REFRACTORY FUNCTIONAL DYSPEPSIA

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Gastroenterologist Arab Board

Functional Dyspepsia

Definition & Key Clinical Facts

Definition

Functional dyspepsia is a syndrome characterized by unexplained upper abdominal symptoms.

Main symptoms:

- Epigastric pain or burning
- Postprandial fullness
- Early satiety
- Bloating
- Nausea

Key Numbers

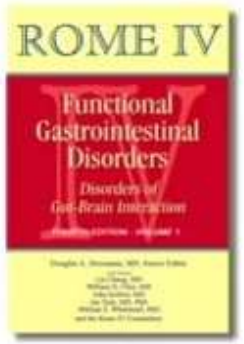
7–10%	1.6×	1/3	1/3–1/2
of adults are affected	more common in women	have anxiety disorder	have IBS overlap

Heavy smoking is a strong risk factor

Symptoms occur without identifiable structural disease.

DYSPEPSIA
Rome III and Rome IV definitions

Dyspepsia: symptoms thought to originate from the gastroduodenum



Uninvestigated dyspepsia

Endoscopy, etc.

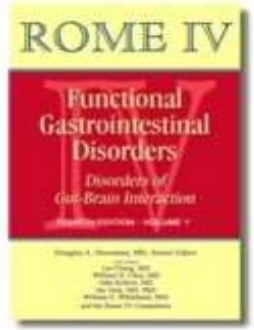
70%

Functional dyspepsia

Organic dyspepsia
(ulcer, esophagitis, cancer, …)

FUNCTIONAL DYSPEPSIA
Rome IV definitions

Functional Dyspepsia



Postprandial distress syndrome (PDS):
Meal-related FD

- Early satiation
- Postprandial fullness
- **Other postprandial symptoms**

Epigastric pain syndrome (EPS):
Meal-unrelated FD

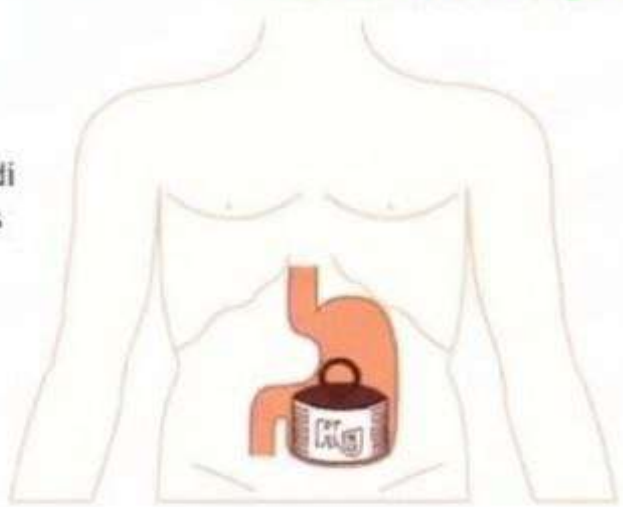
- Epigastric pain
- Epigastric burning

ueg.eu

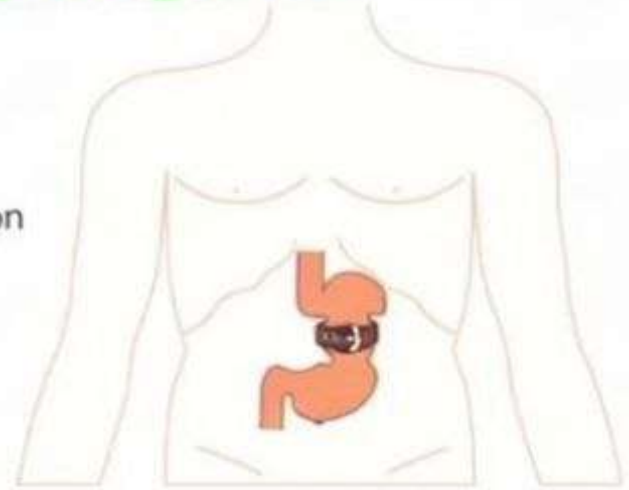
Stanghellini et al., Gastroenterology 2016

FUNCTIONAL DYSPEPSIA
Cardinal symptoms - pictograms

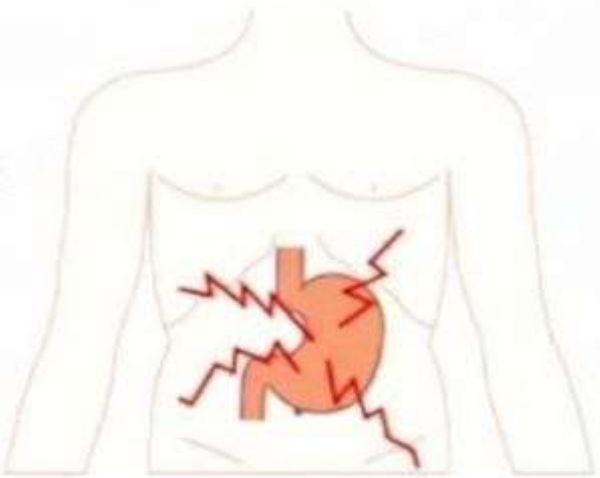
Postprandial fullness



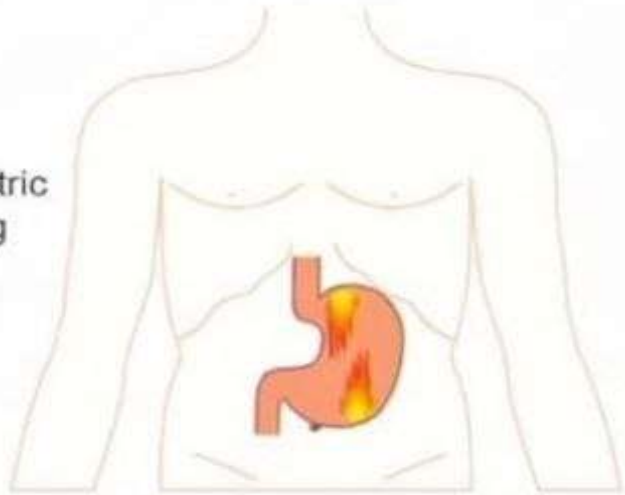
Early satiation



Epigastric pain

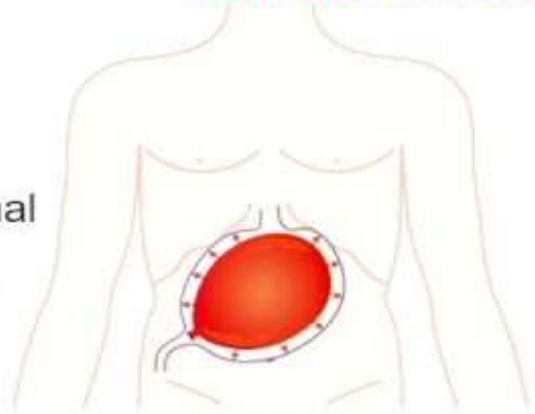


Epigastric burning



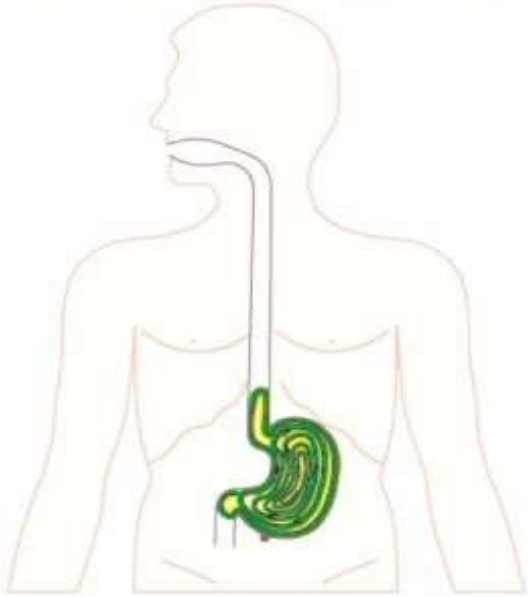
FUNCTIONAL DYSPEPSIA
Associated symptoms - pictograms

Upper abdominal bloating

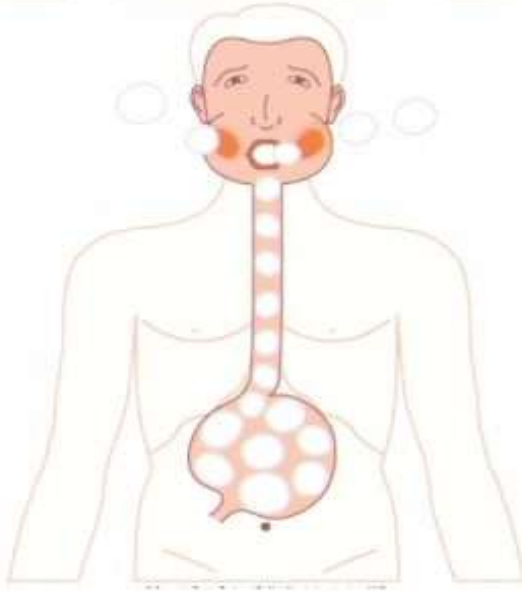


Heartburn

Nausea



Belching



FUNCTIONAL DYSPEPSIA
UEG and ESNM consensus

United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on Functional Dyspepsia

Functional dyspepsia is defined as the presence of chronic dyspeptic symptoms in the absence of organic disease that readily explains the symptoms

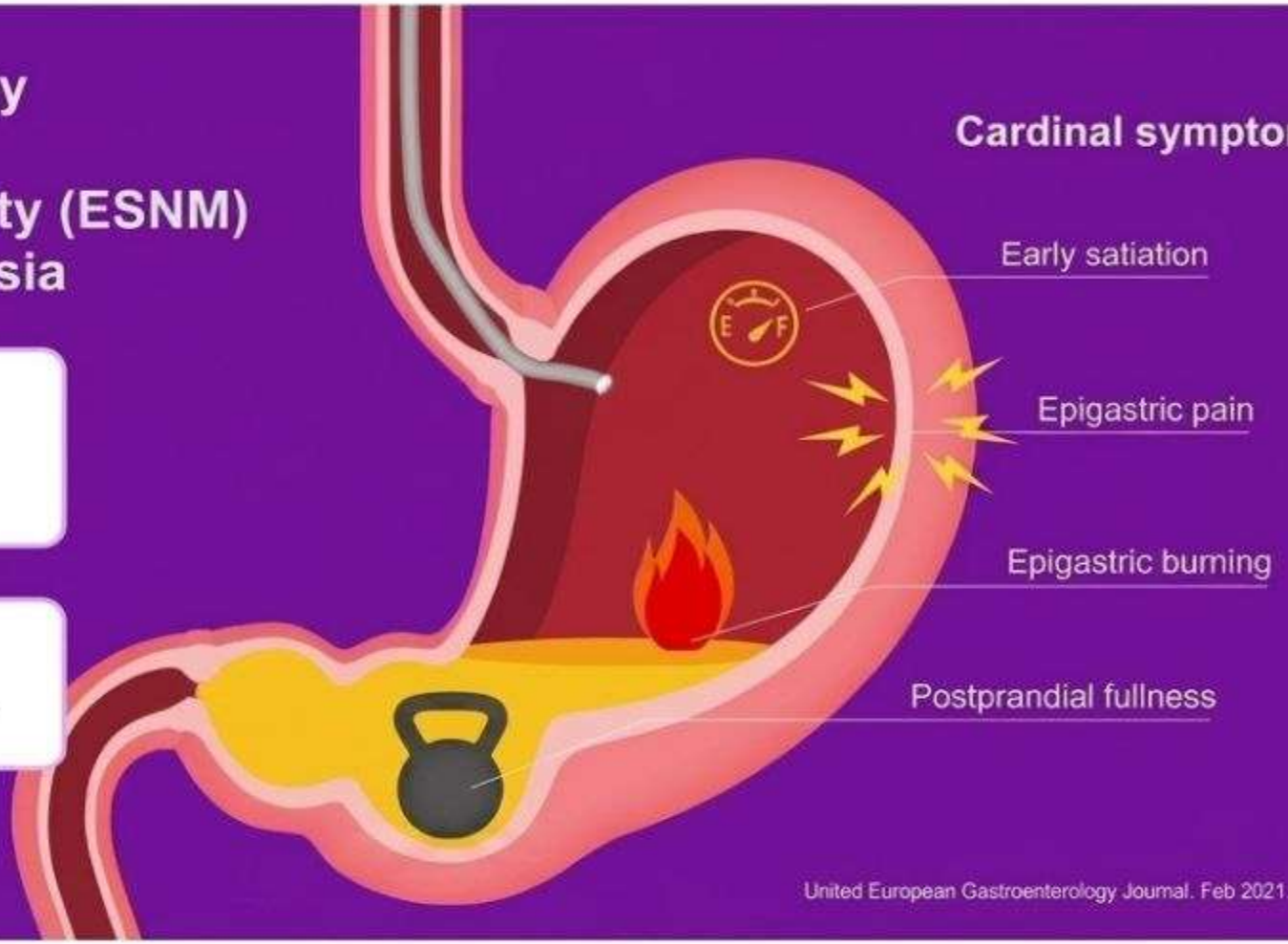
Diagnosis:
- Endoscopy for establishing firm diagnosis

Accessory symptoms:
- Upper abdominal bloating
- Nausea
- Belching

Treatment:
- Proton pump inhibitory therapy

41 experts from 22 European countries.

Consensus (defined as >80% agreement) was reached by 87 statements.



United European Gastroenterology Journal. Feb 2021.

