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7th EMIRATES FAMILY MEDICINE SOCIETY CONGRESS 2024

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DUBAI WORLD TRADE CENTRE

Untangling the Overlap of Fuunctional GI Disorders

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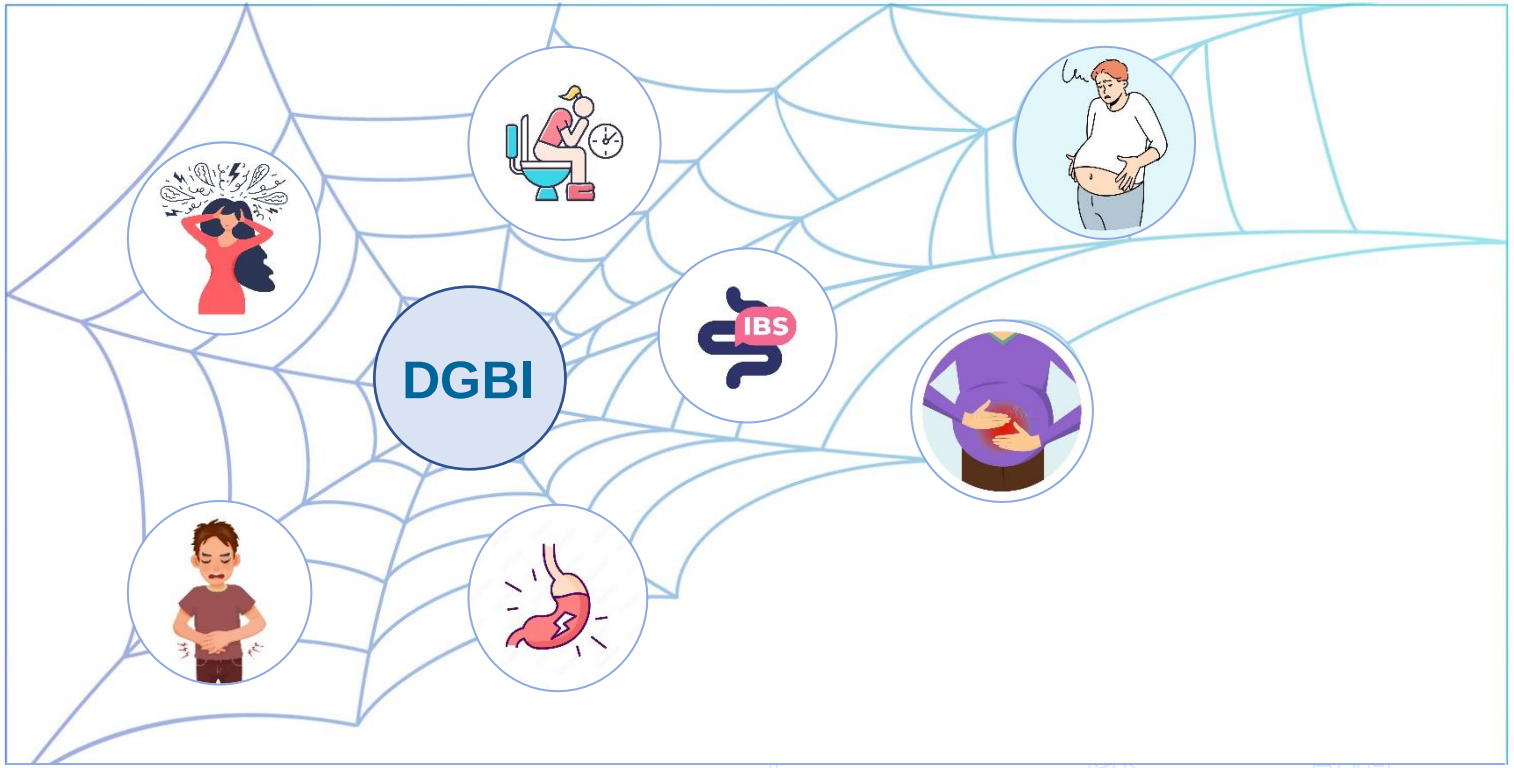
Untangling the Web of Disorders of Gut-Brain Interactions



Disorders of Gut-Brain Interactions

B. GASTRODUODENAL DISORDERS

B1. FUNCTIONAL DYSPEPSIA*

*Diagnostic criteria***

1. One or more of the following:
   a. Bothersome postprandial fullness
   b. Bothersome early satiation
   c. Bothersome epigastric pain
   d. Bothersome epigastric burning
   AND
2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

*Must fulfill criteria for B1a. PDS and/or B1b. EPS

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

C. BOWEL DISORDERS

C1. IRRITABLE BOWEL SYNDROME

*Diagnostic criteria**

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria:

