath testing : 13C breath testing using otanoic acid, acetate or spirulina

Gastric Emptying Scintigraphy





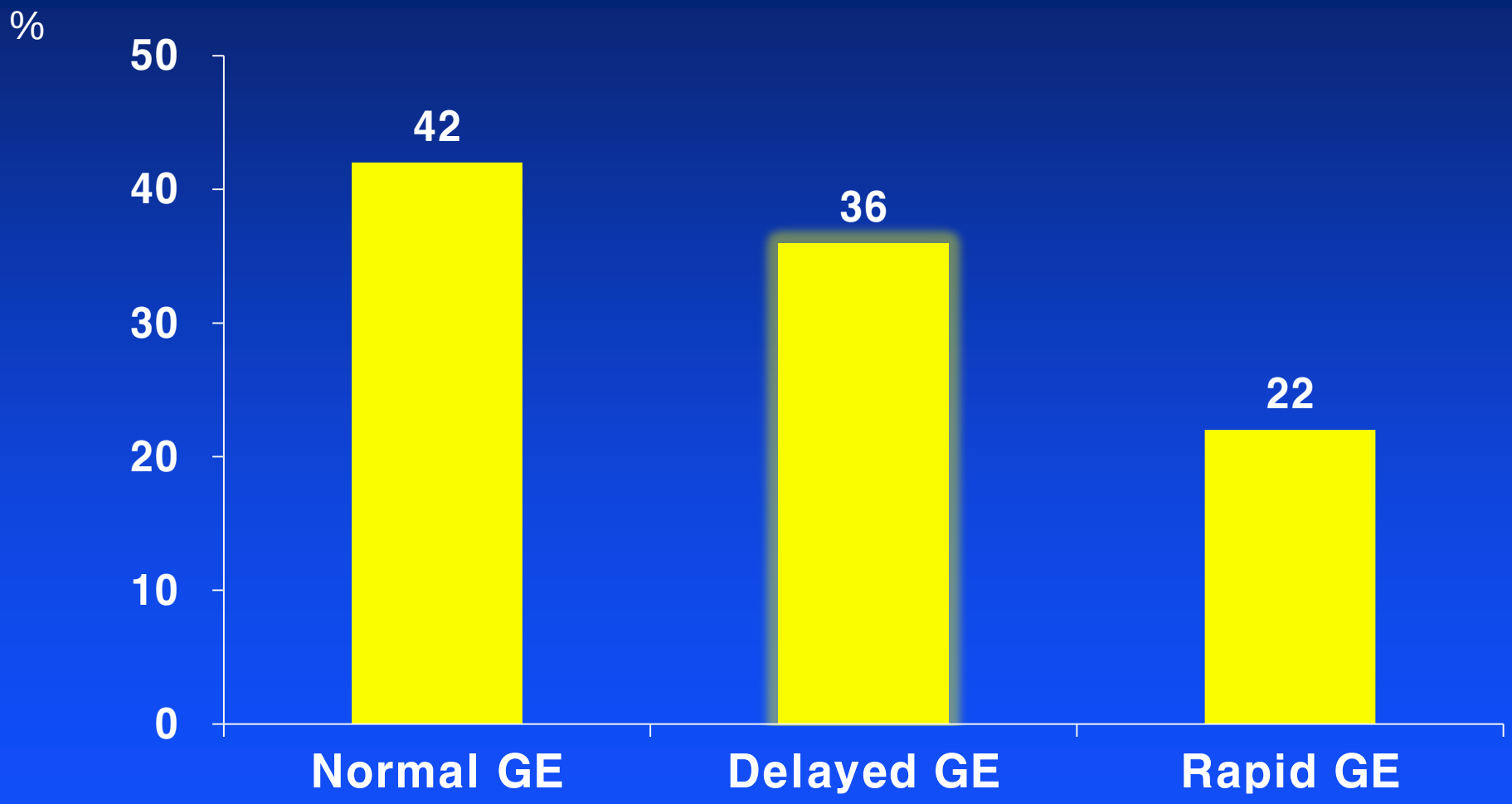
Delayed gastric emptying
as greater than 60% retention at 2 hours
and/or 10% at 4 hours

Consensus recommendations for gastric emptying scintigraphy

- Normal gastric emptying
  - the retention of <10% of a solid meal at 4 hours
- Delayed gastric emptying
  - as greater than 60% retention at 2 hours
  - and/or 10% at 4 hours
- Rapid gastric emptying
  - 30% retention at 1 hour

Abell TL. Am J Gastroenterol 2008
Tougas G. Am J Gastroenterol 2000

Relationship between clinical features and gastric emptying disturbances in diabetes mellitus