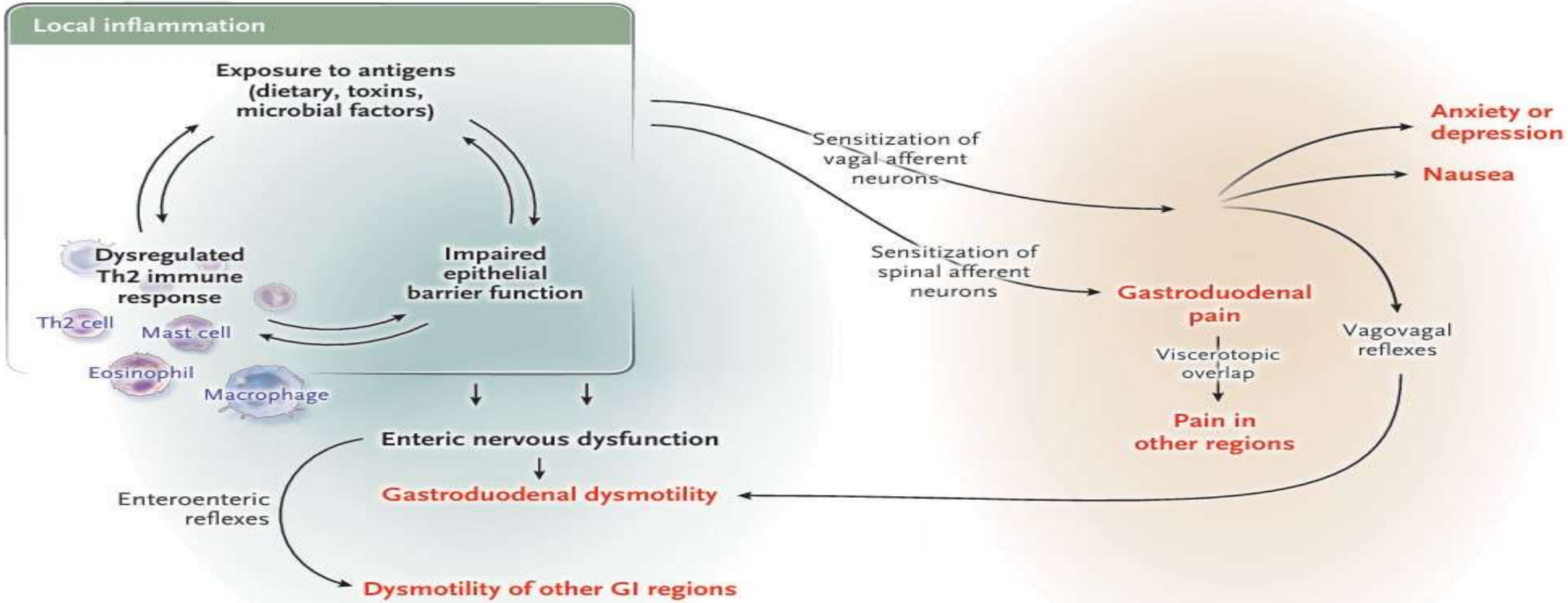
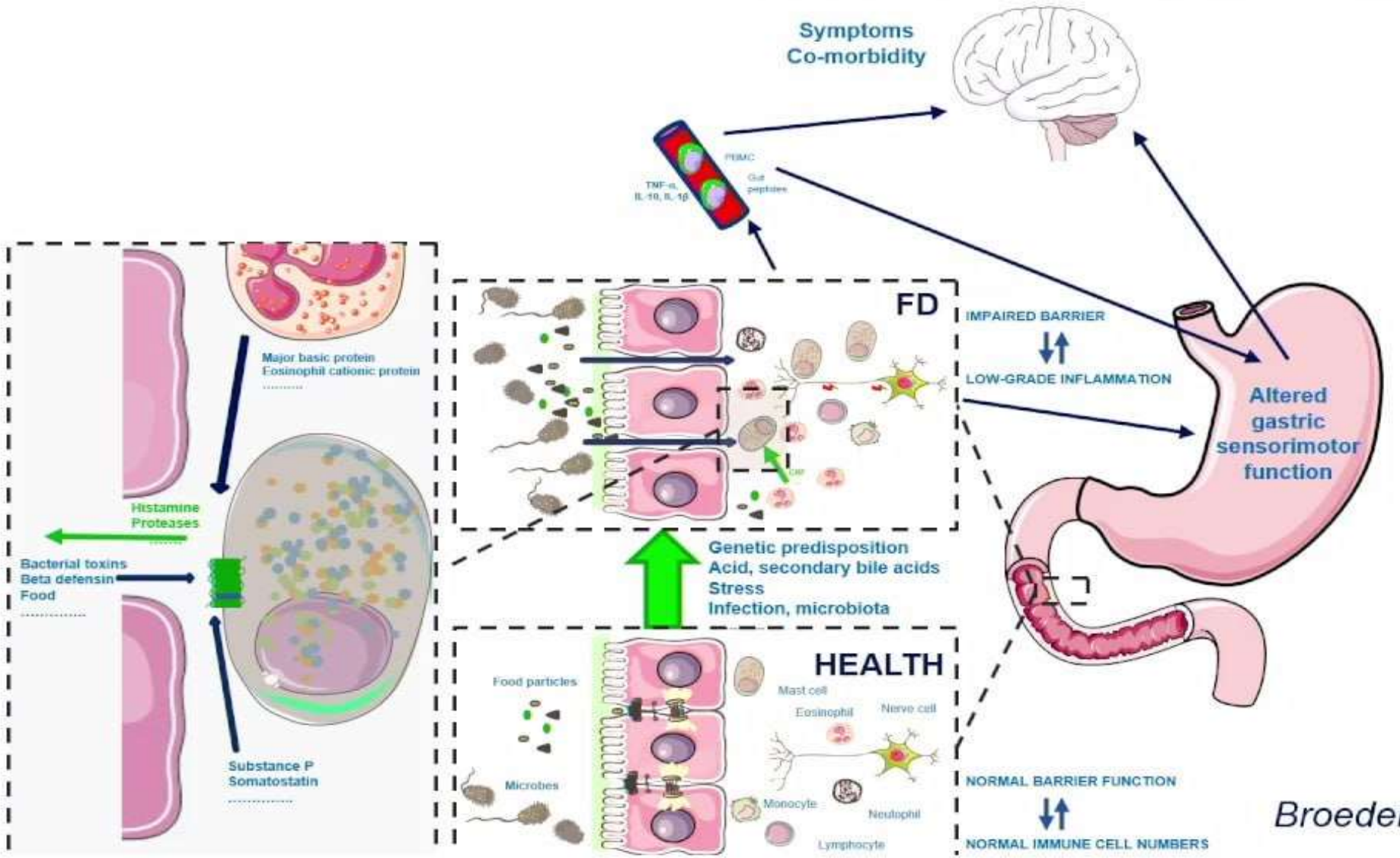
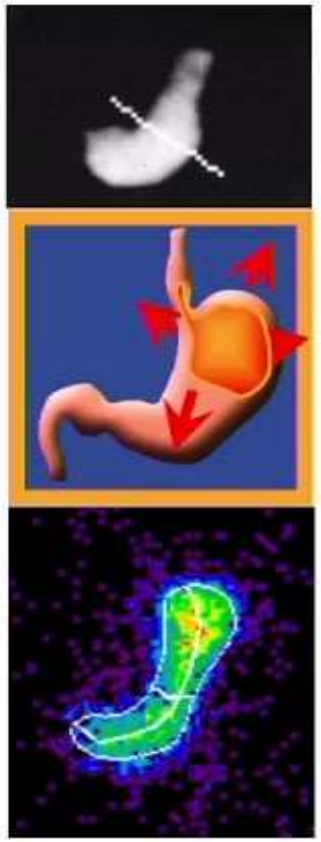


Figure 1. Proposed Pathophysiological Model of Functional Dyspepsia.

Local gastroduodenal inflammation triggered by luminal antigens leads to a dysregulated immune response by type 2 helper T (Th2) cells and activation of eosinophils, mast cells, and macrophages. The resulting impairment of the epithelial barrier function may further facilitate antigen penetration and perpetuate the microinflammation. These changes drive enteric nervous dysfunction, leading to dysmotility of the gastroduodenal region and other regions of the gut. The changes also result in the sensitization of vagal and spinal afferent pathways, leading to pain felt in the epigastrium (as well as other regions of the gut), nausea, and changes in affect. This conceptual model is probably applicable only to a subgroup of patients with functional dyspepsia rather than all persons who meet symptomatic criteria for this disorder. GI denotes gastrointestinal.

FUNCTIONAL DYSPEPSIA
Meal-related symptoms, pathophysiology





Broeders et al., AP&T 2023

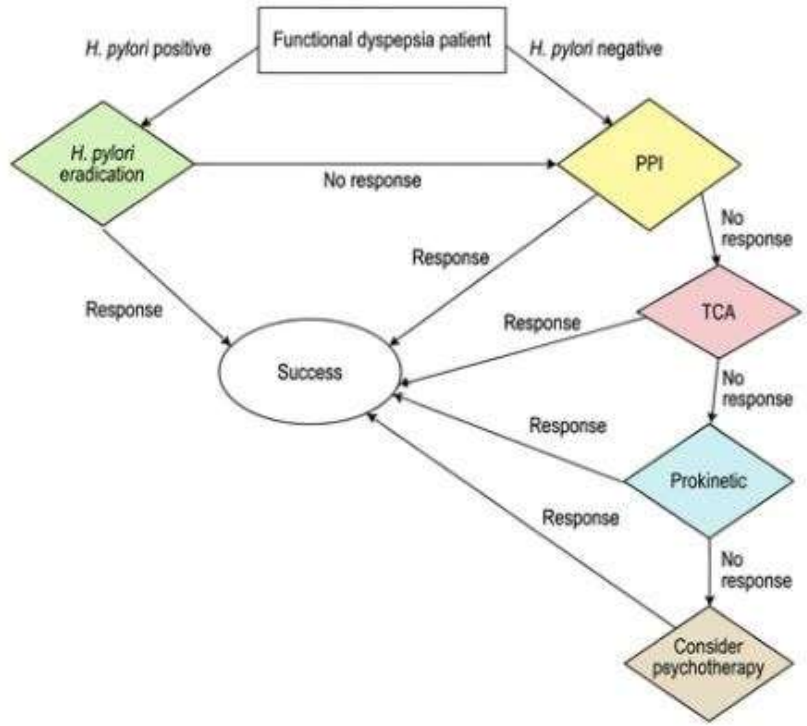
FUNCTIONAL DYSPEPSIA
Management of refractory patients

- Definitions
- Initial management: guidelines

FUNCTIONAL DYSPEPSIA
ACG ALGORITHM

ACG and CAG Clinical Guideline: Management of Dyspepsia

Paul M. Moayyedi, MB, ChB, PhD, MPH, FACG[1], Brian E. Lacy, MD, PhD, FACG[2], Christopher N. Andrews, MD[3], Robert A. Enns, MD[4], Colin W. Howden, MD, FACG[5] and Nimish Vakil, MD, FACG[6]



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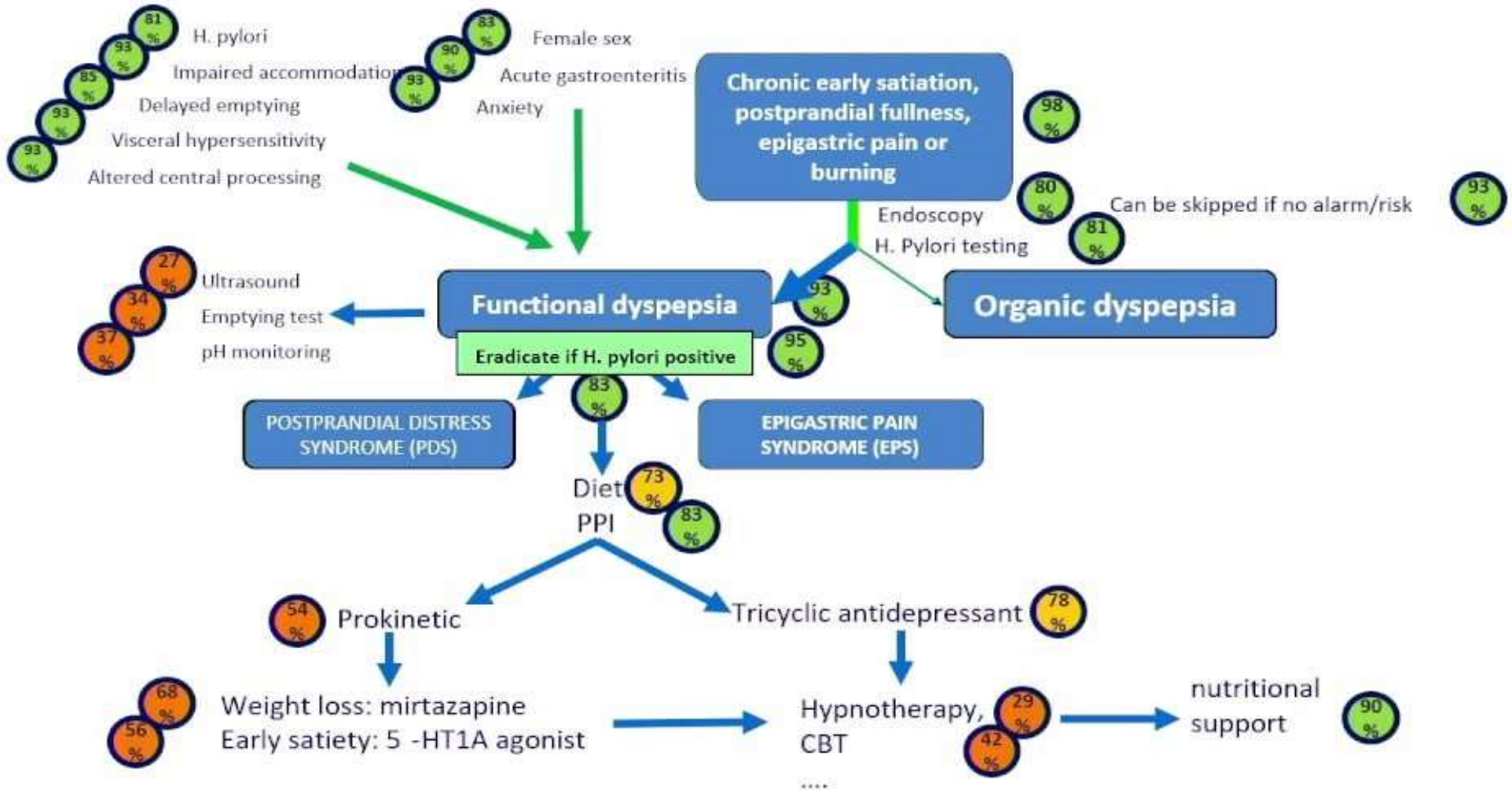
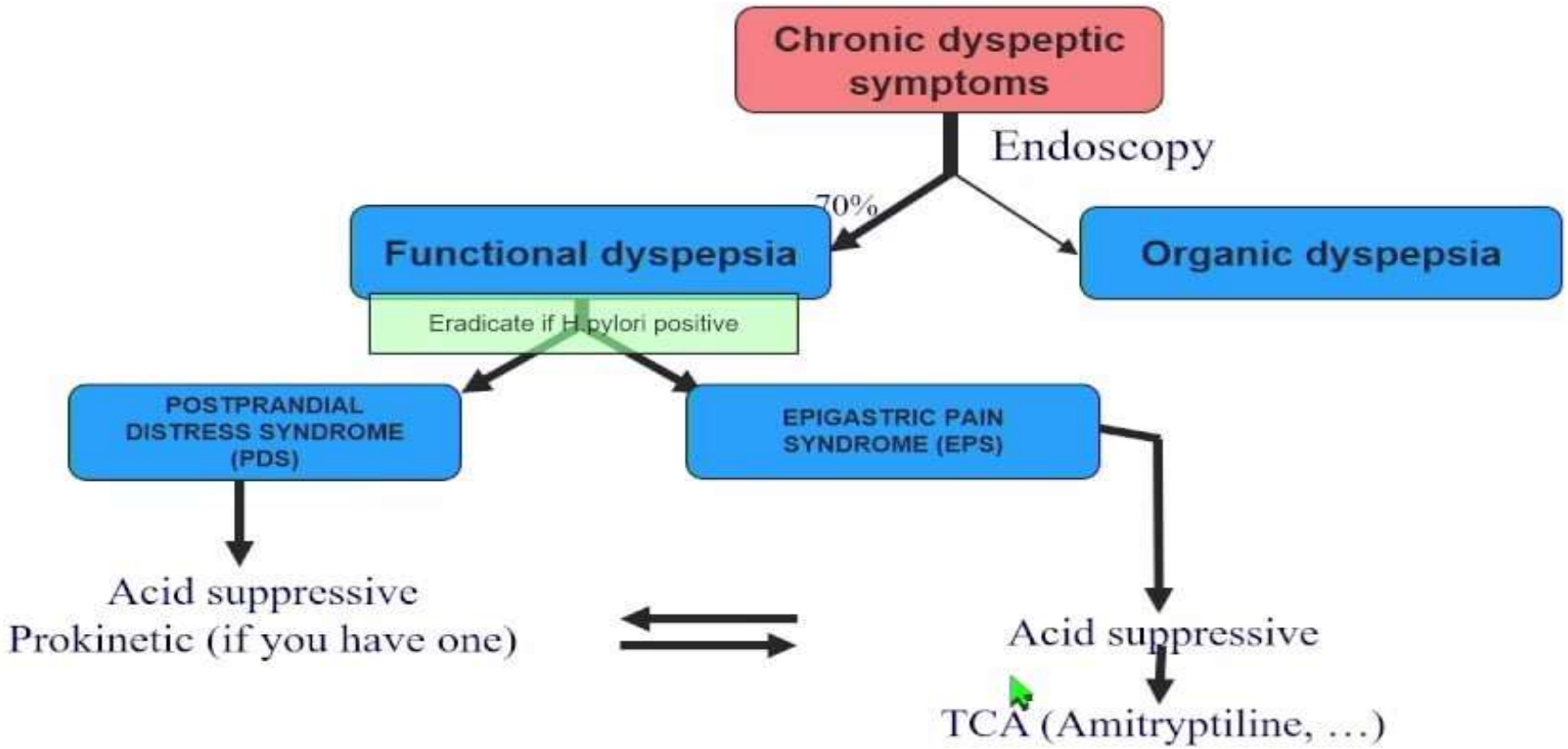
Moayyedi et al., AJG 2018