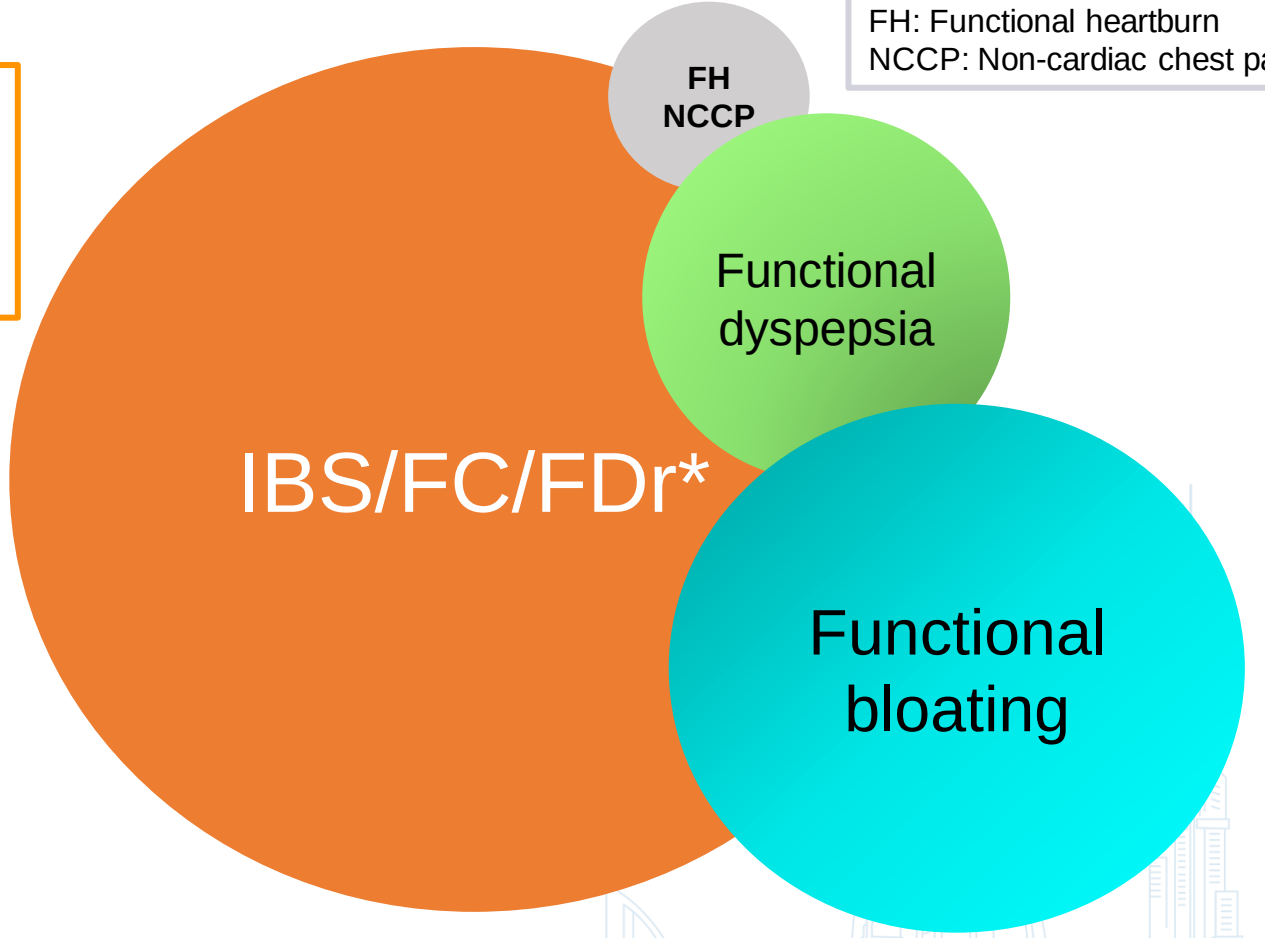
1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

The World of Disorders of Gut-Brain Interactions

FC: Functional constipation
FDr: Functional diarrhea
IBS-C: IBS with predominant constipation
IBS-D: IBS with predominant diarrhea
IBS-M: IBS with mixed bowel habits
IBS-U: IBS unclassified