GE: gastric emptying

Bharucha. Clin Endocrinol 2009

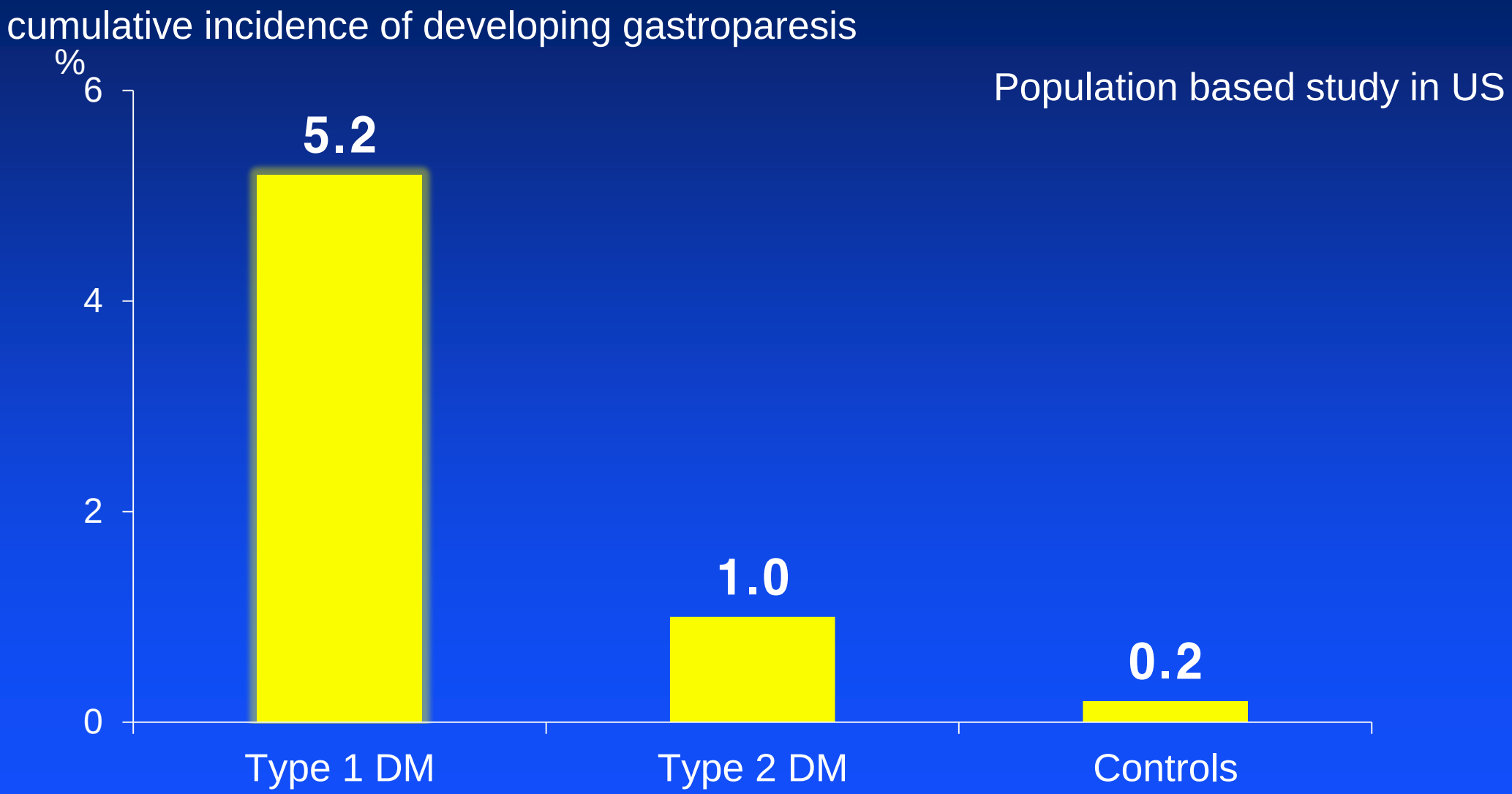
Before the test

- Withdrawal Medications
  - stimulating (e.g., metoclopramide) gastric smooth muscle contractions.
  - Inhibiting medications (e.g., narcotics, anticholinergic agents)
  - GLP-1 analogs (exenatide)

DPP IV inhibitors, do not delay gastric emptying

- Measuring blood glucose
  - Hyperglycemia (> 270 mg / dl) should be treated

Gastroparesis is uncommon in DM



Choung RS. Am J Gastroenterol 2012

the tip of a large hidden iceberg

- Gastroparesis like syndrome
  - 11%-18% reported symptoms consistent with upper GI dysmotility
- Mild gastroparesis
- Increasing incidence of diabetes

Rey E, J Neurogastroenterol Motil 2012

Difference in Type 1 vs 2

Factors	Type 1 DM	Type 2 DM
Age	Young	Old
Delayed gastric emptying	Severe	Mild
Predominant symptom	Nausea	Early satiety
Aggravating factors	Neuropathy and poor glycemic control	Less clear

Pathophysiology

- Delayed gastric emptying
  - Sx vs delayed gastric emptying: poor
  - The role of delayed emptying in symptom generation in gastroparesis is unclear.
- Autonomic neuropathy
- Sustained hyperglycemia

Pathophysiological changes in diabetic gastroparesis

Vagus neuropathy

Impaired fundic accommodation

Gastric dysrhythmia

Loss of nNOS

Loss of ICC

Pylorospasm

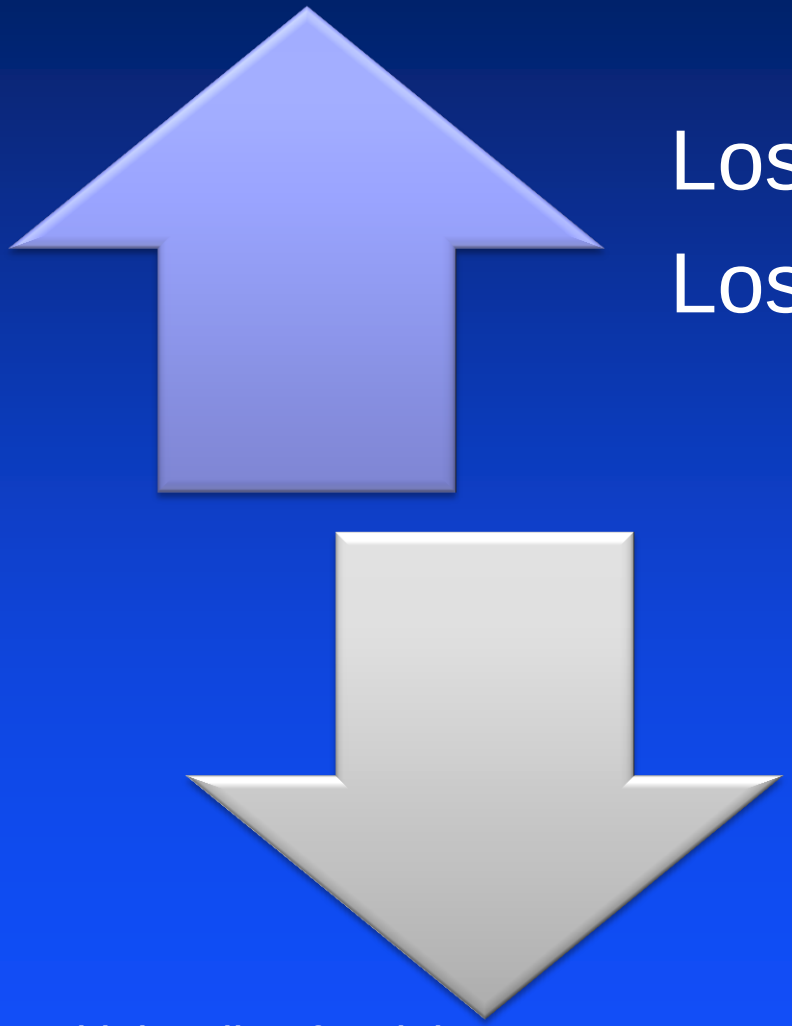
Altered function of type 2 Macrophages
(CD206-positive M2 macrophages)