FUNCTIONAL DYSPEPSIA
European consensus 2023



Wauters et al., UEGJ 2021

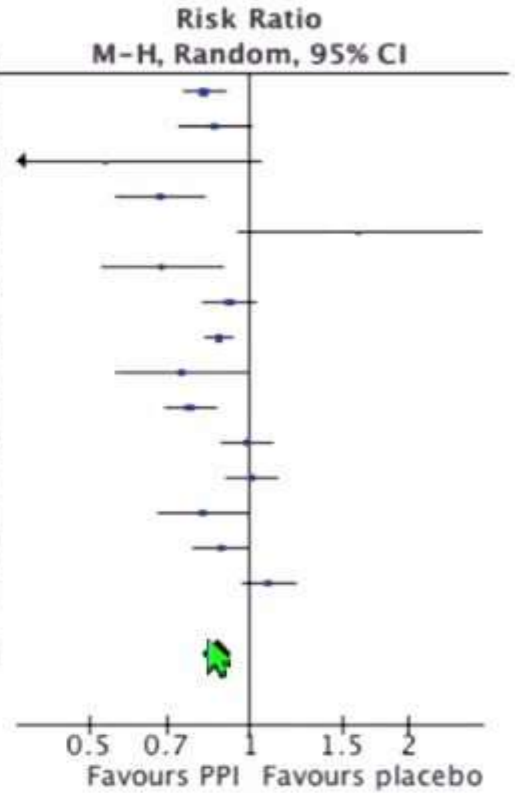
FUNCTIONAL DYSPEPSIA
Management algorithm



FUNCTIONAL DYSPEPSIA
Response to proton pump inhibitors

Study or Subgroup	PPI Events	PPI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Blum 2000	272	395	170	203	9.4%	0.82 [0.75, 0.90]
Bolling-Sternevald 2002	71	100	80	97	7.1%	0.86 [0.74, 1.01]
Farup 1999	6	14	8	10	0.9%	0.54 [0.27, 1.06]
Fletcher 2011	45	70	33	35	5.9%	0.68 [0.56, 0.83]
Gerson 2005	16	21	9	19	1.4%	1.61 [0.95, 2.74]
Hengels 1998	50	131	77	138	4.2%	0.68 [0.53, 0.89]
Iwakiri 2013	194	253	71	85	8.5%	0.92 [0.82, 1.03]
Peura 2004	474	613	271	308	10.4%	0.88 [0.83, 0.93]
Suzuki 2013 (ELF)	16	23	28	30	3.8%	0.75 [0.56, 0.99]
Talley 1998 (BOND)	242	423	162	219	8.6%	0.77 [0.69, 0.87]
Talley 1998 (OPERA)	277	403	141	203	8.6%	0.99 [0.88, 1.11]
Talley 2007	653	853	84	111	8.7%	1.01 [0.90, 1.13]
Van Rensburg 2008	93	207	116	212	5.9%	0.82 [0.68, 1.00]
Van Zanten 2006	84	109	100	115	8.2%	0.89 [0.78, 1.00]
Wong 2002	231	301	107	152	8.3%	1.09 [0.97, 1.23]
Total (95% CI)		**3916**		**1937**	**100.0%**	**0.87 [0.82, 0.94]**
Total events	2724		1457			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 48.93$, df = 14 ($P < 0.00001$); $I^2 = 71\%$
Test for overall effect: Z = 3.87 (P = 0.0001)



No dose-response effect

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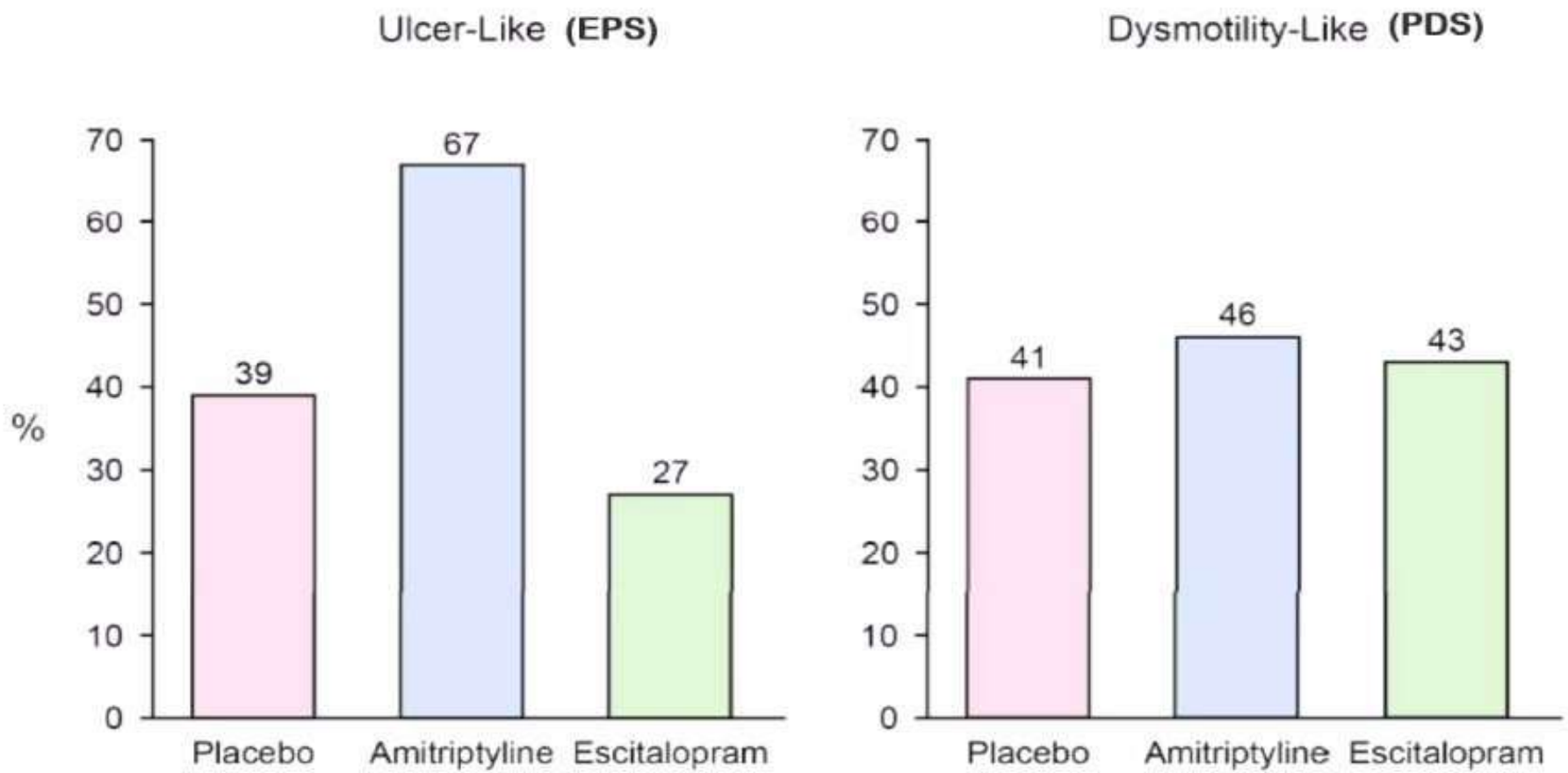
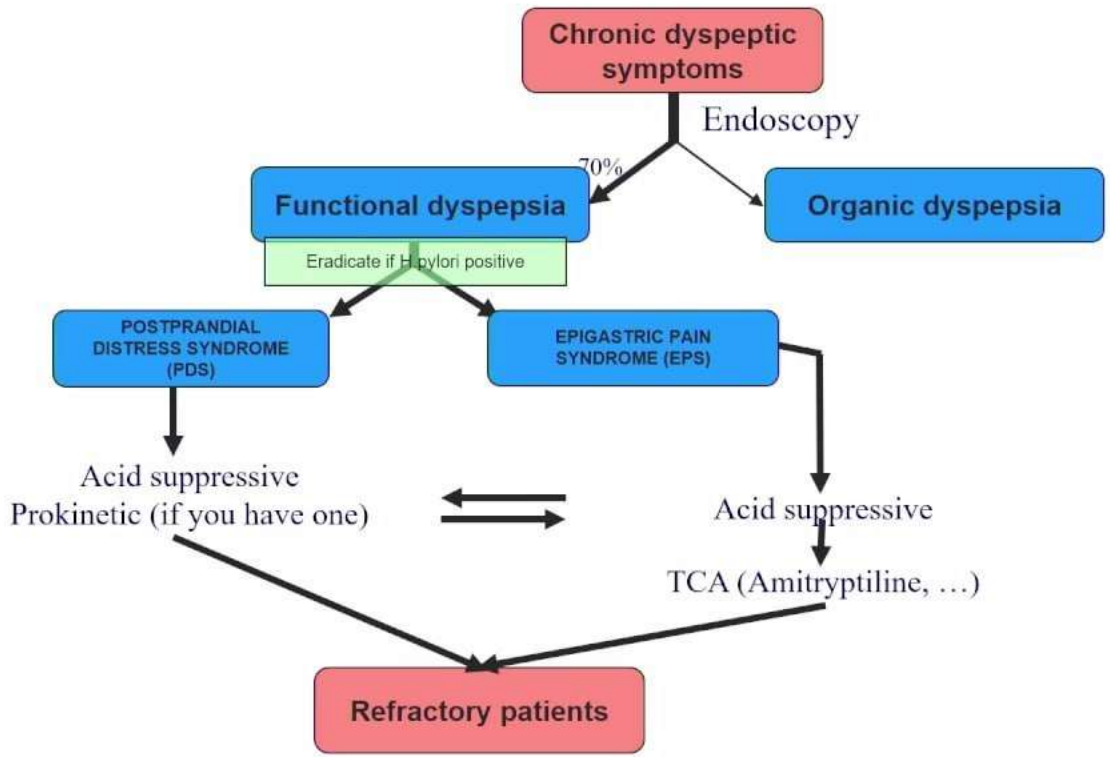
Moayyedi et al., AJG 2018

FUNCTIONAL DYSPEPSIA
Antidepressants in functional dyspepsia



FUNCTIONAL DYSPEPSIA
Management algorithm



FUNCTIONAL DYSPEPSIA
Management

- No overall well-established effective therapy
- Management is highly empirical
- Management of refractory patients is beyond evidence-base

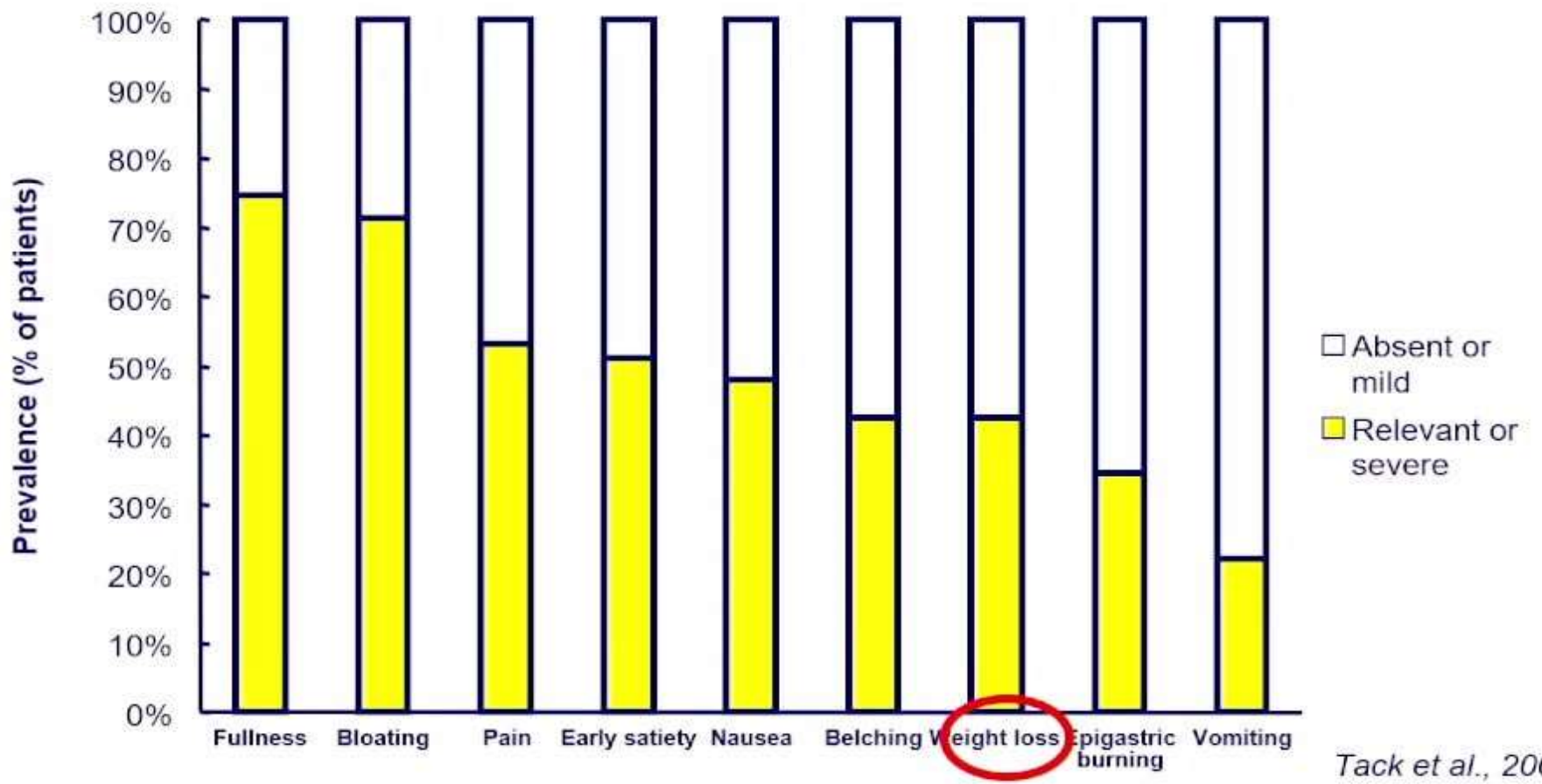
FUNCTIONAL DYSPEPSIA
Management of refractory patients

- Definitions
- Initial management
- Management of refractory patients

FUNCTIONAL DYSPEPSIA
Management of refractory patients

- Which symptom is refractory?
- Which additional examinations should be performed?
- Which additional treatment options do we have?