FH: Functional heartburn
NCCP: Non-cardiac chest pain



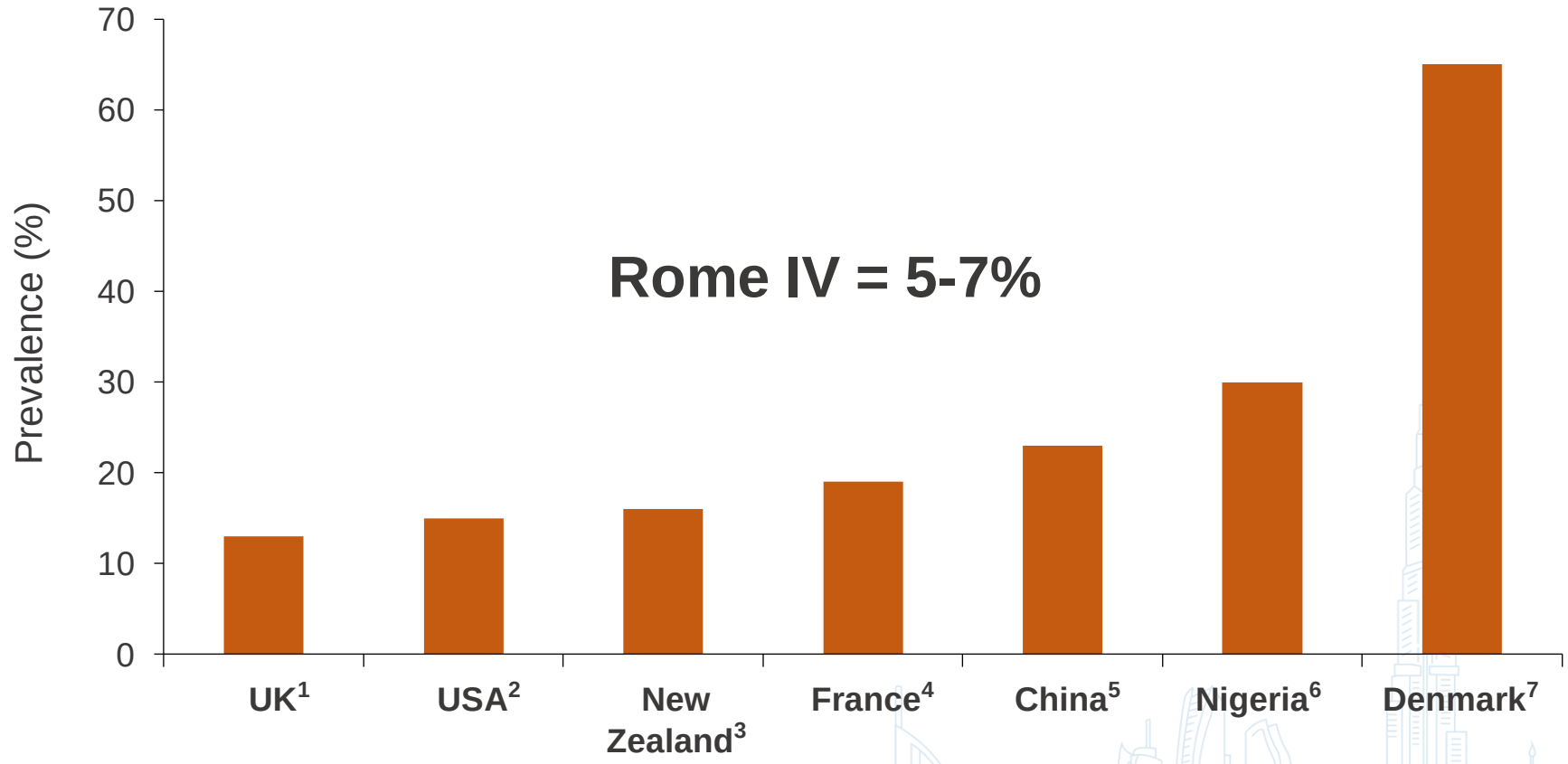
Biopsychosocial disorders

Overlap of Rome IV Irritable Bowel Syndrome and Functional Dyspepsia

- Overlap of FD with IBS is common (20%-55%)
- Those with overlap of IBS and FD report significantly more severe IBS symptoms, continuous abdominal pain, and lower QoL
- They have higher levels of somatization and are more likely to have anxiety and depression

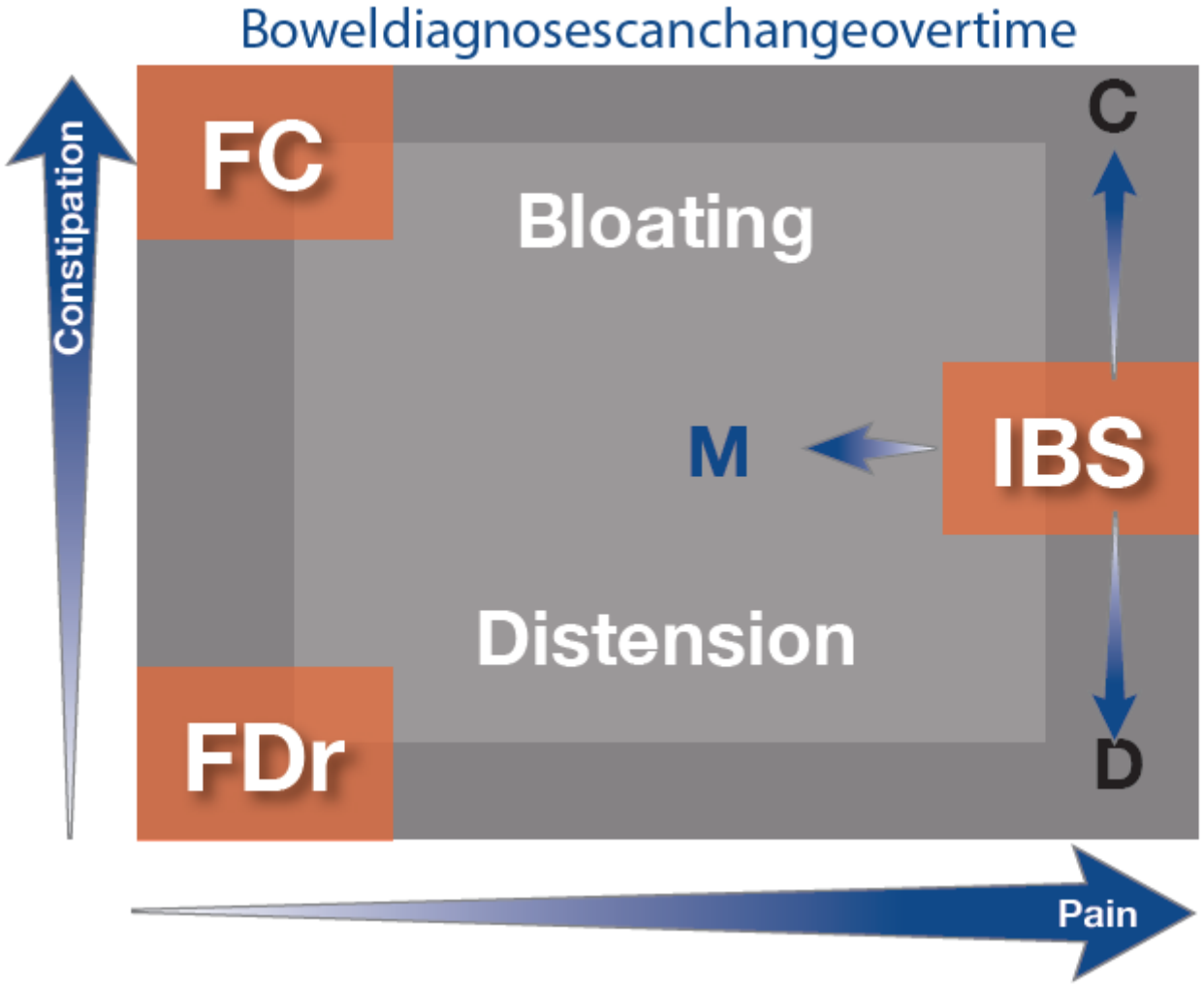
Barberio B, et al. Clin Gastroenterol Hepatol 2022;20:e89–e101.