Incoordinated antroduodenal emptying

ICC: Interstitial Cells of Cajal
nNOS: neuronal nitric oxide synthase

Kashyap P, Farrugia G. Gut 2010
Tack J, Curr Opin Gastroenterol 2015

Pathophysiology



Loss of ICC

Loss of nNOS

Delayed gastric emptying

Autonomic neuropathy

ICC: Interstitial Cells of Cajal
nNOS: neuronal nitric oxide synthase

Oh JH, Pasricha PJ. JNM 2013

Treatment

Diet

- Smaller, more frequent meals
- Low-fat, more liquid meals

→ efficacy is not proven

Classes of prokinetic agents

Prokinetic class	Agents
Dopamine 2 receptor Antagonists	Metoclopramide
	Domperidone
Motilin Receptor Agonists	Erythromycin
Serotonin 5 -HT4 Agonists	Prucalopride
	Velusetrag
Acetylcholinesterase Inhibitors	Neostigmine Pyridostigmine
GABA B Receptor Agonists	Baclofen

Malamood M. Expert Opin Pharmacother. 2015

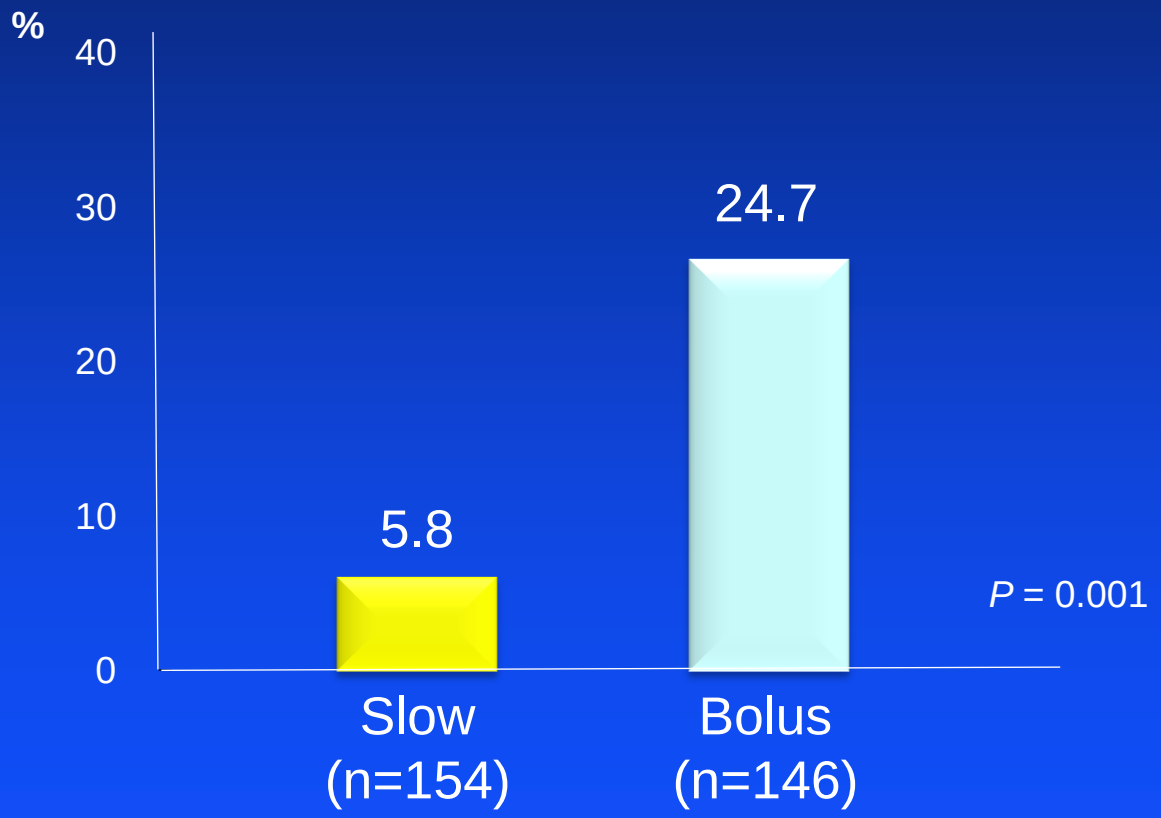
Metoclopramide (MCP)

- Prokinetic and anti-emetic properties
  D_2 antagonist and 5-HT_3 antagonist
- the only drug approved by the FDA for gastroparesis
- Recommended duration : 3 months

Side effects

- Extrapyramidal side effects,
  - mild restlessness, agitation, and akathisia, overt dystonia and dyskinesia
- Adverse effects : particularly common in young children and the elderly

Metoclopramide and akathisia



Slow : 10 mg MCP iv + 100 ml NS for 15 min
Bolus: 10 mg MCP iv + 100 ml NS for 2 min

Parlak. Emerg Med J 2005

Clinical Gastroenterology and Hepatology 2015;13:1256–1263

Metoclopramide Nasal Spray Reduces Symptoms of Gastroparesis in Women, but not Men, With Diabetes: Results of a Phase 2B Randomized Study

Henry P. Parkman,* Marilyn R. Carlson,‡ and Dave Gonyer‡

*Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania; ‡Evoke Pharma, Solana Beach, California

Metoclopramide nasal spray reduces symptoms of gastroparesis in women, but not in men, with diabetes. Patient sex therefore might be considered in the selection of treatment for diabetic gastroparesis. ClinicalTrials.gov no: NCT00845858.

Domperidone

- a dopamine antagonist, peripheral
- does not cross the blood-brain barrier
- Available throughout Europe, as well as in Canada but not in the US
- Side effect? EKG

Side effect of domperidone

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

07 March 2014
EMA/129231/2014

The review of domperidone was carried out at the request of the Belgian medicines authority over concerns about the medicine's effects on the heart. The injectable form of domperidone was withdrawn in 1985 because of such side effects. Serious effects on the heart, including QT prolongation (an alteration of the electrical activity of the heart) and arrhythmias (unstable heartbeats), have previously been evaluated by the EMA's former Pharmacovigilance Working Party (PhVWP). In 2011, the PhVWP

The PRAC recommended that domperidone-containing medicines should remain available and may continue to be used in the EU for the management of the symptoms of nausea and vomiting, but that the recommended dose should be reduced to 10 mg up to three times daily by mouth for adults and adolescents weighing 35 kg or more. These patients may also be given the medicine as suppositories of 30 mg twice daily. Where the medicine is licensed in children and adolescents weighing less than 35 kg, it should be given by mouth at a dose of 0.25 mg per kg bodyweight up to three times daily. Measuring devices should be included with liquid formulations to allow accurate dosing by bodyweight.

The medicine should not normally be used for longer than one week.