FUNCTIONAL DYSPEPSIA
Symptom pattern in 700 patients



Tack et al., 2005

FUNCTIONAL DYSPEPSIA
Management of weight loss

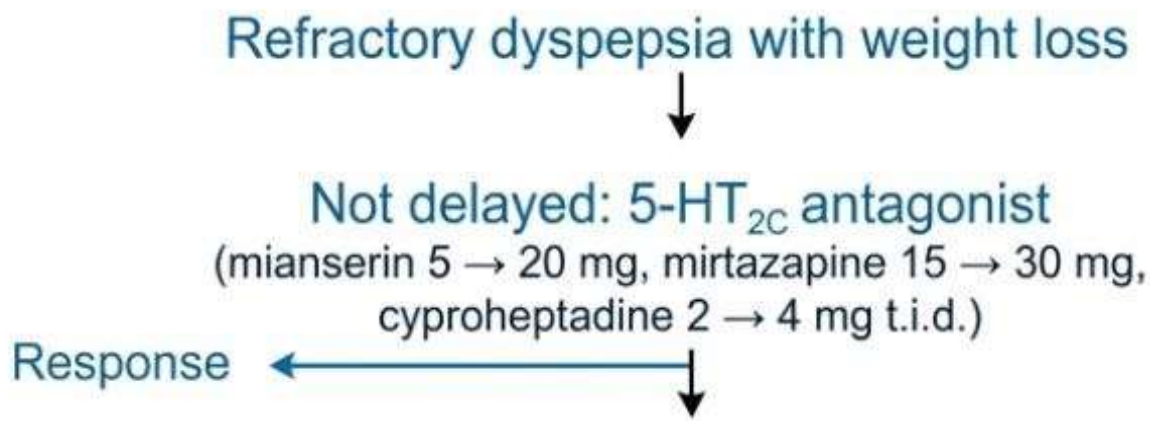
Refractory dyspepsia with weight loss

↓

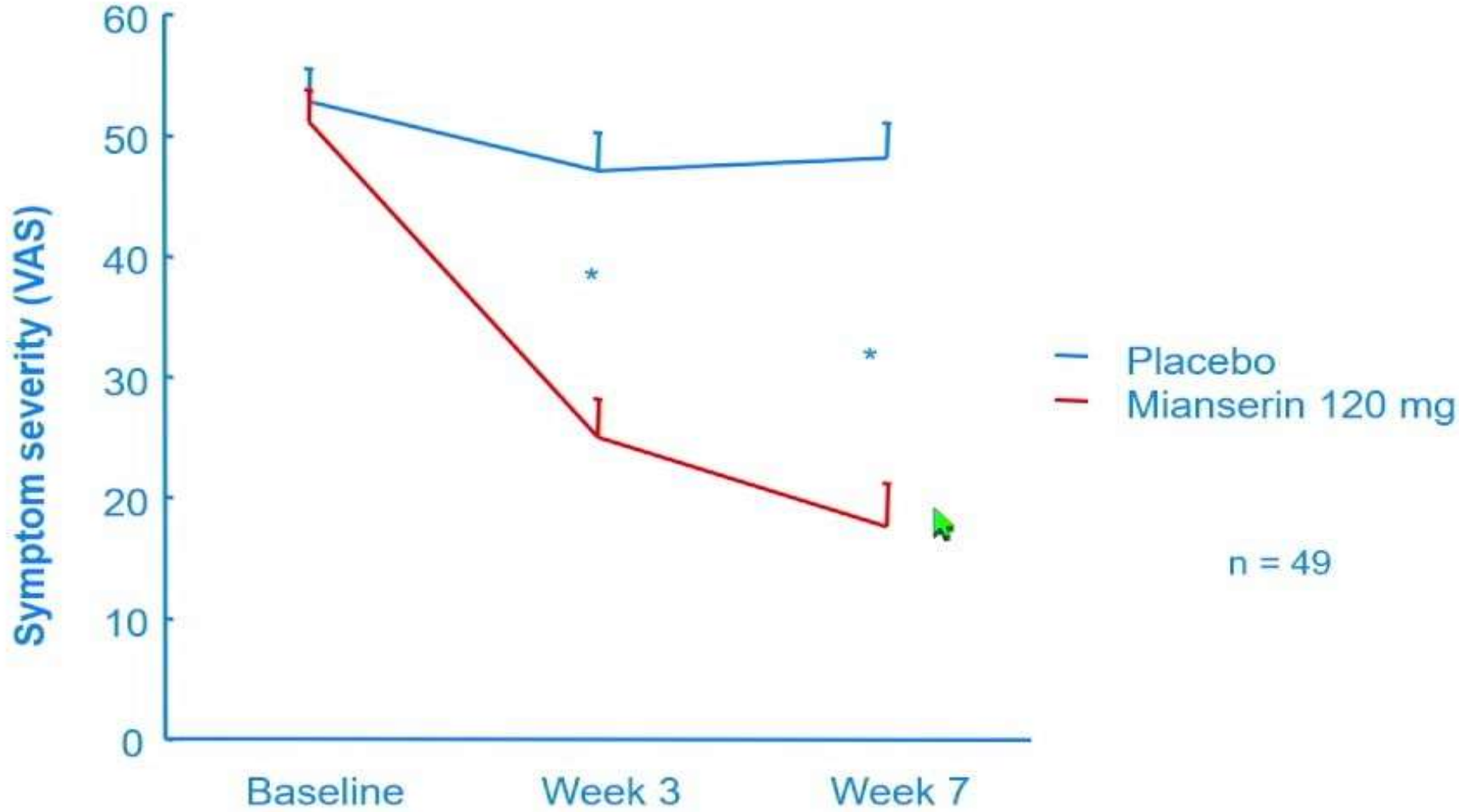
Consider « non-gastric » disease: thyroid dysfunction, coeliac disease, giardiasis, malabsorption, colonic or other cancer, …

Consider psychiatric advice, …

FUNCTIONAL DYSPEPSIA
Management of weight loss

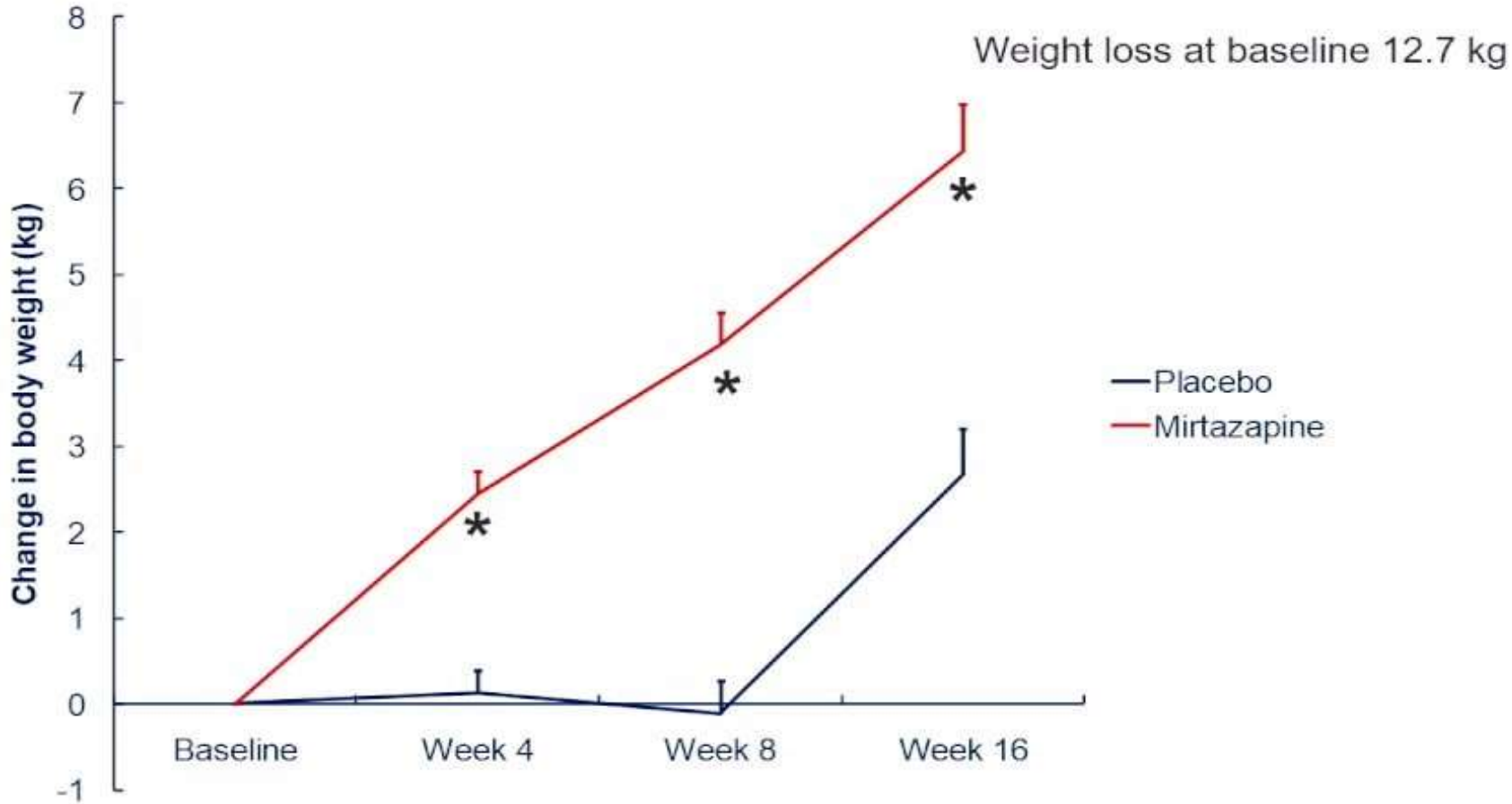


FUNCTIONAL DYSPEPSIA
Therapeutic benefit with mianserin



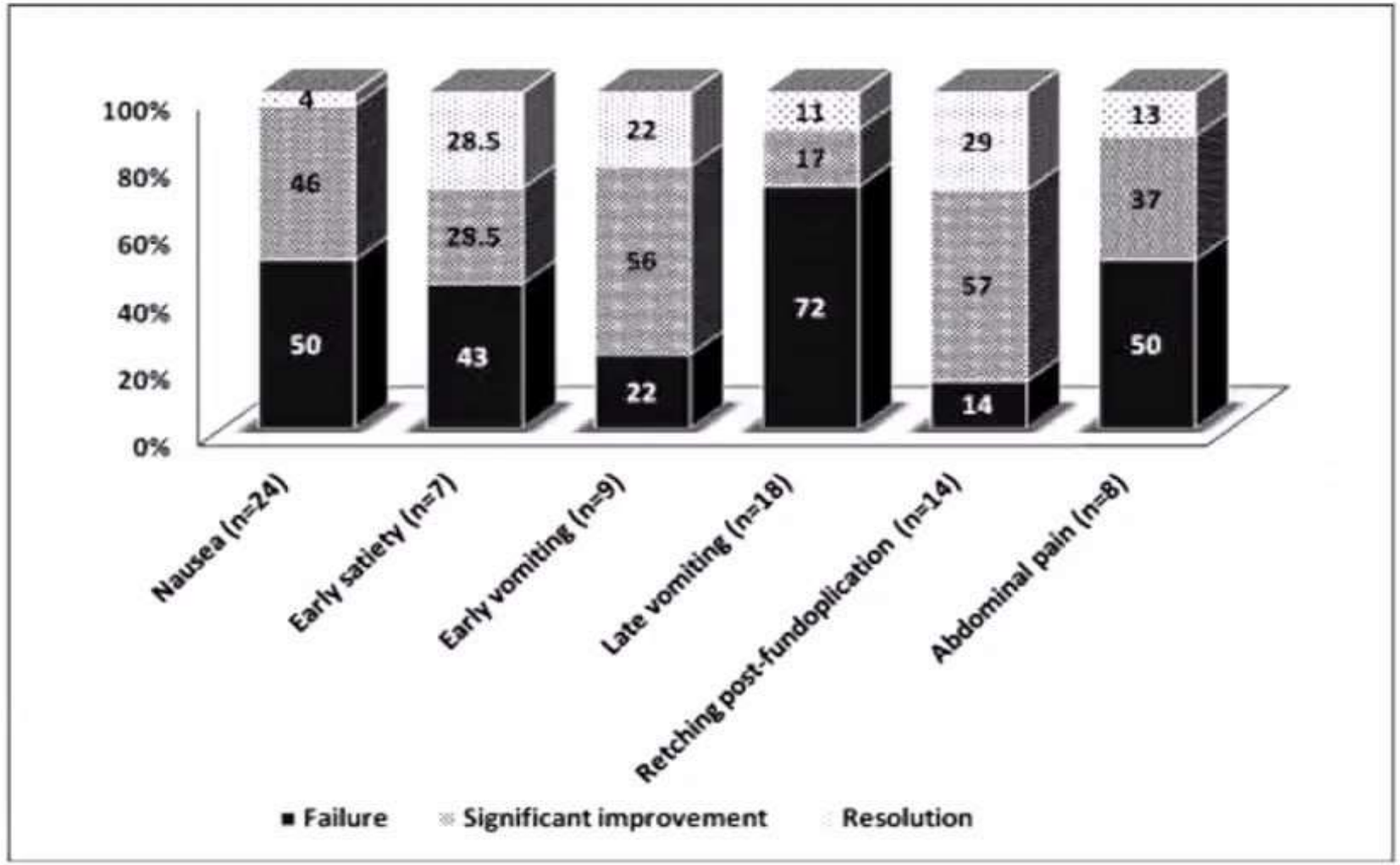
Tanum and Malt, 1996

MIRTAZAPINE IN FUNCTIONAL DYSPEPSIA
Weight regain



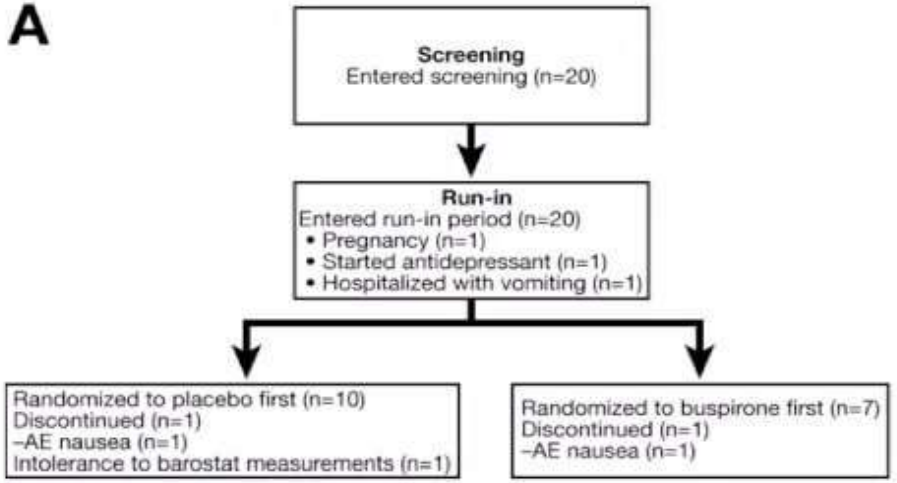
Tack et al., CGH 2016

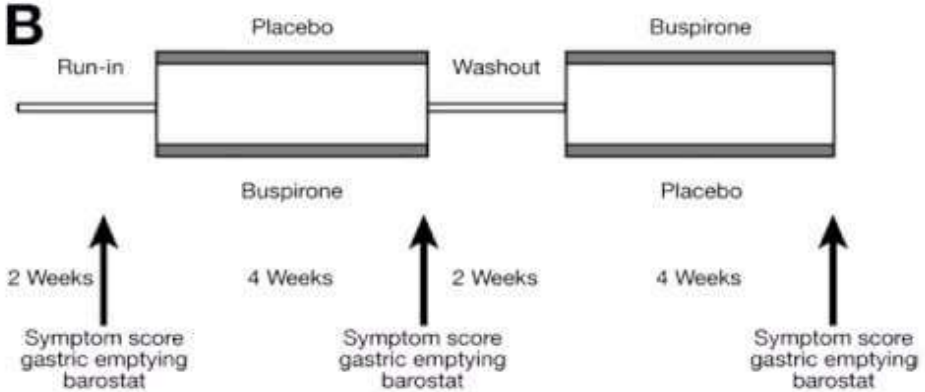
CYPROHEPTADINE IN PEDIATRIC DYSPEPSIA
Symptom control