Worldwide Prevalence of IBS



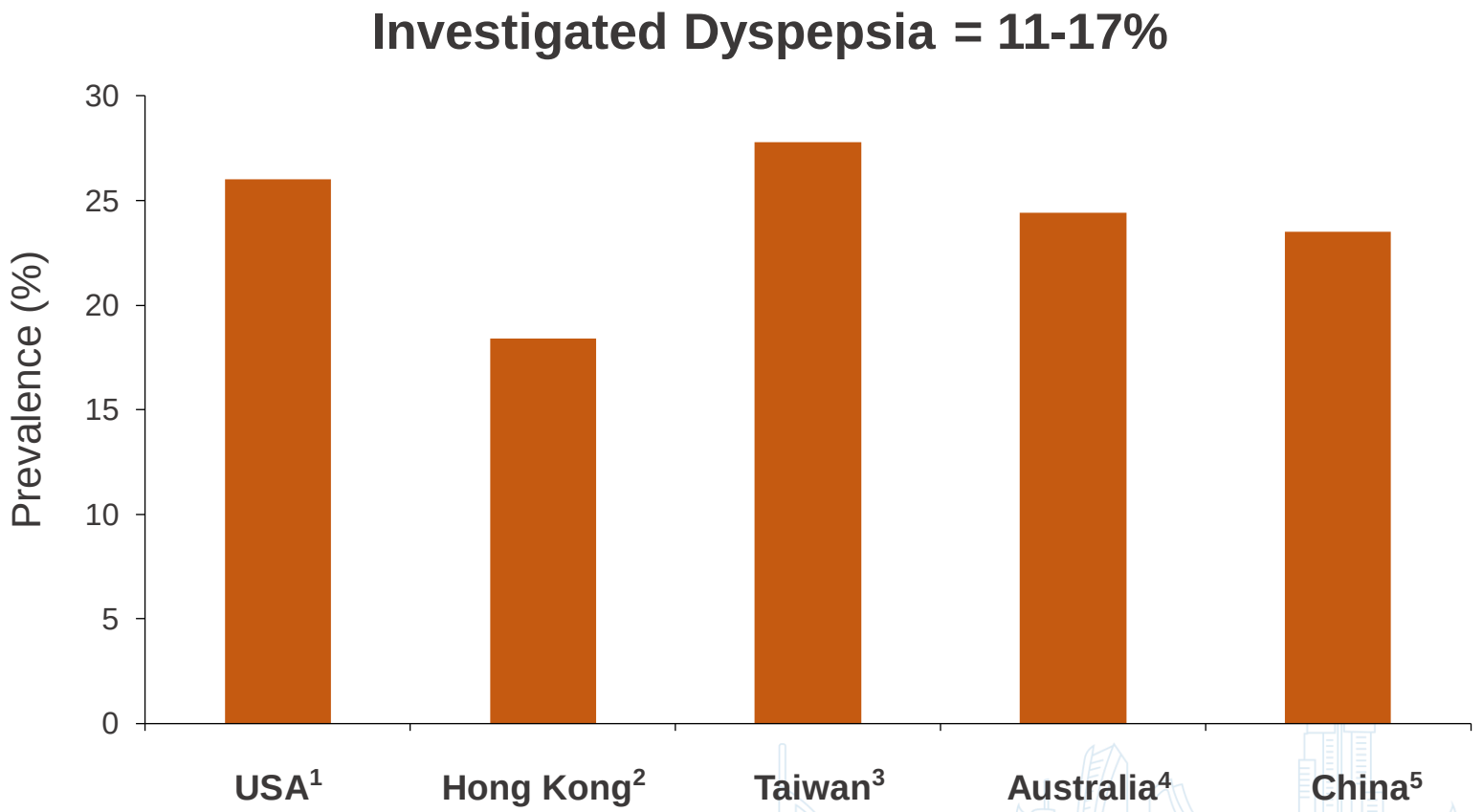
[1]Heaton K et al. 1992; [2]Longstreth G, Wolde-Tsadnik P 1993; [3]Welch G, Pomare W 1990; [4]Bommalaer G et al. 1986
[5]Bi-zhen W, Qi-Ying P 1988; [6]Olubuyide O et al. 1995; [7]Kay L et al. 1994; EB Andrews et al. 2005