Levosulpiride

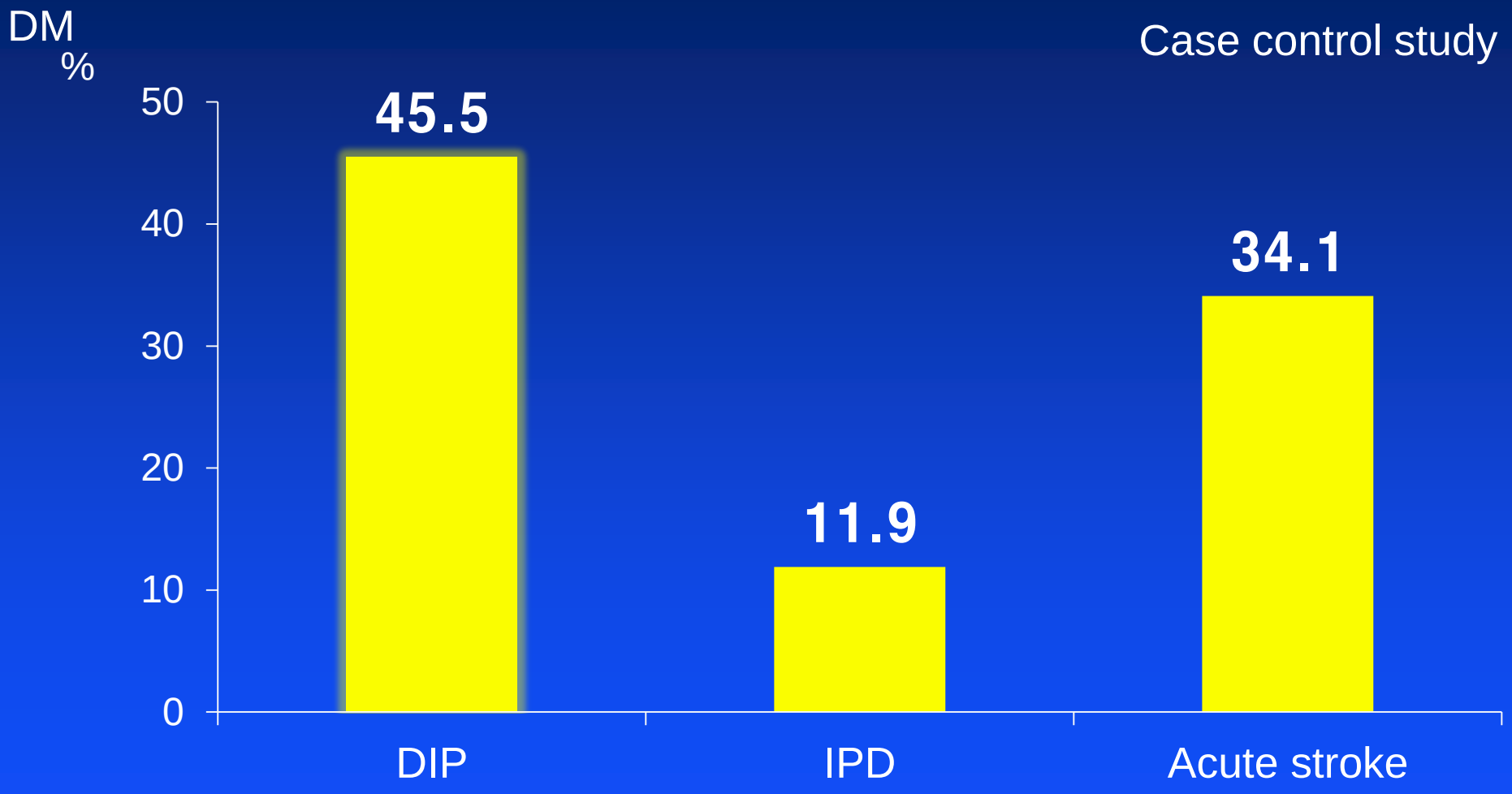
- Dopamine antagonist
- ↑ gastric emptying in diabetics
- improve glycemic control over a 6-month

Melga P, Diabetes Care. 1997

- Levosulpiride-induced movement disorders
  - parkinsonism (93.4%), tardive dyskinesia (9.9%)
  - often irreversible even after the withdrawal

Shin HW, Mov Disord 2009

Drug-induced parkinsonism



Case control study in Korea

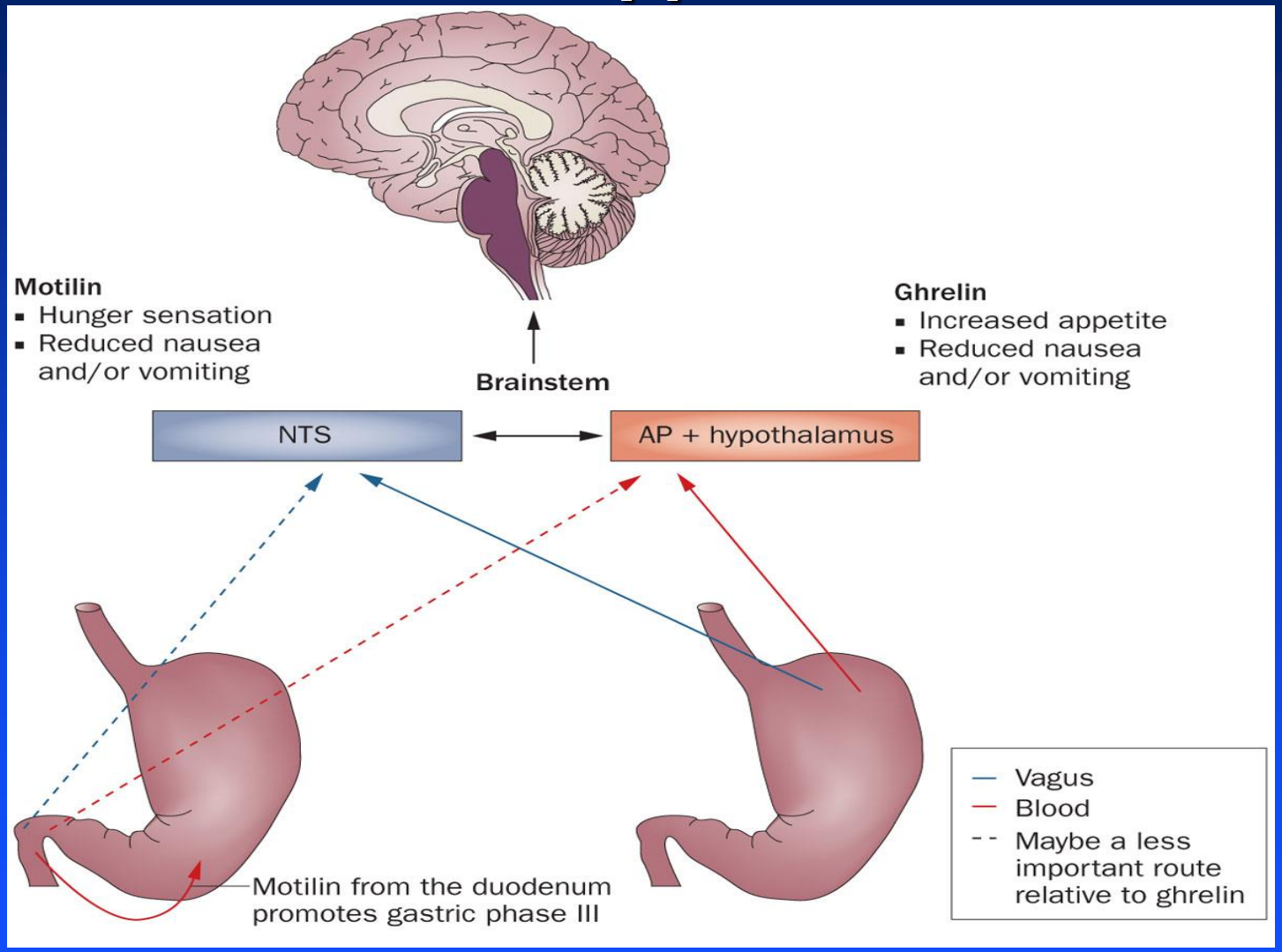
DIP: Drug-induced parkinsonism
IPD: Idiopathic Parkinson disease