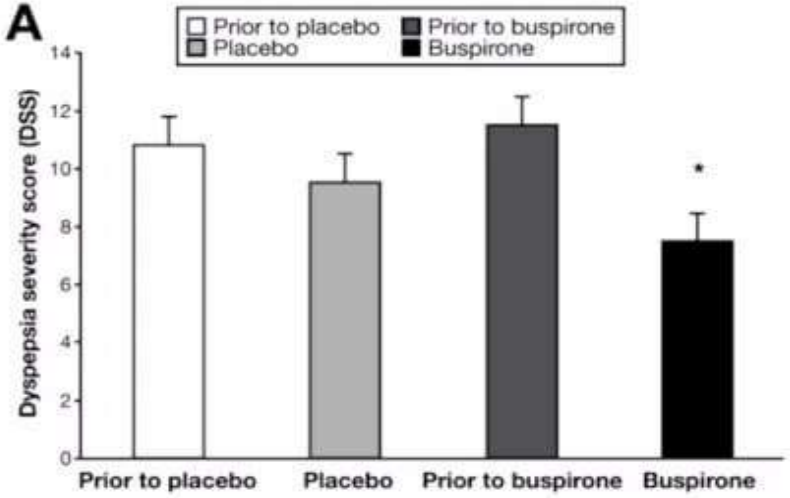


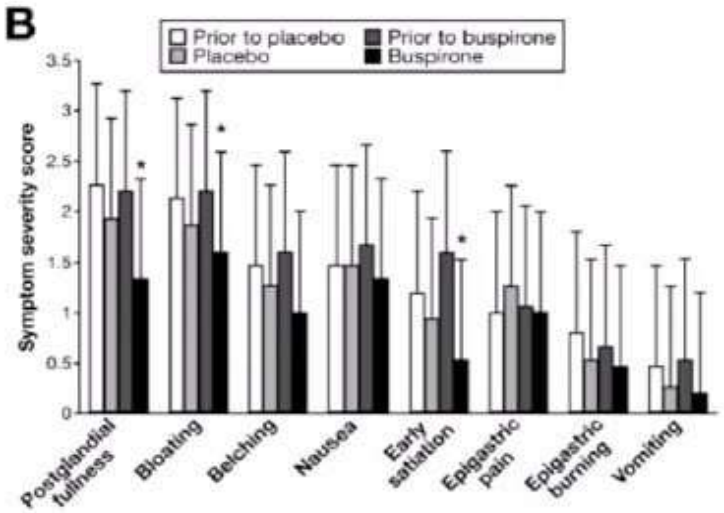
Rodriguez et al., J Ped 2013

BUSPIRONE IN FUNCTIONAL DYSPEPSIA
Effect on symptoms and accommodation









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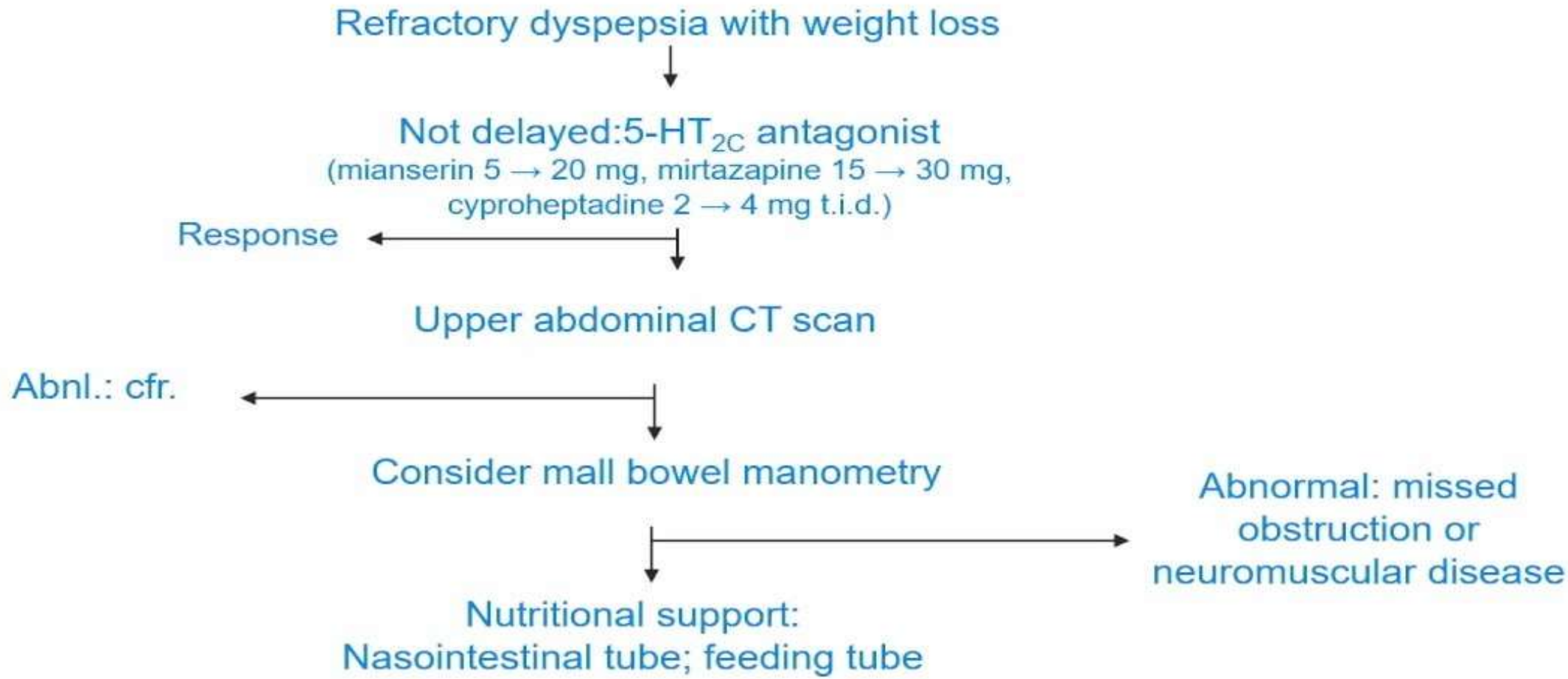
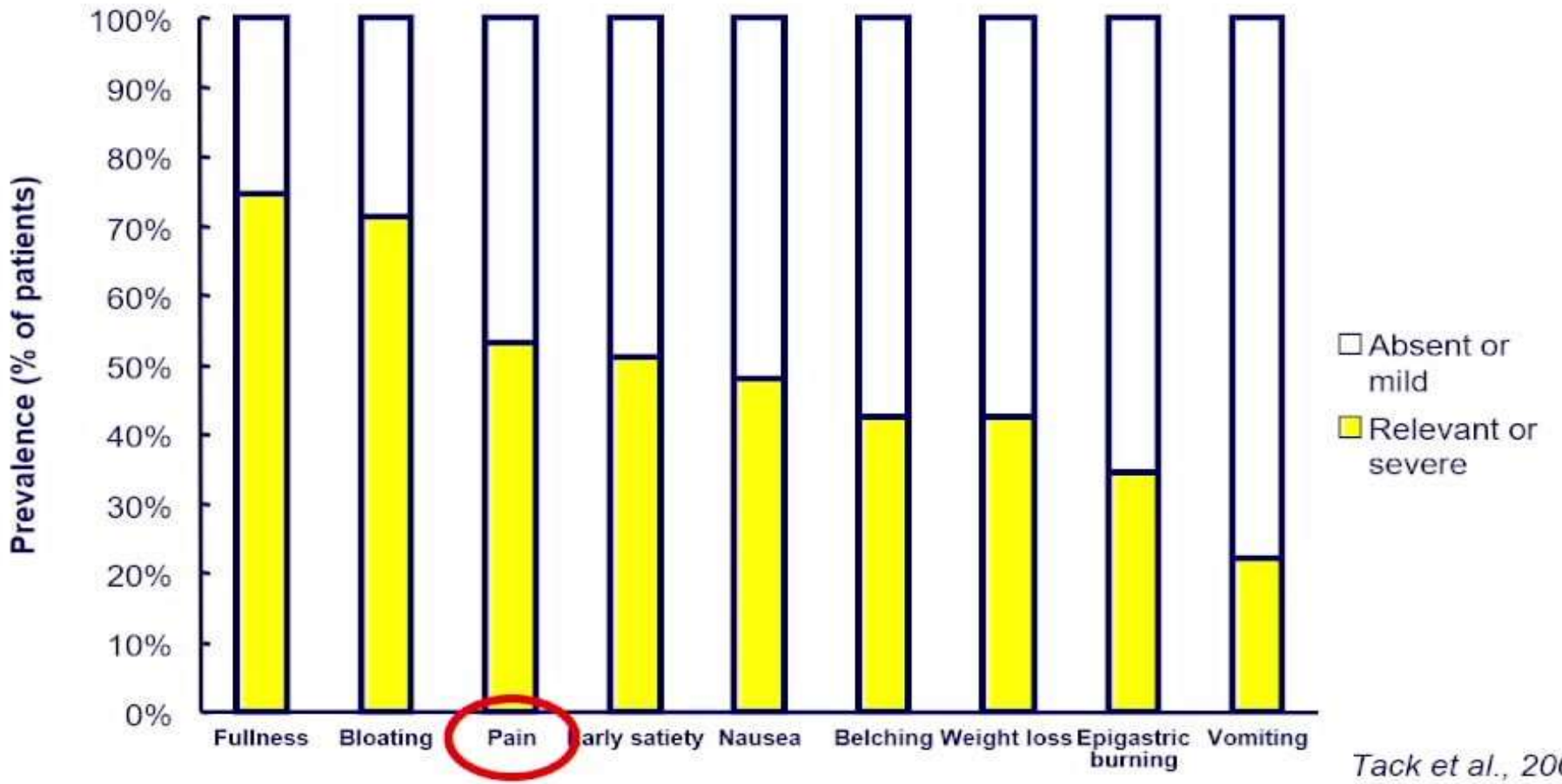
Tack et al., CGH 2012