Classification of IBS



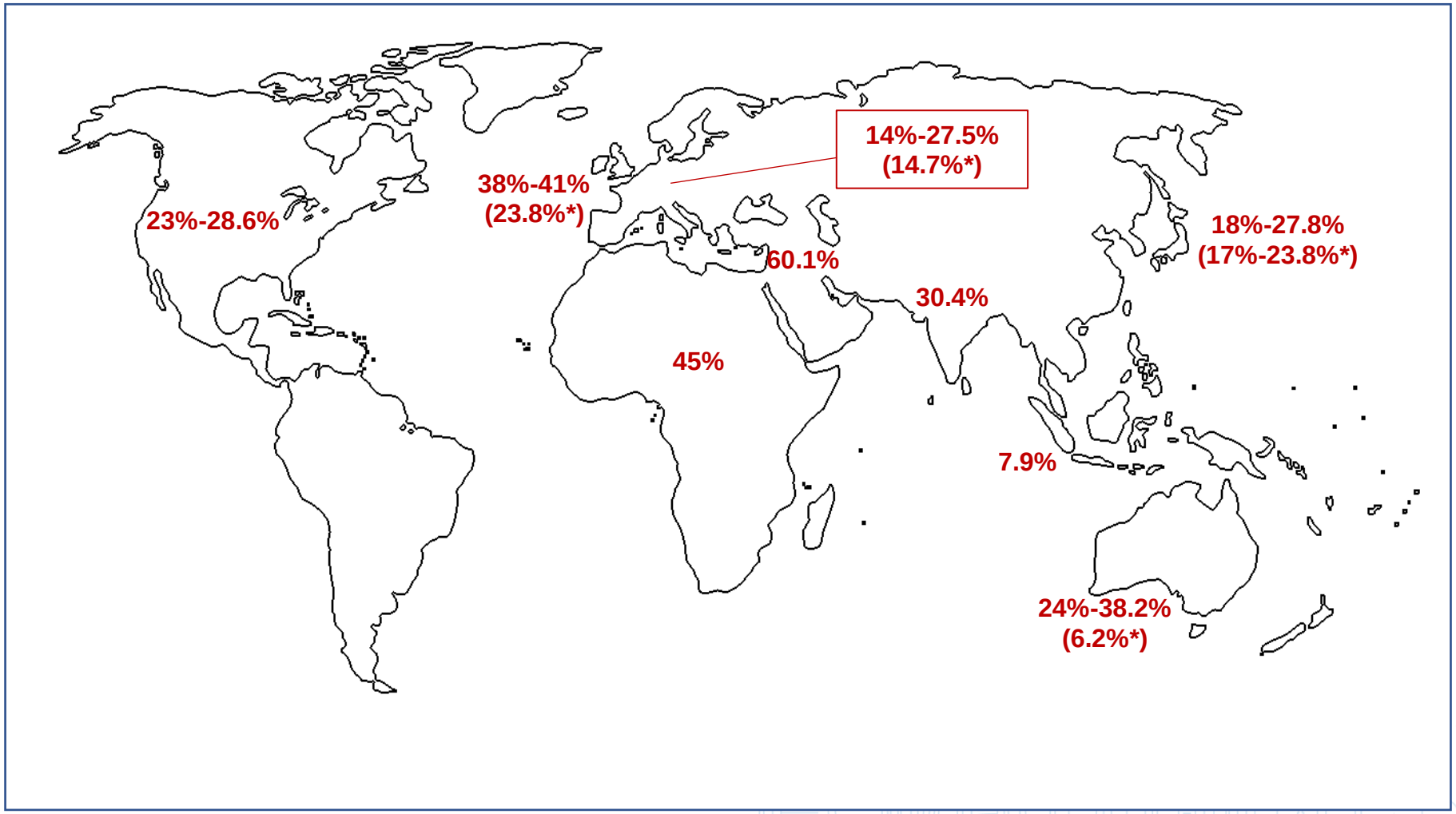
FC: Functional constipation
FDr: Functional diarrhea
IBS-C: IBS with predominant constipation
IBS-D: IBS with predominant diarrhea
IBS-M: IBS with mixed bowel habits
IBS-U: IBS unclassified

Worldwide Prevalence of Dyspepsia



[1]Drossman DA, et al. 1993; [2]Hu WH, et al. 2002; [3]Lu CL, et al. 2005 [4]Westbrook JI, et al. 2002; [5]Li Y, P et al. 2002

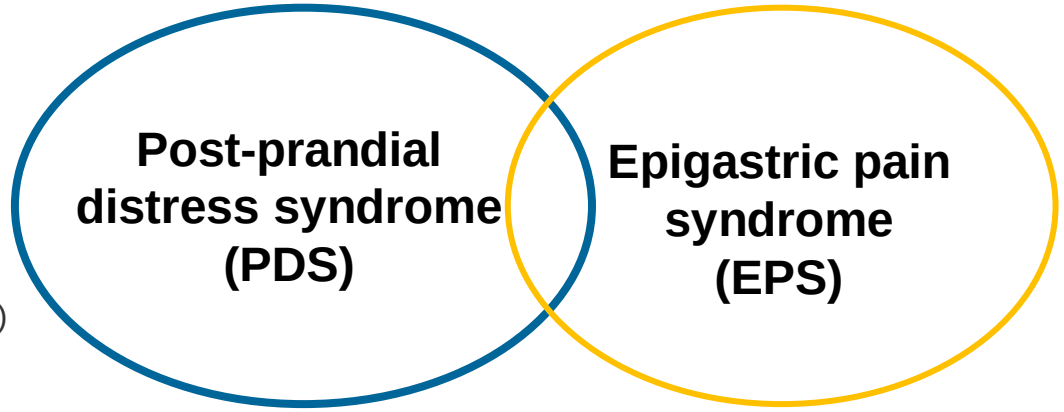
Global Prevalence of Uninvestigated and Functional Dyspepsia*



Modified from Mahadeva S, Goh KL. *World J Gastroenterol* 2006; 12:2661-2666.