Ma HI, J Neurol Sci 2009

Erythromycin

- Macrolides, a motilin agonist
- intravenous erythromycin: useful in acute GP
- long-term oral administration: less obvious
- Tachyphylaxis

Major pathways used by endogenous ghrelin and motilin to modulate upper GI function



AP, area postrema;
NTS, nucleus tractus solitarius.

Sanger GJ. Nat Rev Gastroenterol Hepatol. 2015

New Ghrelin and motilin receptor agonists in development for the treatment of GP

Ghrelin receptor agonists	**compound**	**Rationale**
TZP-102 (Tranzyme)	macrocyclic compound	Ability to increase gastric emptying and increase appetite
Relamorelin (RM131)	a pentapeptide for subcutaneous injection;	
Motilin receptor agonists		
Camicinal(GSK-962040)	small-molecule agonist	Ability to increase gastric emptying Potential additional ability to increase appetite and reduce nausea Effectiveness of low-dose erythromycin
RQ-00201894 (RaQualia)	Non-macrolide small molecule	
CEM-031 (Cempra)	Macrolide	

Anti-emetics?

- Associated nausea and vomiting
  - but will not result in improved gastric emptying.
- Tricyclic antidepressants
  - amitriptyline, nortriptyline, imipramine, desipramine
  - refractory nausea and vomiting
  - doses lower than used for depression
  - higher doses: impairing GI motility