FUNCTIONAL DYSPEPSIA
Management of weight loss

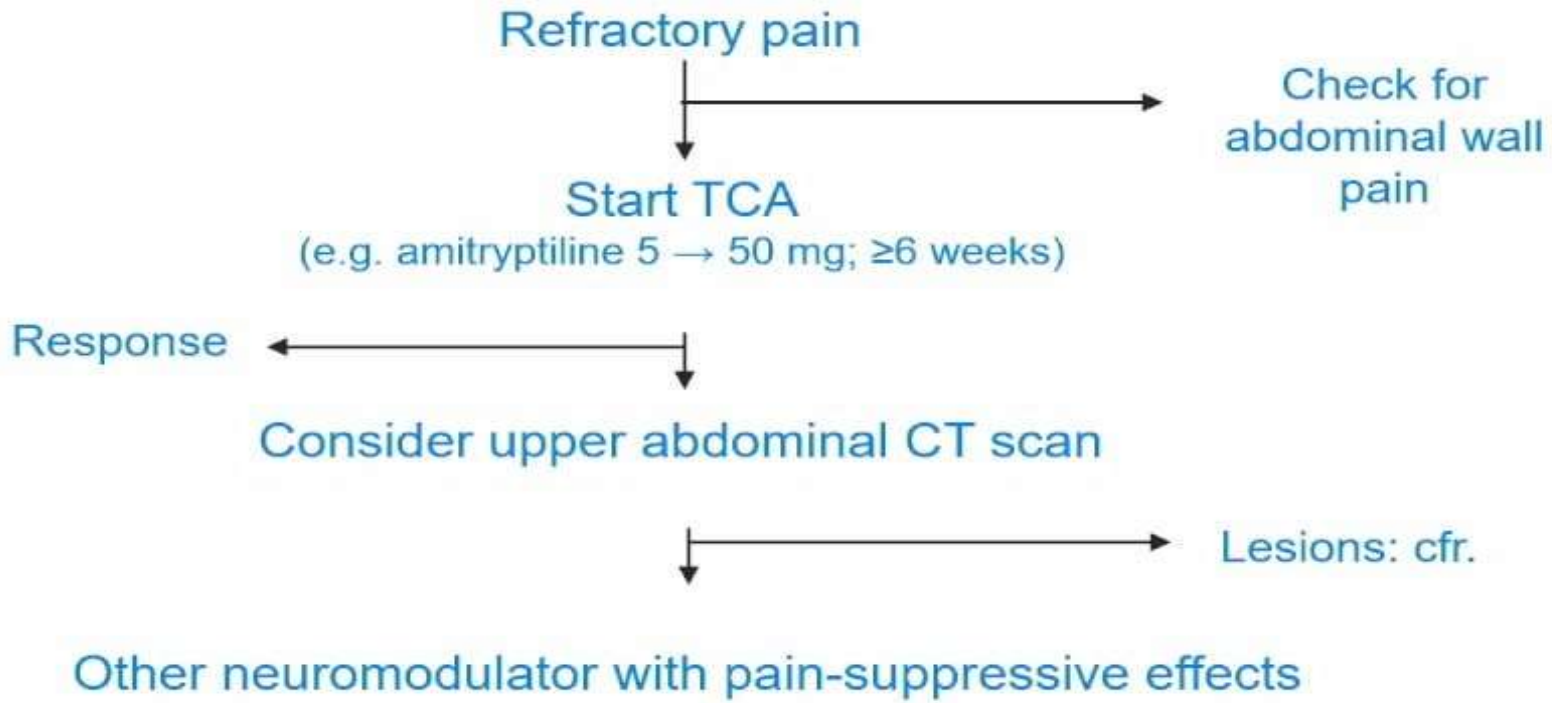


FUNCTIONAL DYSPEPSIA
Symptom pattern in 700 patients

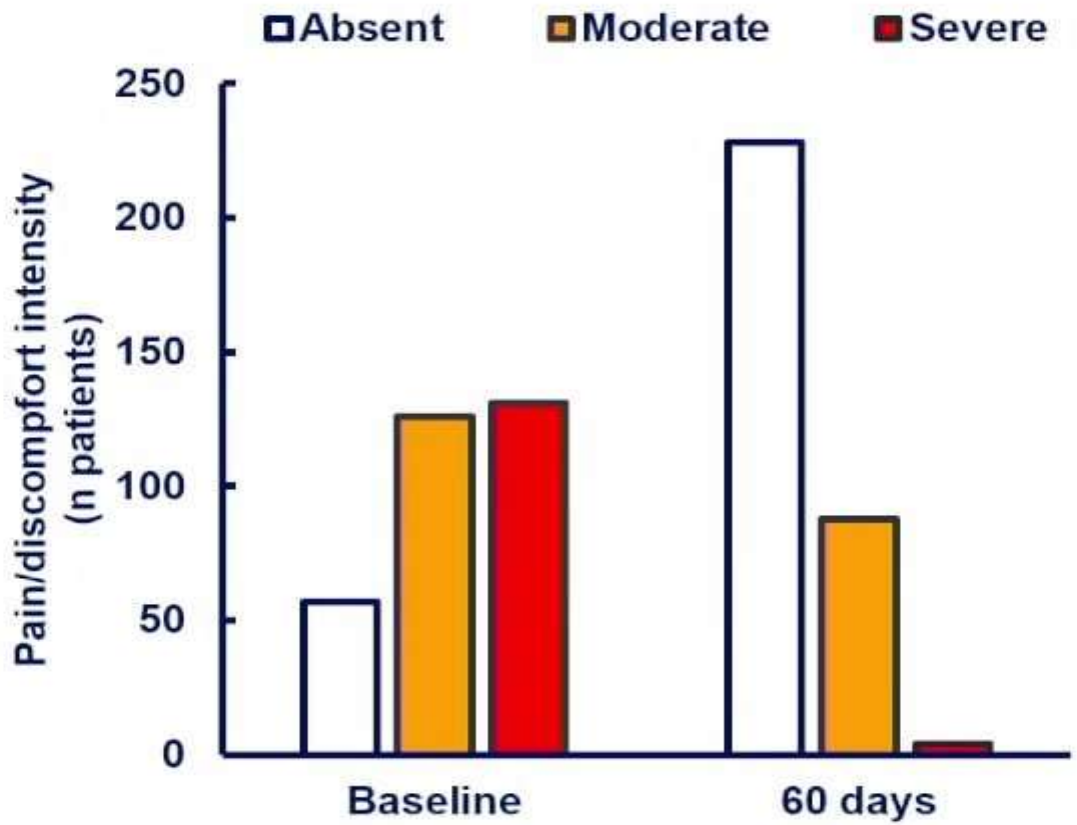


Tack et al., 2005

FUNCTIONAL DYSPEPSIA
Management of refractory pain

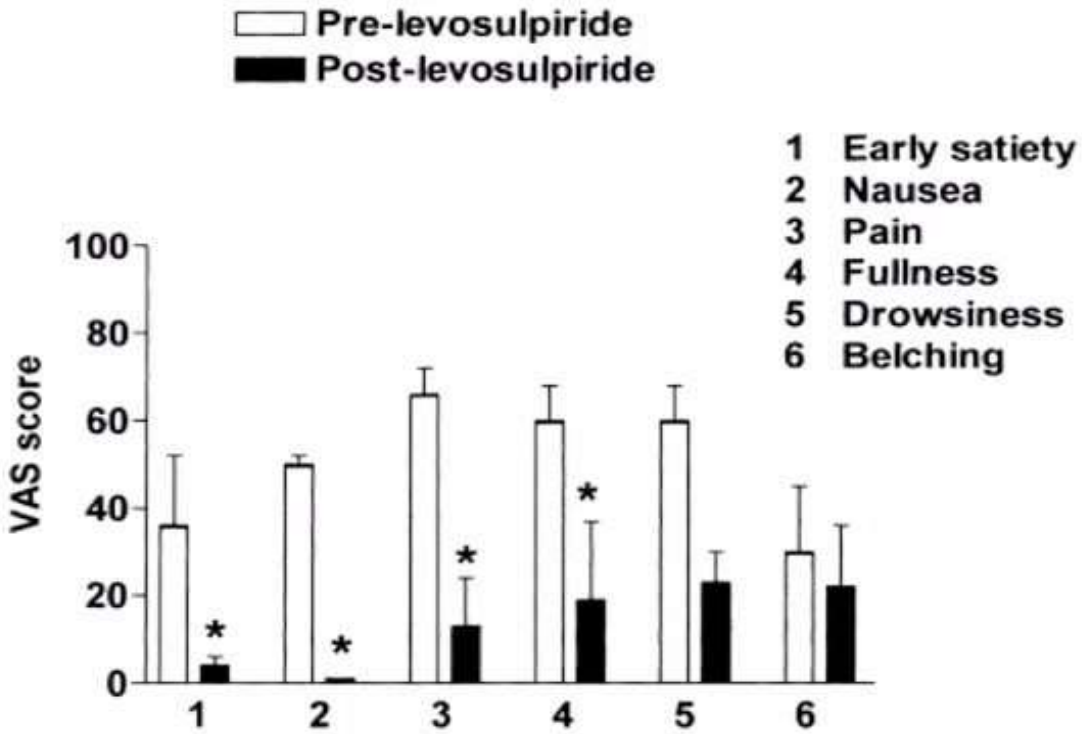


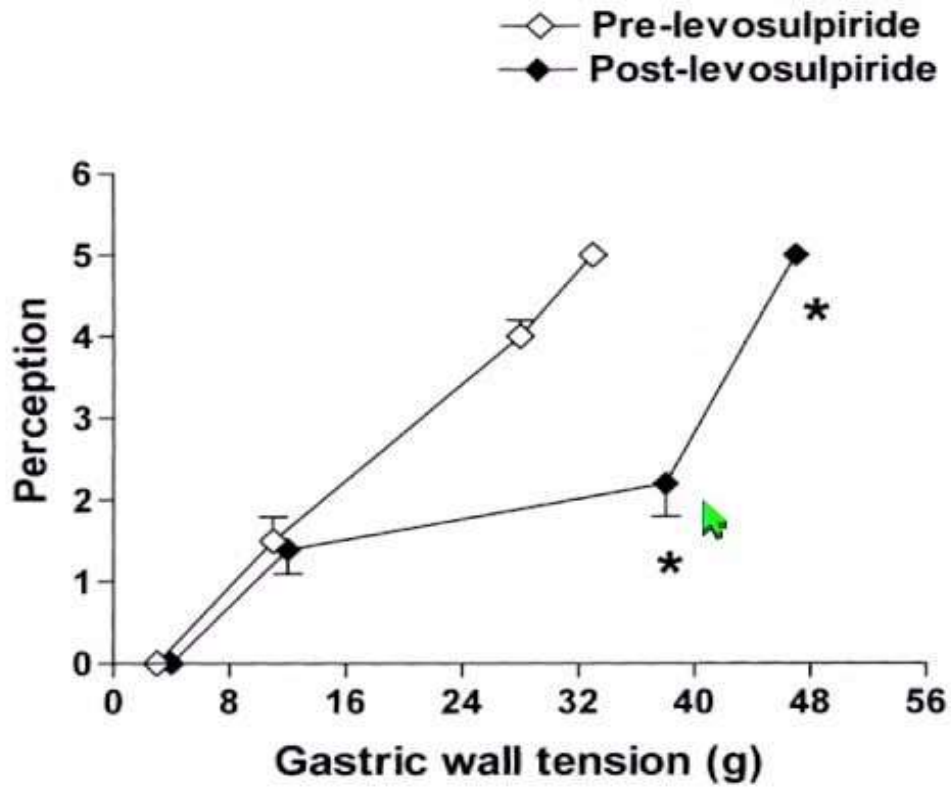
FUNCTIONAL DYSPEPSIA
Management of refractory pain: levosulpiride



Lozano et al., Ther Clin Risk Mgmt 2007

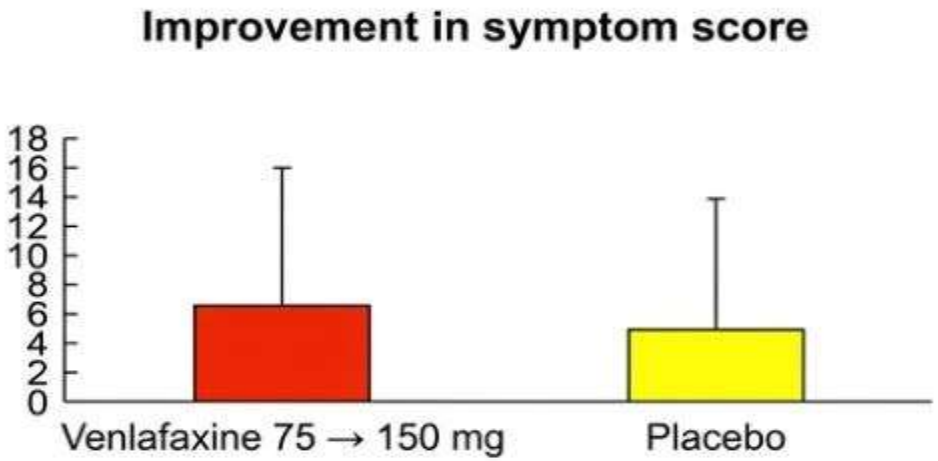
FUNCTIONAL DYSPEPSIA
Management of refractory pain: levosulpiride

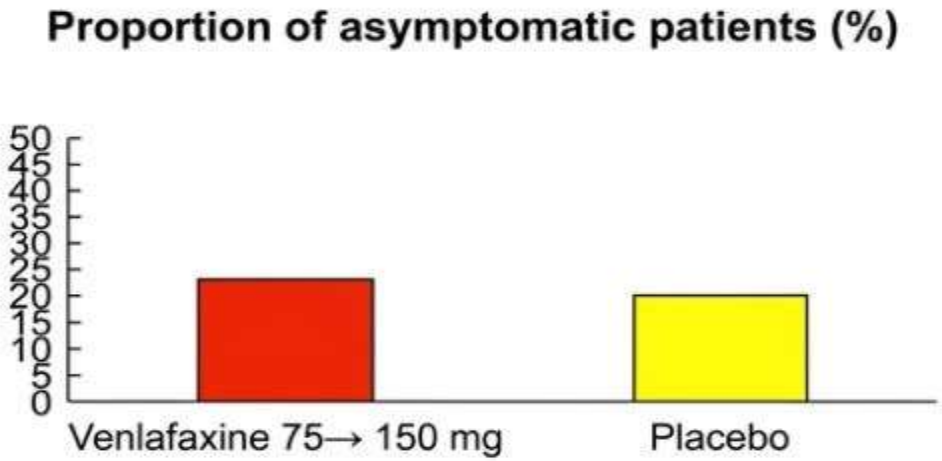




Distrutti et al., AP&T 2002

FUNCTIONAL DYSPEPSIA
Venlafaxine in functional dyspepsia



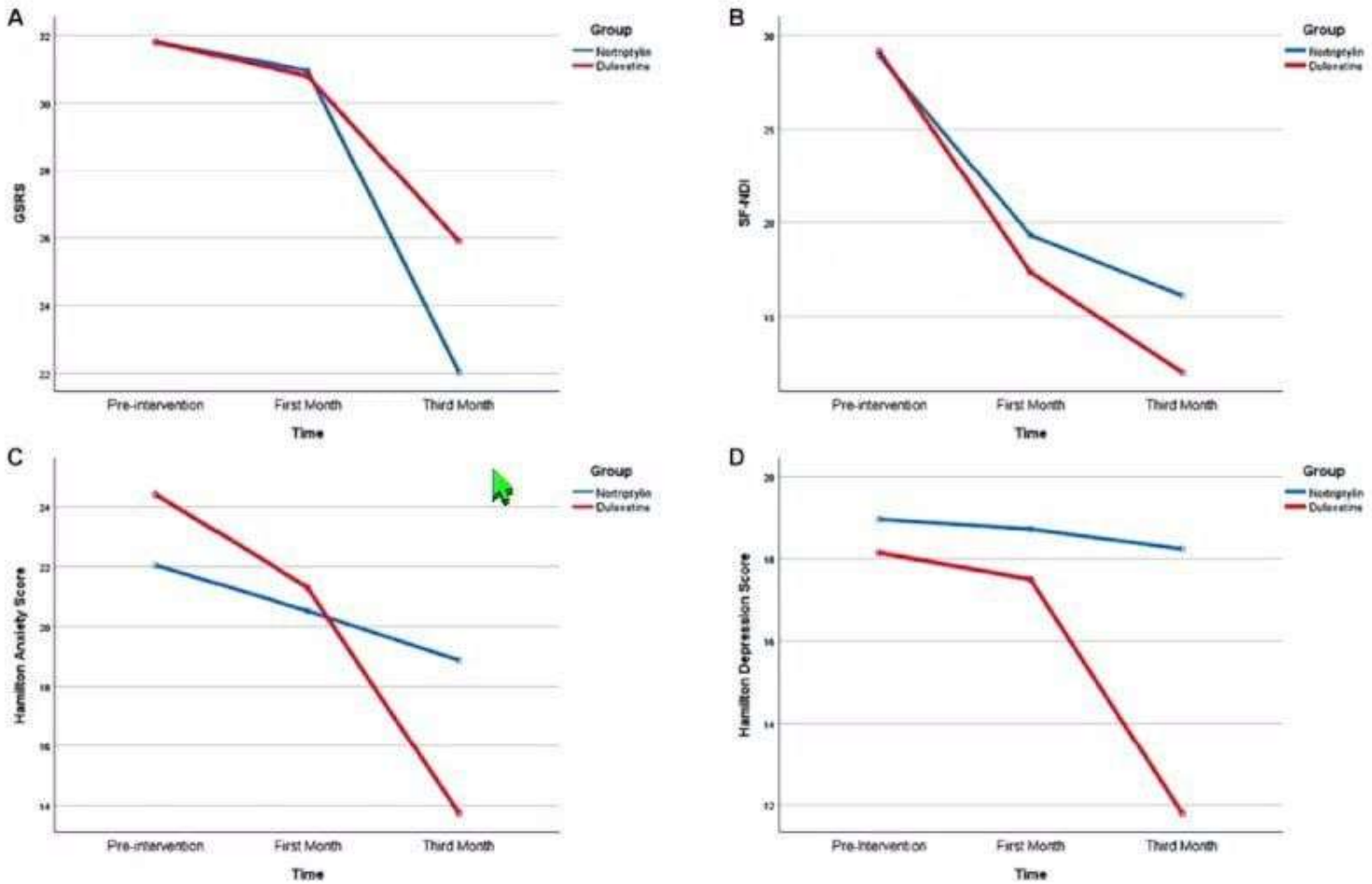


n = 160
8 weeks treatment
Completion 59% and 74% resp.
Per protocol 43% and 37% symptomfree (NS)

Van Kerkhoven et al., 2008

FUNCTIONAL DYSPEPSIA
Management of refractory pain: duloxetine

45 FD patients
Duloxetine 20-30 mg
Nortryptiline 25 mg



Banihashem et al., Front. Psych 2024

FUNCTIONAL DYSPEPSIA
Management of refractory pain: Gabapentin open label

TABLE 3. Proportion of Gabapentin Responders Based on PAGI-SYM Significant Clinical Difference Threshold

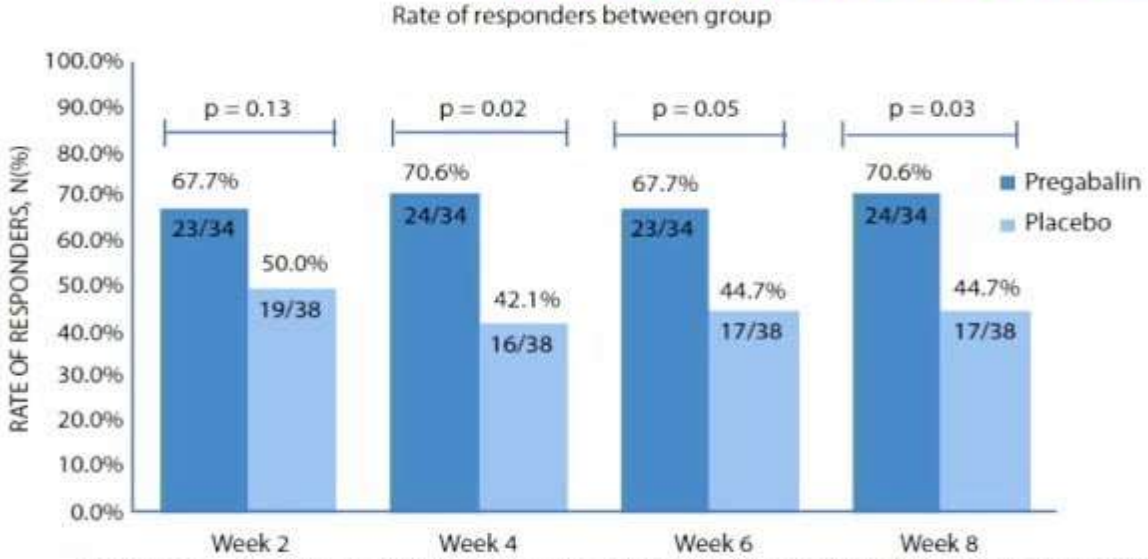
PAGI-SYM Scale	Group [n (%
Overall score	32 (51.6)
Postprandial fullness	38 (61.3)
Upper abdominal pain	37 (60.0)
Nausea/vomiting	32 (51.6)
Lower abdominal pain	30 (48.4)
Heartburn	30 (48.4)
Bloating	13 (21.0)

PAGI-SYM indicates Patient Assessment of Gastrointestinal Disorders Symptom Severity Index.