Subtypes of Functional Dyspepsia

Diagnostic criteria - Must include **one or both** of the following at least 3 days a week:*
1. Bothersome **postprandial fullness** (i.e., severe enough to impact on usual activities)
2. Bothersome **early satiation** (i.e., severe enough to prevent finishing a regular size meal)

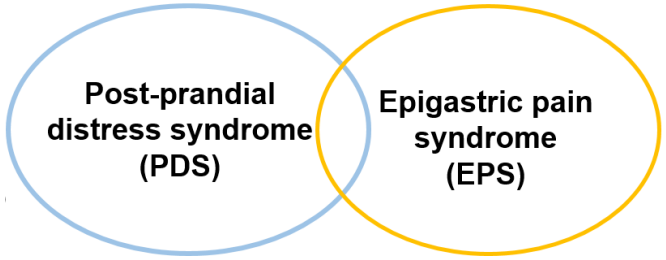


Diagnostic criteria* - Must include one or both of the following symptoms at least 1 day a week:
1. Bothersome epigastric **pain** (i.e., severe enough to impact on usual activities)
2. Bothersome epigastric **burning** (i.e., severe enough to impact on usual activities)

Poorly defined with significant overlap (5-30%)

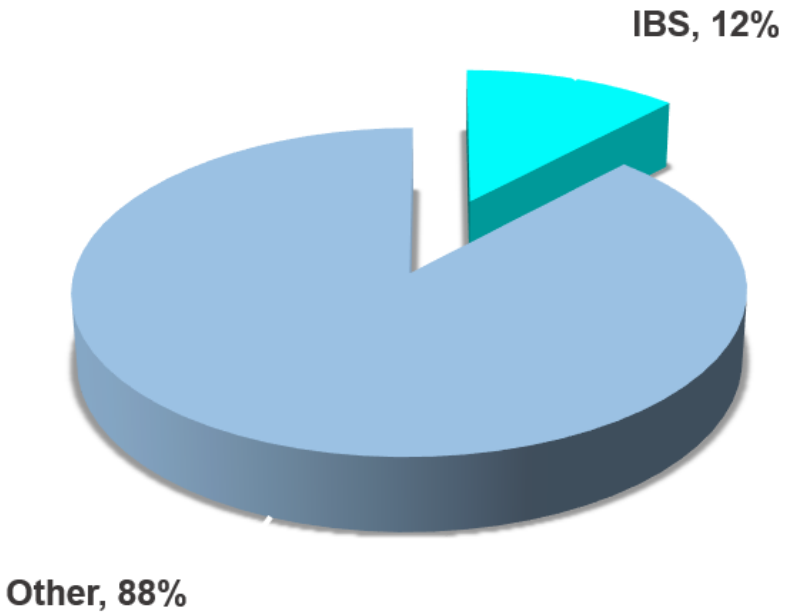
The Kalixanda Study

- Prevalence of FD **15.7%** (PDS 12.2%; EPS 5.2%; overlap 1.7%)
- Major anxiety associated with:
  - uninvestigated dyspepsia (OR 3.01, 95% CI 1.39-6.54)
  - Functional dyspepsia (OR 2.56, 95% CI 1.06-6.19)
  - PDS FD (OR 4.35, 95% CI 1.81-10.46)
- Depression was not associated with any FD group

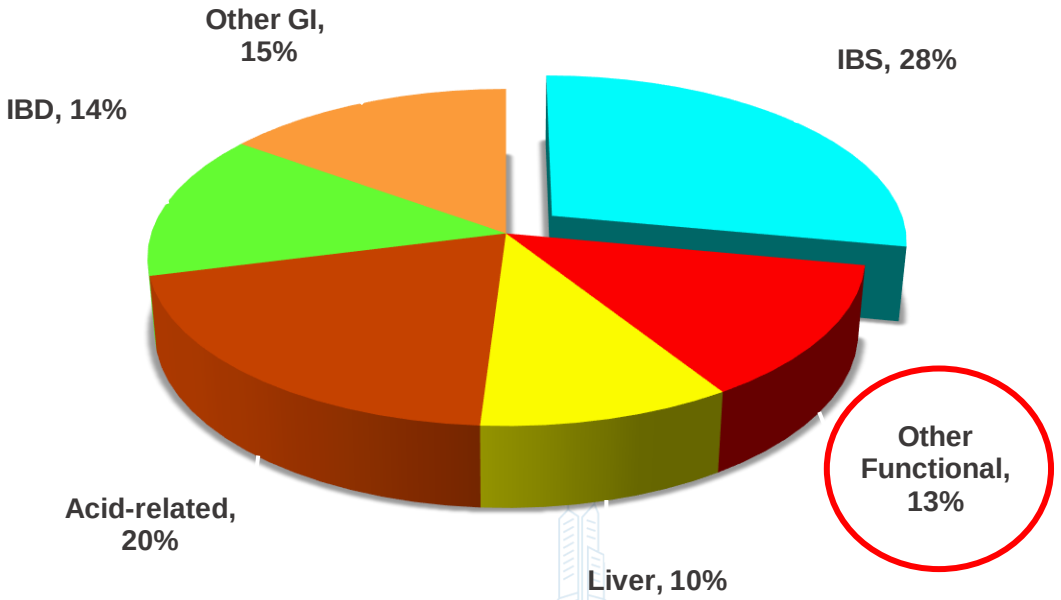


Aro P, et al. *Gastroenterology* 2009;137:94-100.