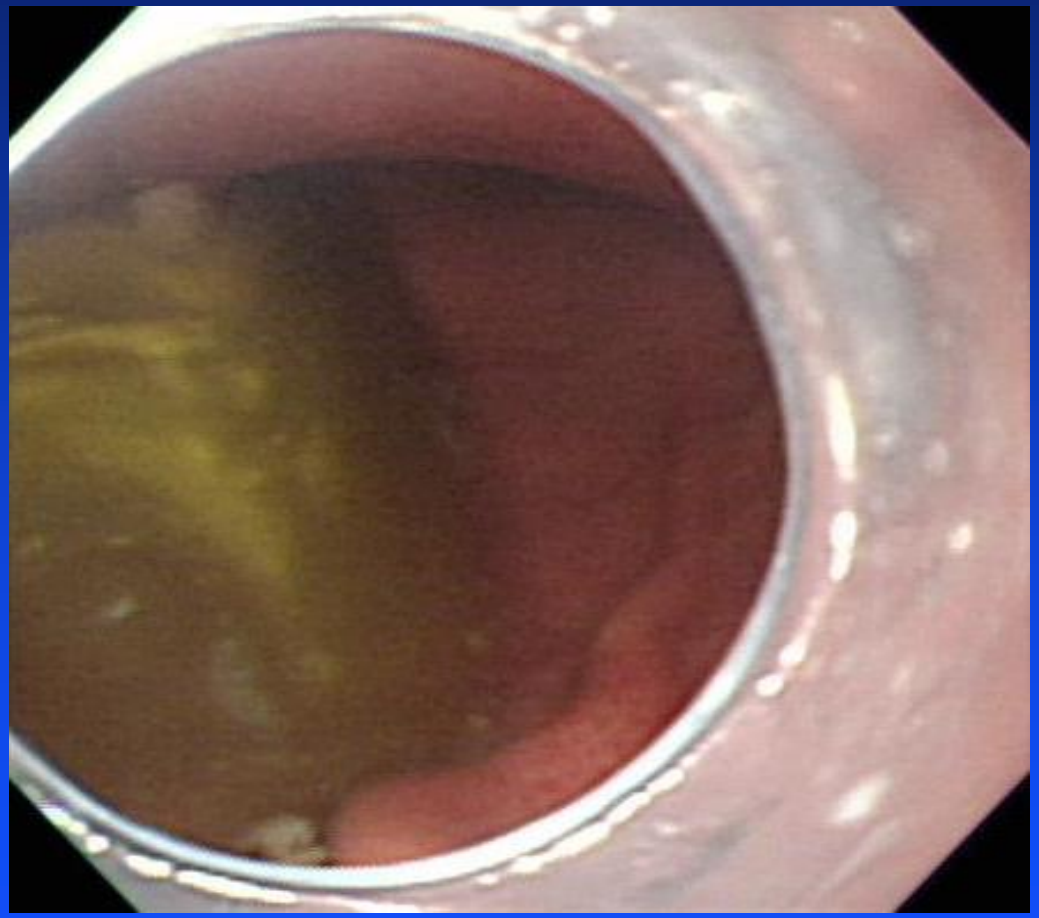
Pain modulators

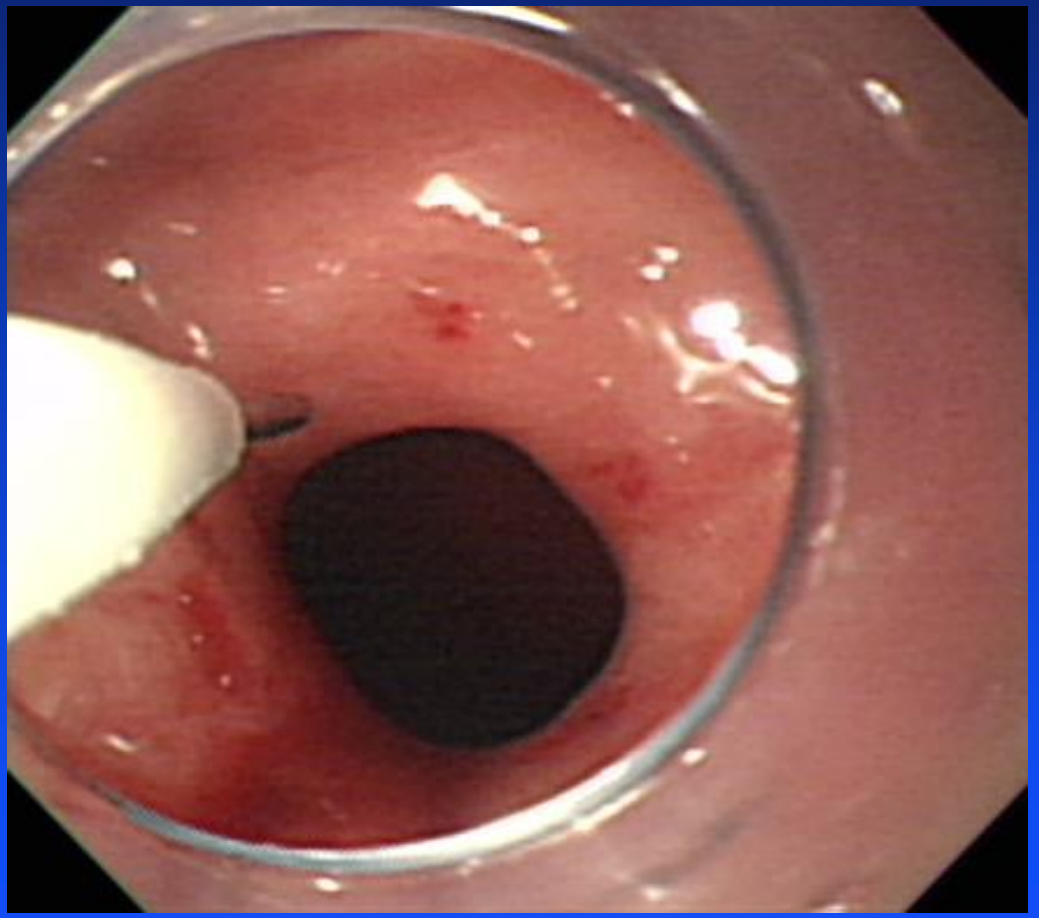
- Stop! : narcotic opiate analgesics
- Tramadol, gabapentin, pregabalin
- nortriptyline (tricyclic antidepressants)

Other Options

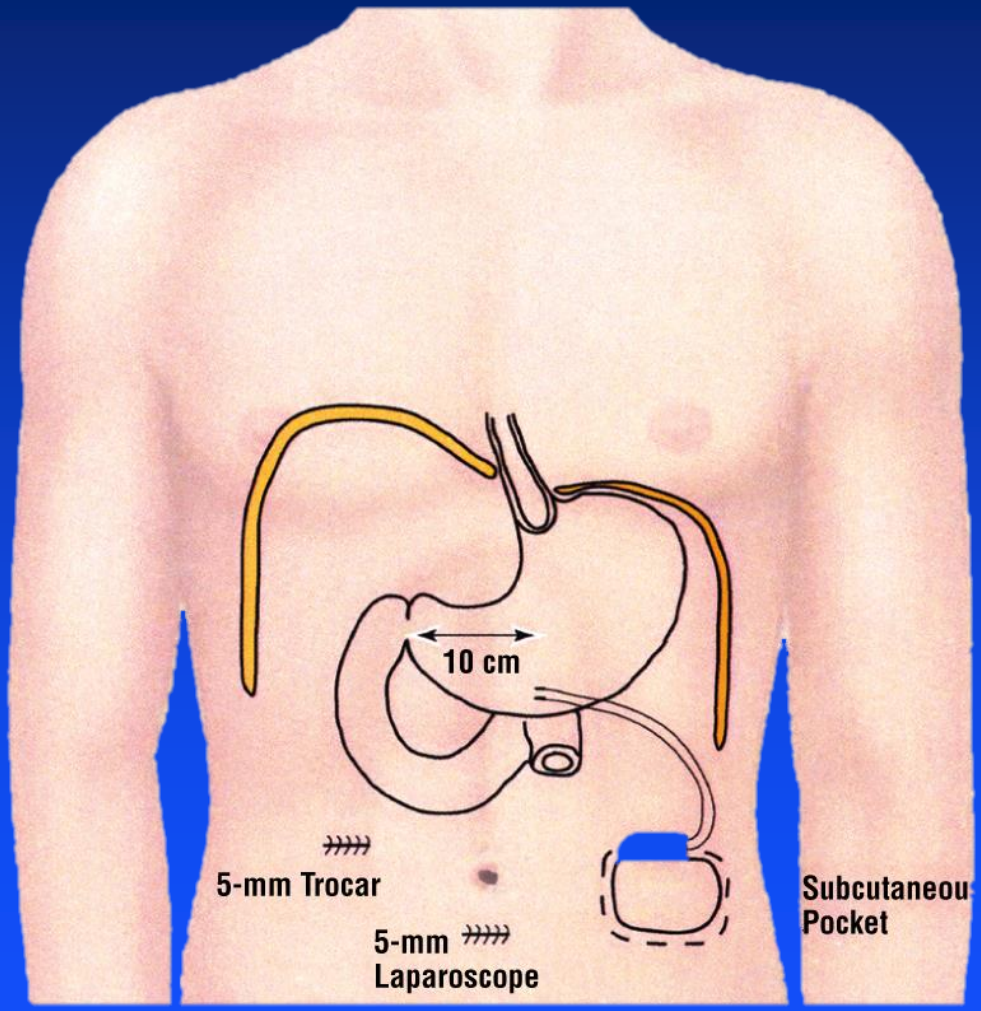
- Intrapyloric botulinum toxin injection
- Gastric electrical stimulation
- Surgery
  - Feeding jejunostomy,
  - vending gastrostomy,
  - partial gastrectomy, pyloplasty

Botulinum toxin injection





Gastric electrical stimulation (GES)