62 patients
On average 1000 mg/day

Staller et al., JCG 2019

FUNCTIONAL DYSPEPSIA
Management of refractory pain: pregabalin



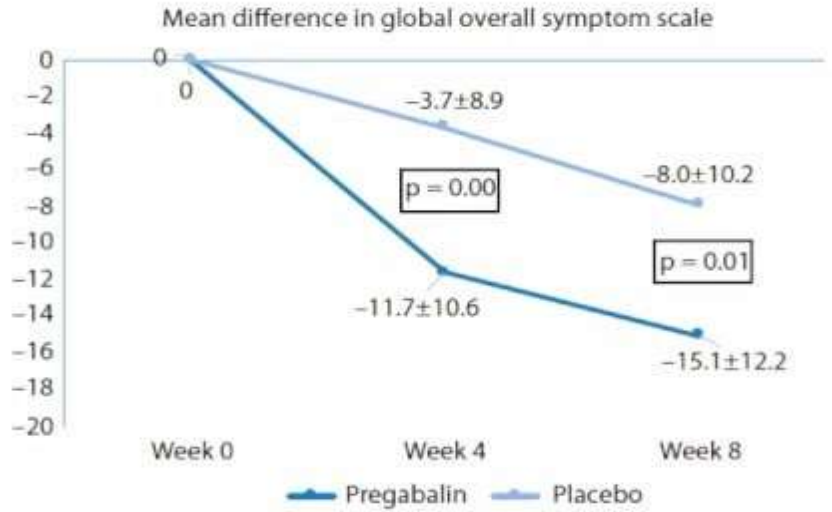


TABLE 2 Secondary outcome showing 7-point Global Overall Symptom scale between groups, mean ± SD

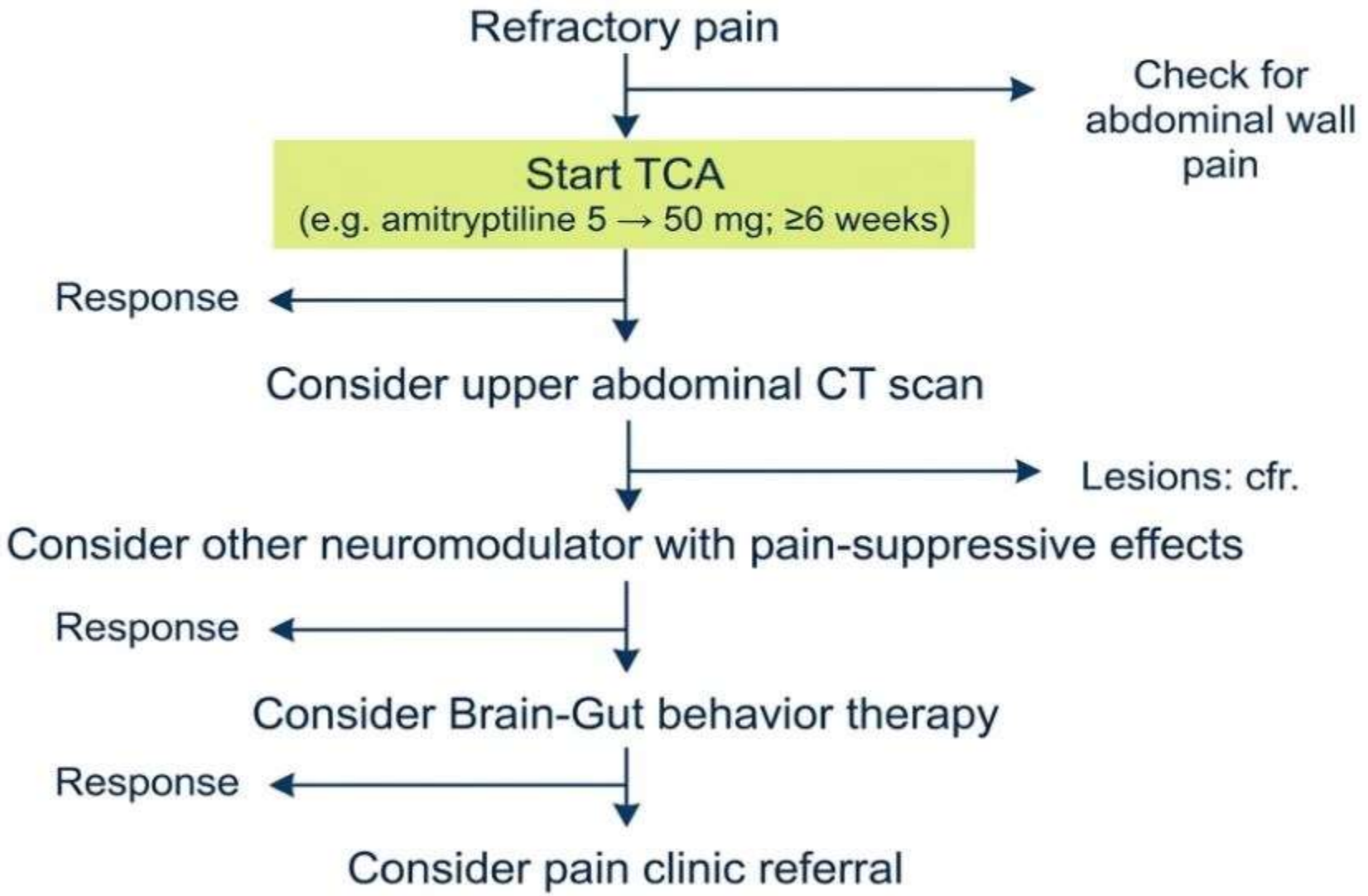
Modalities	Pregabalin (N = 31)			Placebo (N = 34)			P-value
	Week 0	Week 4	Change	Week 0	Week 4	Change	
Total scores	33.3 ± 10.9	21.6 ± 8.8	−11.7 ± 10.6	30.0 ± 6.7	26.3 ± 10.0	−3.7 ± 8.9	0.00[a]
Epigastric pain	4.7 ± 2.0	3.0 ± 1.5	−1.7 ± 2.0	4.3 ± 1.7	4.0 ± 2.0	−0.3 ± 2.0	0.01[a]
Epigastric burning	4.4 ± 2.2	3.0 ± 1.6	−1.4 ± 1.9	3.6 ± 1.9	3.4 ± 2.2	−0.2 ± 2.1	0.03[a]
Sensation of reflux of gastric acid	3.9 ± 2.5	2.3 ± 1.3	−1.7 ± 2.1	3.0 ± 1.8	3.0 ± 1. 8	0.1 ± 2.1	0.00[b]
Postprandial fullness	4.5 ± 2.2	2.9 ± 1.6	−1.6 ± 2.4	4.4 ± 1.7	3.6 ± 1.8	−0.8 ± 1.5	0.08[a]
Early satiety	3.9 ± 2.2	2.7 ± 1. 9	−1.3 ± 2.2	3.6 ± 1.9	2.9 ± 1.6	−0.7 ± 1.8	0.22[a]
Nausea	2.3 ± 2.0	1.4 ± 1.0	−0.9 ± 2.1	2.0 ± 1.2	1.6 ± 1.3	−0.4 ± 1.5	0.95[b]
Abdominal bloating	4.0 ± 2.0	2.7 ± 1.4	−1.4 ± 2.0	4.0 ± 1.8	3.1 ± 1.5	−0.9 ± 1.9	0.32[a]

72 patients
Pregabalin 75 mg once daily

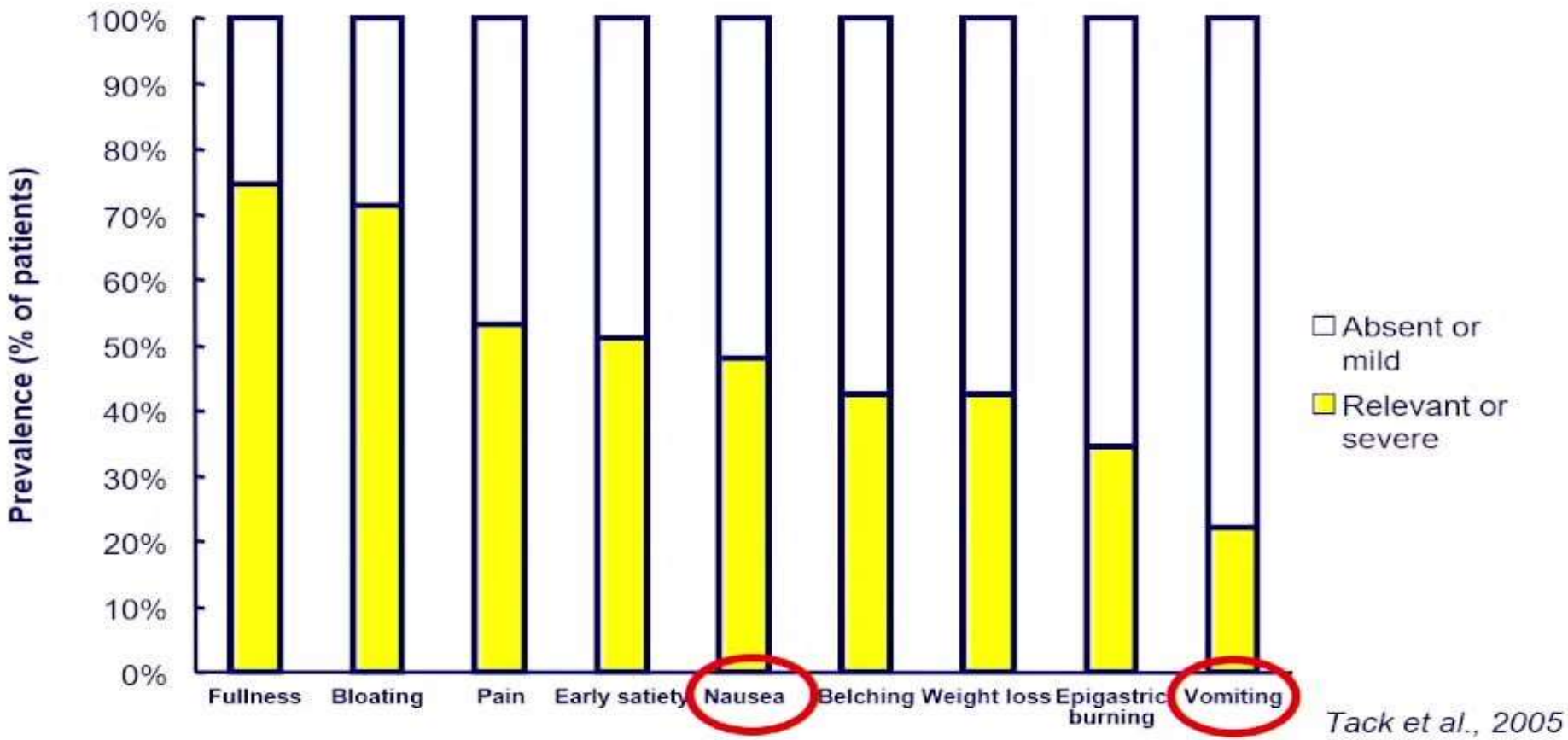
Kotikula et al., AP&T 2021

FUNCTIONAL DYSPEPSIA

Management of refractory pain

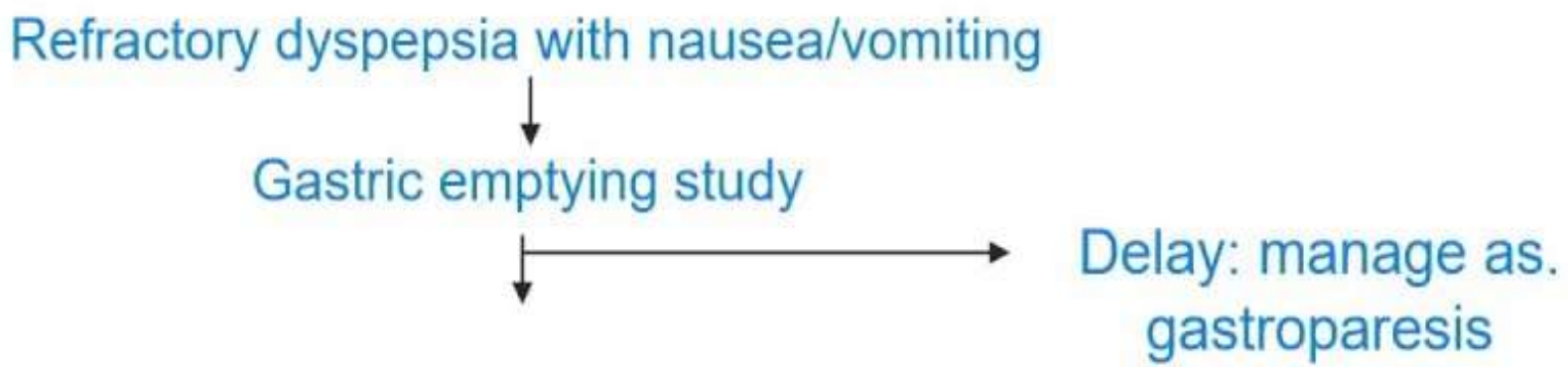


FUNCTIONAL DYSPEPSIA
Symptom pattern in 700 patients



Tack et al., 2005

FUNCTIONAL DYSPEPSIA
Management of nausea / vomiting



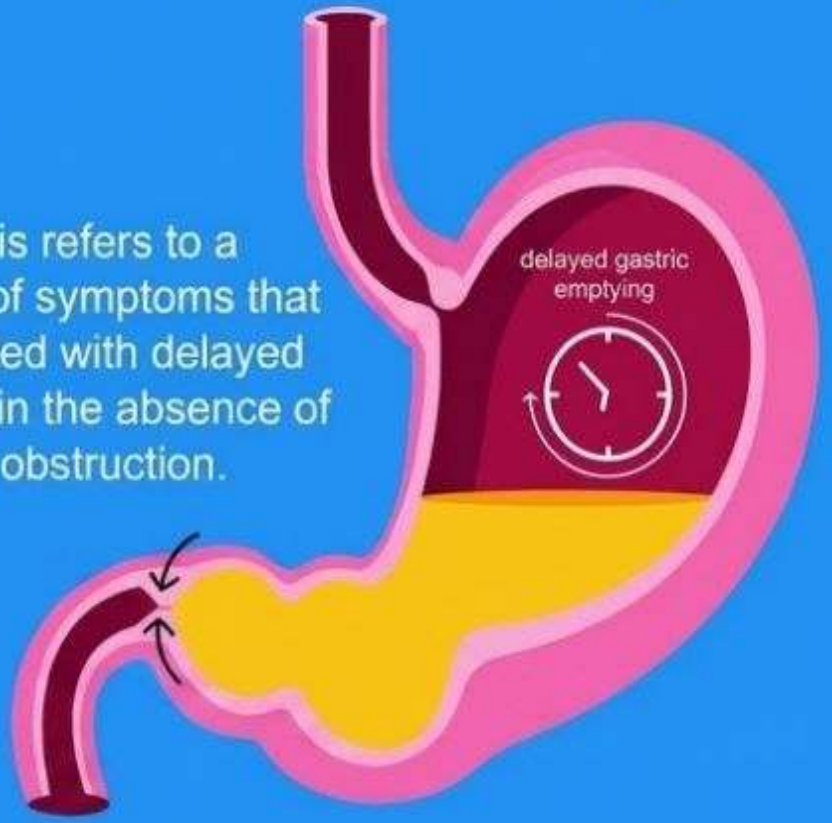
GASTRIC MOTILITY DISORDERS
Gastroparesis

European Society for Neurogastroenterology and Motility (ESNM) consensus on Gastroparesis

Risk factors:
- Diabetes
- Drugs
- Neurological disorders
- Connective tissue disorders
- Surgeries

Symptoms:
- Chronic nausea
- Vomiting
- Postprandial Distress Syndrome symptoms
  (Early satiation, Postprandial fullness)

Gastroparesis refers to a symptom or set of symptoms that is (are) associated with delayed gastric emptying in the absence of mechanical obstruction.