Prevalence of Diagnosis



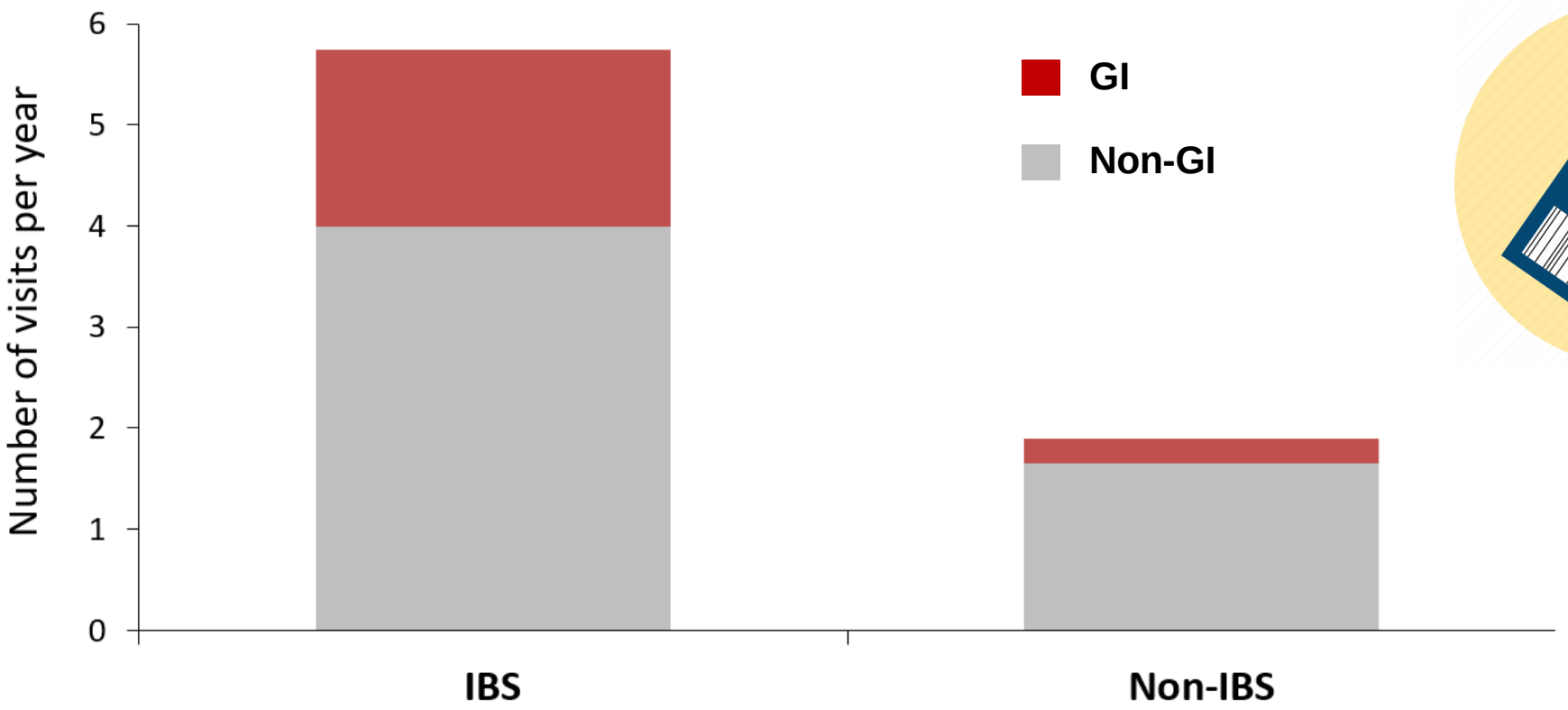
Primary Care Practice



Gastroenterology Practice

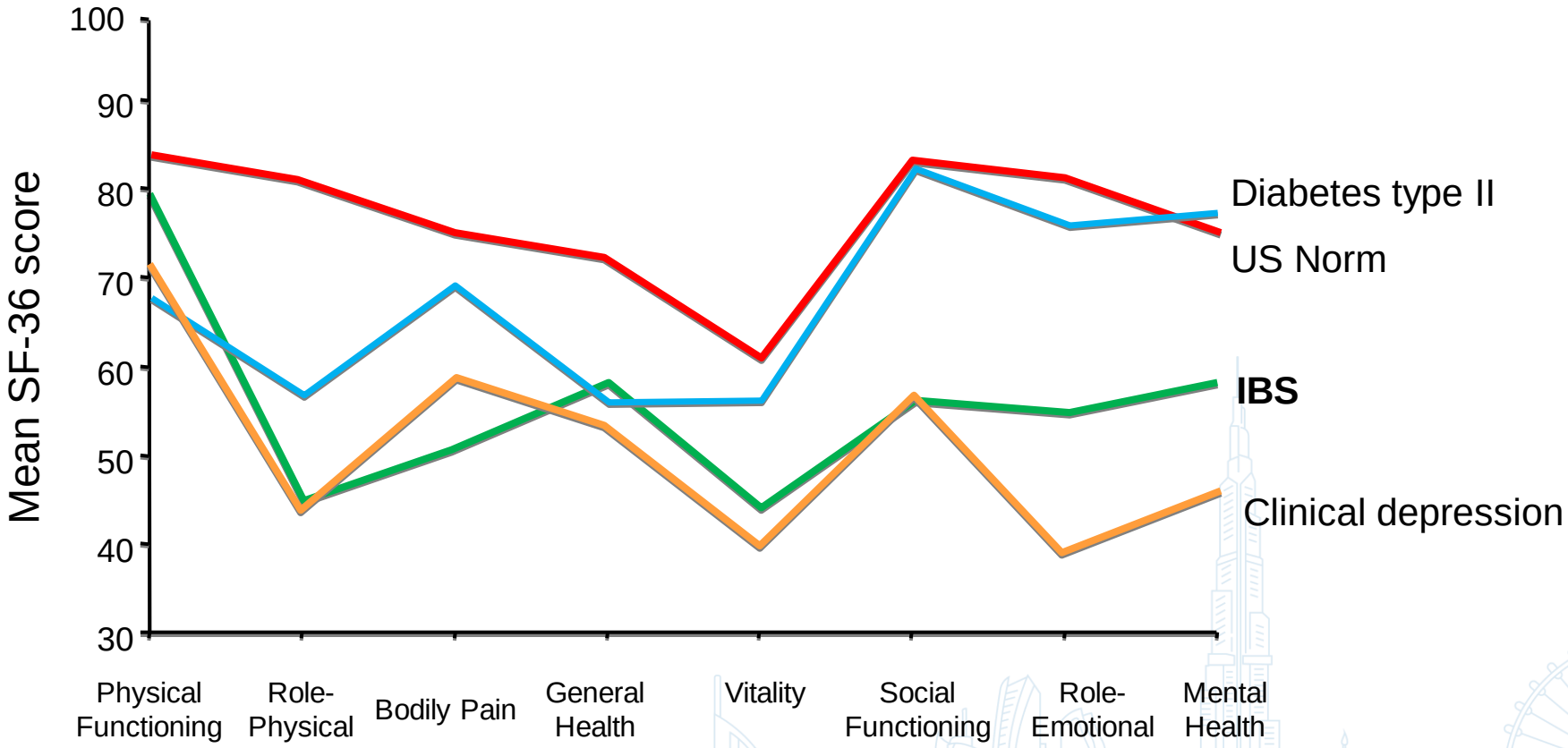
Mitchell CM, et al. *Gastroenterology* 1987; 92:1282-4.
Talley NJ, et al. *Gastroenterology* 1995;109:1736-41.