Risk factors for Gastroparesis

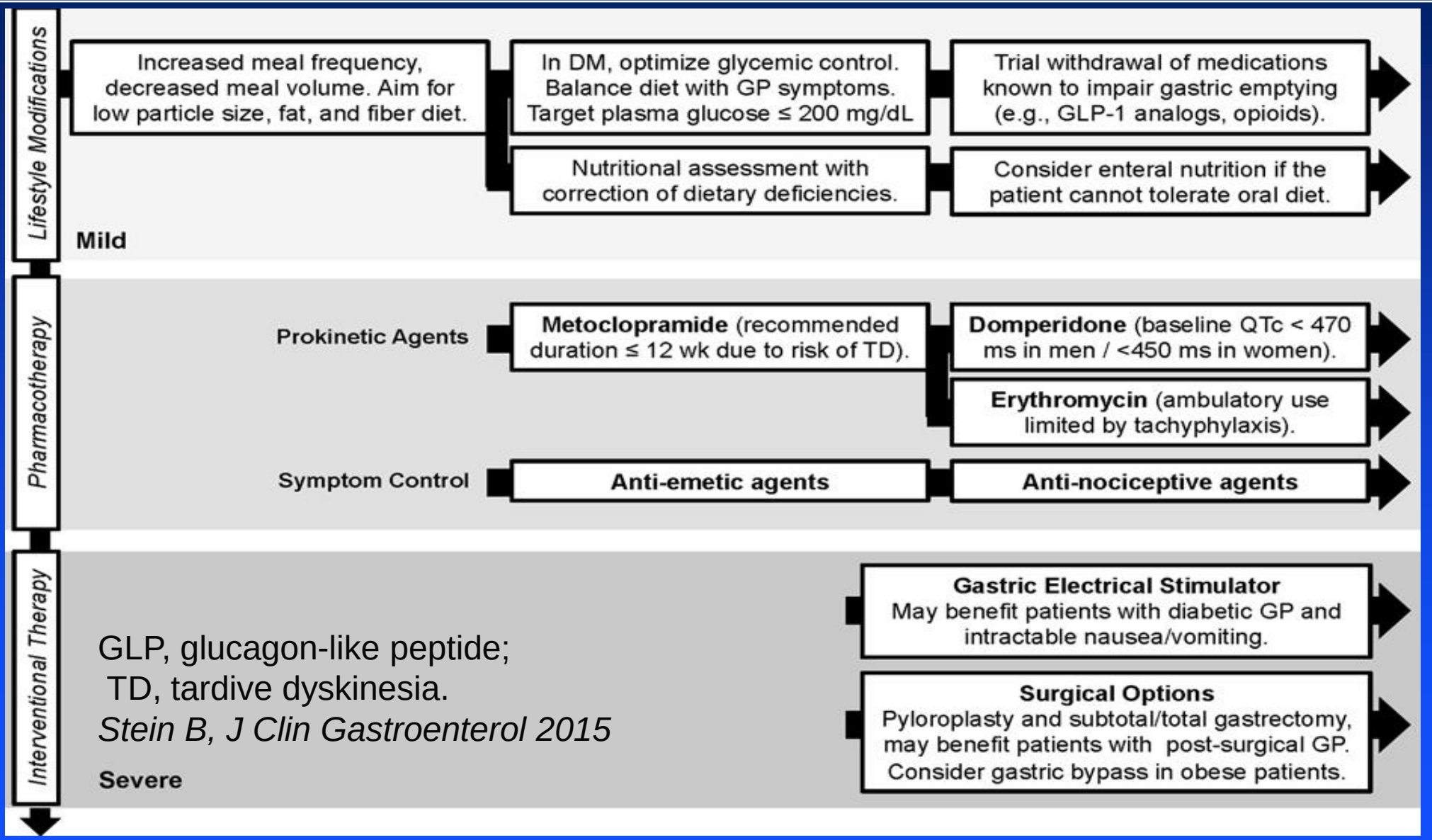
- Longstanding duration
- Poor glycemic control
  - Severe hyperglycemia (≥270 mg/dL)
- Neuropathy
- Female

Predictive factors?

Factors reduced symptoms	Factors associated with NO reduction
Male sex	Overweight or obesity
Age ≥50 y	history of smoking
Initial infectious prodrome	use of pain modulators
antidepressant use	Moderate to severe abdominal pain
4 hr gastric retention>20%	Moderate to severe depression
	Severe gastroesophageal reflex