Diagnosis:
- Endoscopy
- Gastric emptying test

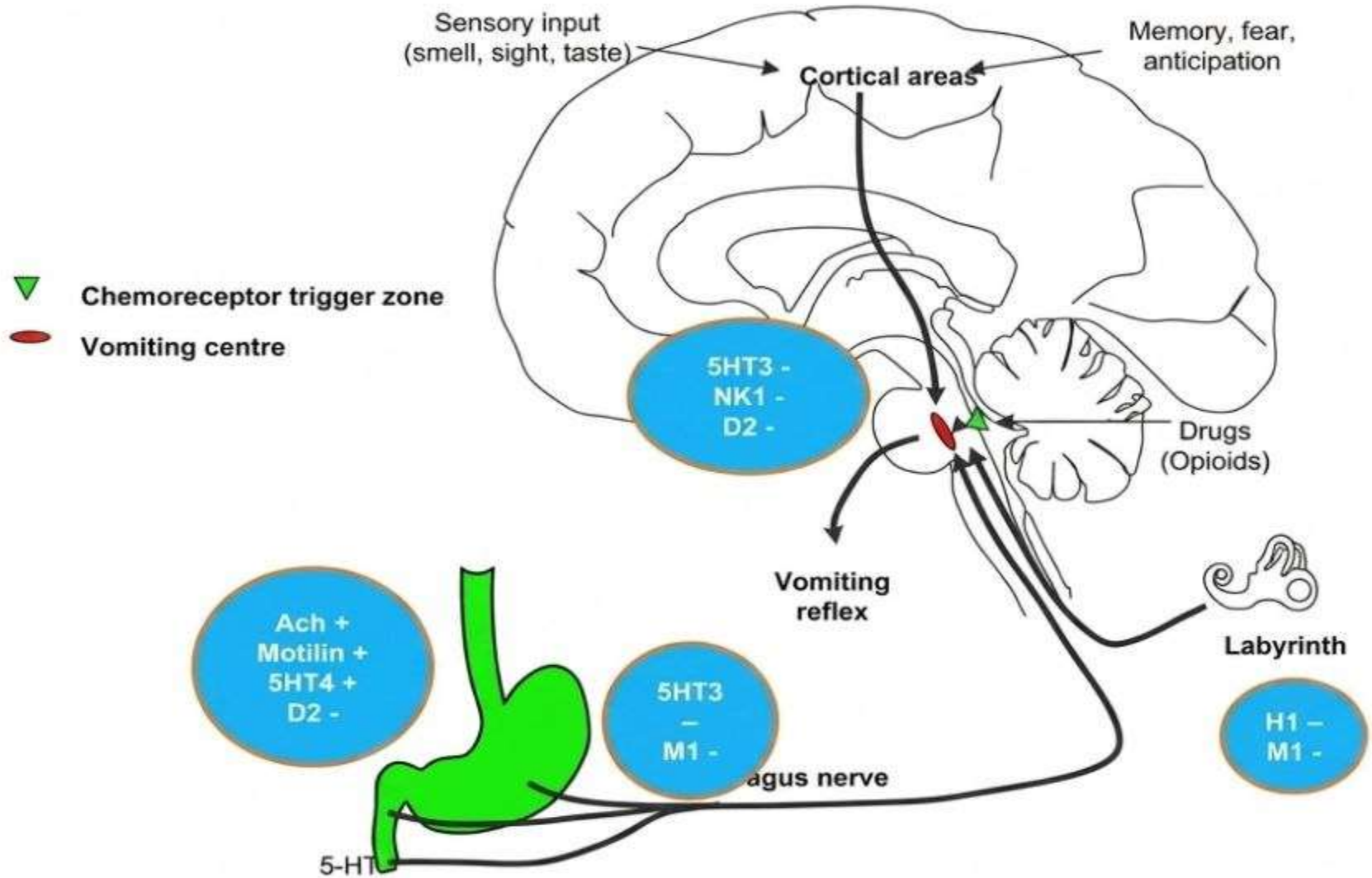
Treatment:
- Dietary therapy
- Dopamine-2 antagonists
- 5-HT4 receptor agonists
- Nutritional support

40 experts from 19 European countries.

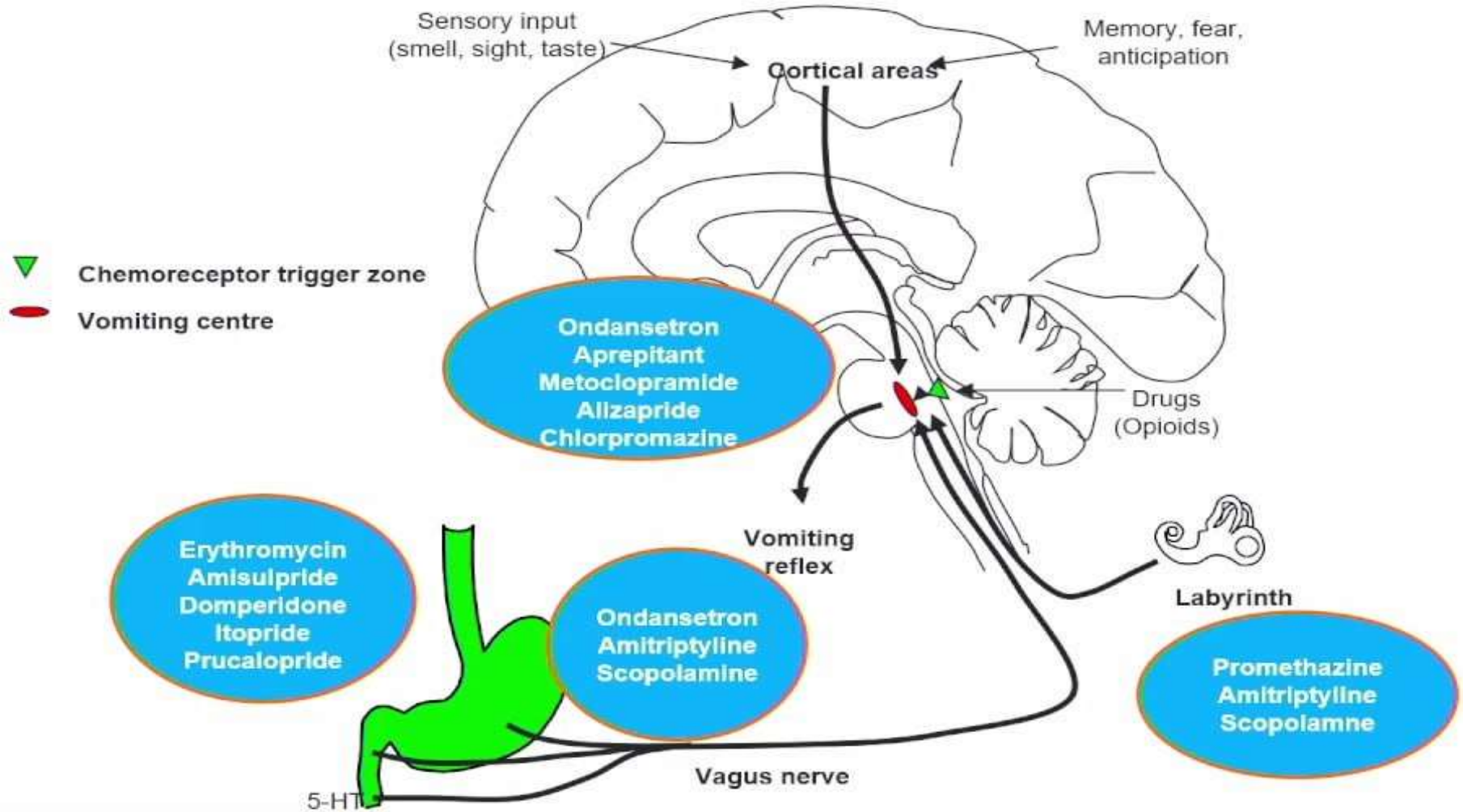
Consensus (defined as ≥80% agreement) was reached for 25 statements.

United European Gastroenterology Journal. Feb 2021.

NAUSEA AND VOMITING
Pathophysiology

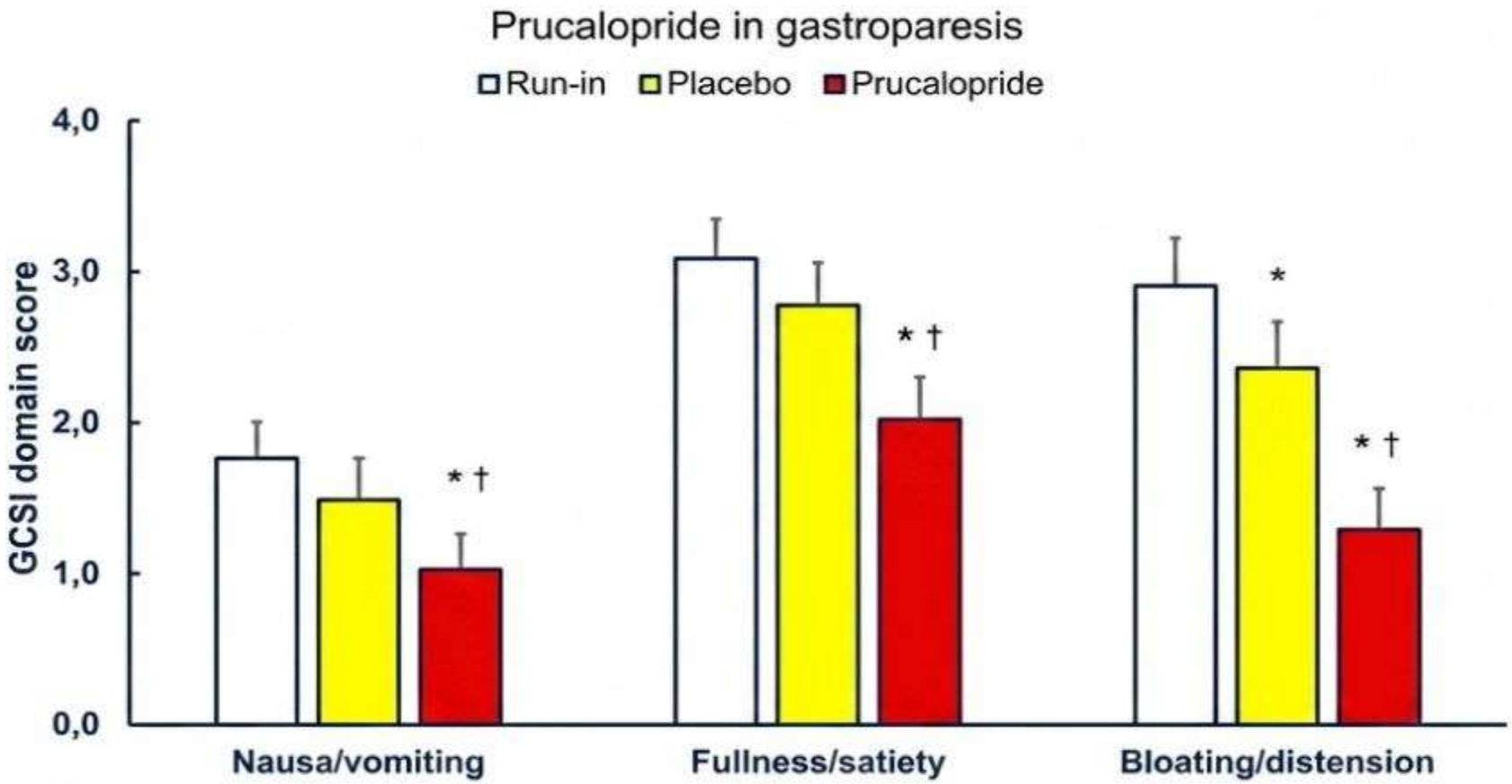


NAUSEA AND VOMITING
Management options



ueg.eu

PRUCALOPRIDE IN FD WITH DELAYED EMPTYING: GCSI domain scores



* p<0.05 compared to run-in
† p<0.05 compared to placebo

Table 1. Differential Diagnosis of Symptoms Associated with Functional Dyspepsia.

Symptoms and Other Potential Causes	Relevant Symptoms	Tests to Rule Out Other Causes
Early satiety (fullness)		
Gastric cancer	Unexplained weight loss; chronic untreated *Heliobacter pylori* infection; age >60 yr; risk factors related to geographic location, ethnic group, and others	Upper endoscopy
Gastroparesis	Recurrent or frequent vomiting or severe nausea	Gastric emptying test
Epigastric pain		
Peptic ulcer	*H. pylori* infection, use of nonsteroidal antiinflammatory medication	Upper endoscopy
Gallstone disease	Crescendo–decrescendo episodic pain lasting ≥30 min, often severe	Ultrasound of the gallbladder and bile ducts
Anterior cutaneous nerve entrapment syndrome or chronic abdominal-wall pain	Point tenderness	Carnett's sign (pressure on the point of tenderness before and after the patient tenses the abdominal wall reveals increased tenderness on tensing)
Chronic pancreatitis	Risk factors (e.g., alcohol use, genetic predisposition), steatorrhea	Pancreatic imaging
Epigastric burning		
Gastroesophageal reflux	Heartburn, regurgitation	Upper endoscopy, pH testing
Bloating		
Celiac disease	Family history, diarrhea, unexplained iron deficiency	Celiac serologic testing
Small intestinal bacterial overgrowth	Long-term use of proton-pump inhibitor, dysmotility of the small intestines	Breath test, duodenal aspirate for bacteria, empirical treatment with antibiotics

Table 2. Clinical Features Prompting Further Evaluation.*

Evidence of gastrointestinal bleeding (e.g., hematemesis, melena, and bright-red blood from the rectum)
New-onset symptoms in patients 60 years of age or older (in the United States)
Iron-deficiency anemia
Unexplained weight loss (>10% of body weight)
Progressive dysphagia or odynophagia
Persistent vomiting
Long-term use of aspirin or nonsteroidal antiinflammatory drugs
Strong family history of gastrointestinal cancer (especially esophagogastric)
History of upper gastrointestinal cancer
Lymphadenopathy or abdominal mass

* These symptoms and features may indicate a higher risk of peptic-ulcer disease or upper gastrointestinal cancer,[26] prompting further evaluation with esophagogastroduodenoscopy.

Table 3. Treatments to Consider in Functional Dyspepsia.*

Drug Class	Pathophysiological Target	Examples	Relative Strength of Evidence
Acid suppressants	Acid-induced reflexes triggered by enteric and sensory neurons	Proton-pump inhibitor, H2RA	Symptom abatement with standard dose of PPI: relative risk of no improvement, 0.86 (95% CI, 0.78 to 0.95)[27] Symptom abatement with H2RA: relative risk of no improvement, 0.81 (95% CI, 0.73 to 0.90)[28]
Neuromodulators	Increased or aberrant signaling by afferent neurons to the CNS	Tricyclic antidepressants, duloxetine, mirtazapine, pregabalin, gabapentin	Symptom abatement with low-dose tricyclic antidepressant: relative risk of no improvement, 0.75 (95% CI, 0.62 to 0.90)[27] No placebo-controlled trials of duloxetine; not as efficacious as nortriptyline for functional dyspepsia symptoms but better with regard to anxiety, depression, and quality of life[30] Pregabalin: relative risk of no improvement with pregabalin, 0.53 (95% CI, 0.29 to 0.96)[31]
Motility agents†	Delayed gastric emptying, decreased gastric accommodation	Metoclopramide, domperidone, prucalopride, buspirone	Controlled trials of metoclopramide, domperidone, and prucalopride are lacking; buspirone (three small trials of 4-wk duration) led to nonsignificant improvement in functional dyspepsia and gastroparesis symptoms vs. placebo (standardized mean difference, −0.14; 95% CI, −0.44 to 0.17; P=0.39); with regard to individual symptoms, buspirone reduced only the severity of bloating more than placebo[32]
Th2 response modulators	Eosinophil and mast-cell activation	Montelukast, mast-cell antagonists (H1RA, H2RA, ketotifen)	Evidence limited to children only[32]; no evidence for mast-cell antagonists
Agents affecting the microbiota	Dysbiosis	*Bacillus coagulans* and *B. subtilis* combination, rifaximin	Limited evidence: single trials, small numbers, and short-term results
Over-the-counter remedies	Miscellaneous	Peppermint-oil preparations	Limited evidence: few trials, small numbers, and short-term results

* CNS denotes central nervous system, H1RA histamine H_1–receptor antagonist, H2RA histamine H_2–receptor antagonist, and Th2 type 2 helper T.
† Shown are agents that are available in the United States.

Table 4. Professional Society Guidelines and Consensus Statements on Approaches to Patients with Symptoms of Functional Dyspepsia.*

Group	*H. pylori* Testing	Prompt EGD	PPIs	Tricyclic Antidepressant Agents	Prokinetic Agents	Psychological Therapy	Complementary or Alternative Medicine
ACG and CAG[42]	Test all patients and treat	Patients >60 yr of age or who have symptoms that arouse concern	First-line therapy	Second-line therapy	Third-line therapy	In the case of failure of medical treatment	Not recommended
UEG and ESNM[49]	Test all patients and treat	Mandatory for diagnosis but can be deferred in primary care in absence of alarm features	Endorsed	No consensus	No consensus	No consensus	No consensus
BSG[27]	Test all patients and treat	Reserved for patients with risk factors	First-line therapy	Second-line therapy	Recommended drugs not available in the United States	In the case of failure of medical treatment or for other considerations (e.g., weight loss)	No statement

* ACG denotes American College of Gastroenterology, BSG British Society of Gastroenterology, CAG Canadian Association of Gastroenterology, EGD esophagogastroduodenoscopy, ESNM European Society of Neurogastroenterology, PPI proton-pump inhibitor, and UEG United European Gastroenterology.

THANK YOU