Pasricha PJ. Gastroenterology 2015

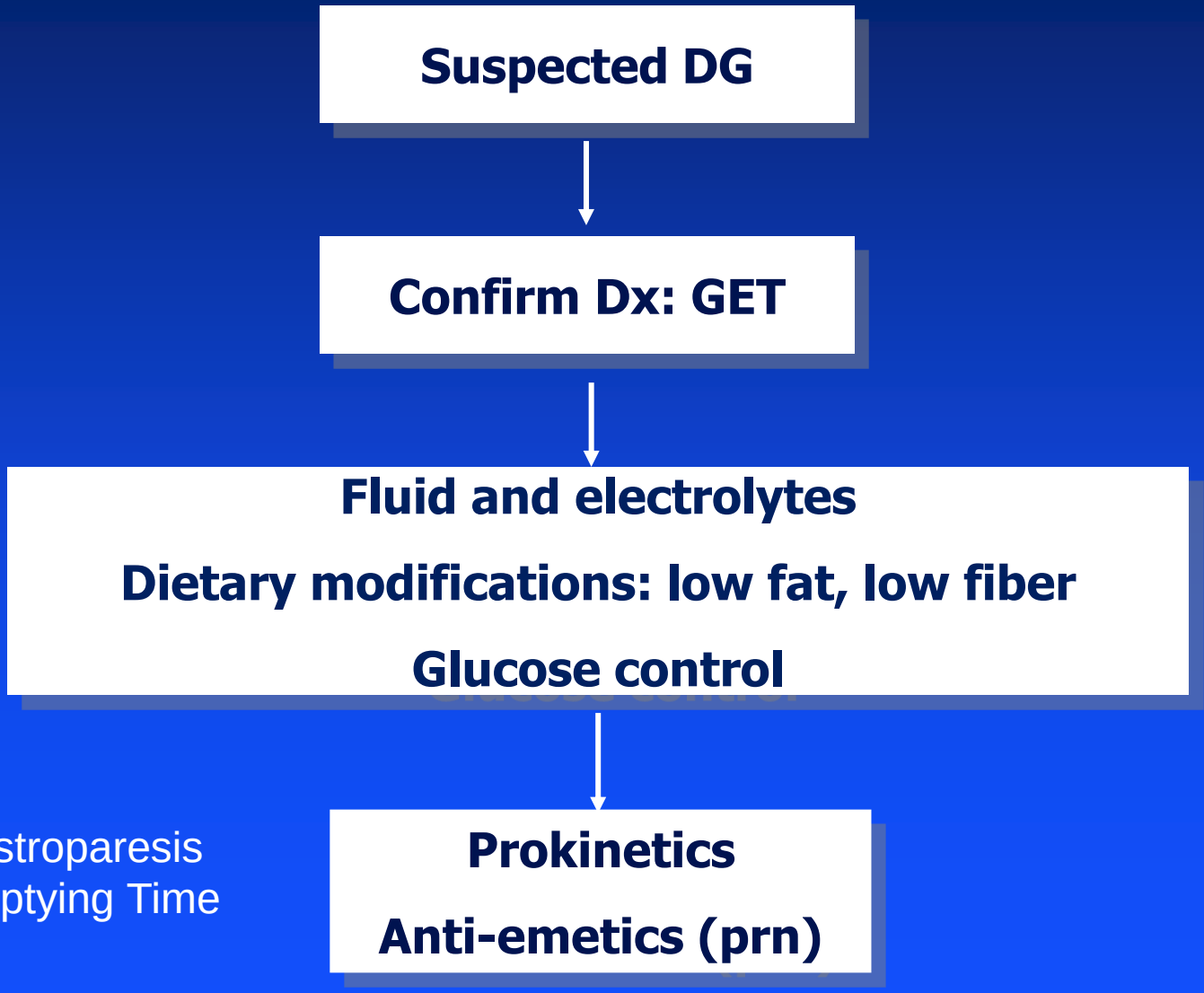
Therapeutic options by symptom severity



GLP, glucagon-like peptide;
TD, tardive dyskinesia.

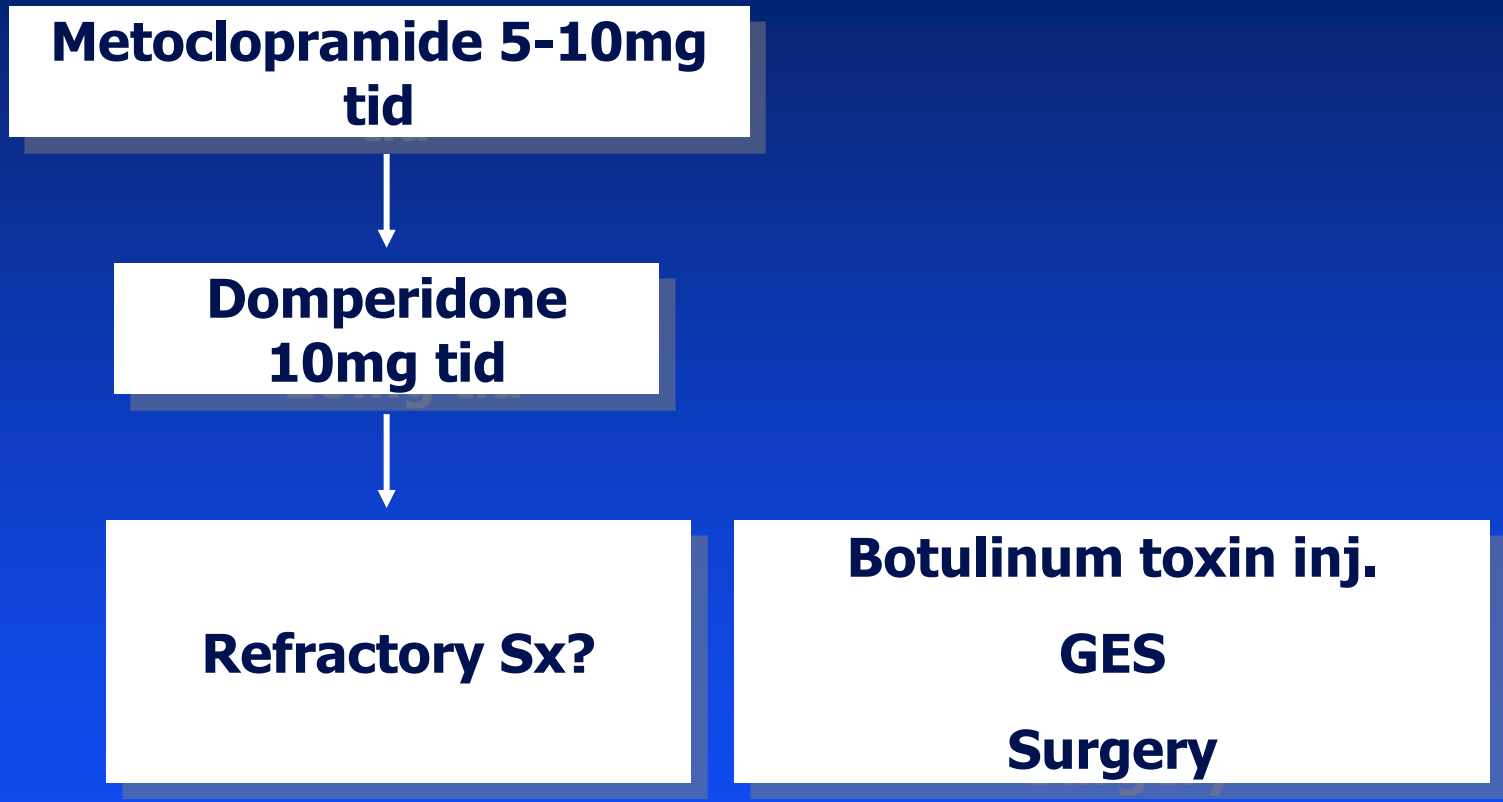
Stein B, J Clin Gastroenterol 2015

Summary



DG: Diabetic Gastroparesis
GET: Gastric Emptying Time

Summary



GES: Gastric electrical stimulation

Thank you for your attention

APNM2016

The 6th Asian Postgraduate Course on Neurogastroenterology & Motility
in conjunction with The 27th Annual Conference of the Korean Society of Neurogastroenterology and Motility

April 1-3, 2016 | Sheraton Grande Walkerhill Hotel, Seoul, Korea

Scientific Program Overview

DAY 1 Friday, April 1, 2016

- Session I. Update on Diagnostic Methods for Functional Gastrointestinal Disorders

DAY 2 Saturday, April 2, 2016

- Session II. Current and Emerging Treatments for Functional Gastrointestinal Disorders
- Session III: ANMA-ESNM-KSNM Joint Symposium: Update on Pathophysiology of Irritable Bowel Syndrome

DAY 3 Sunday, April 3, 2016

- State-of-the-art Lecture in Basic Research
- Session VI. Rome Symposium
- APNM Educational Workshop

Important Dates

✓ *Deadline for Abstract Submission*
February 1, 2016