Physicians Visits per Year

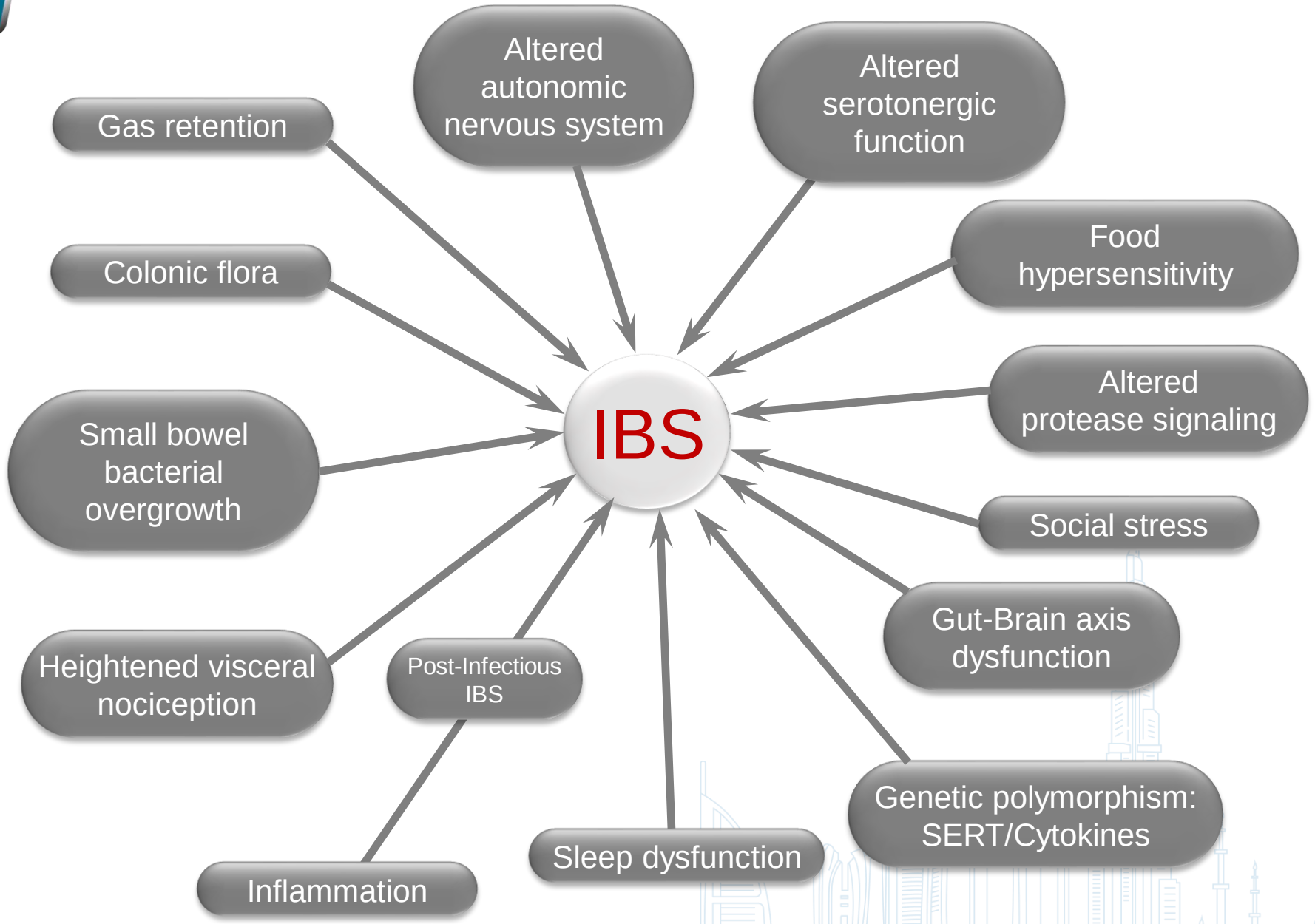


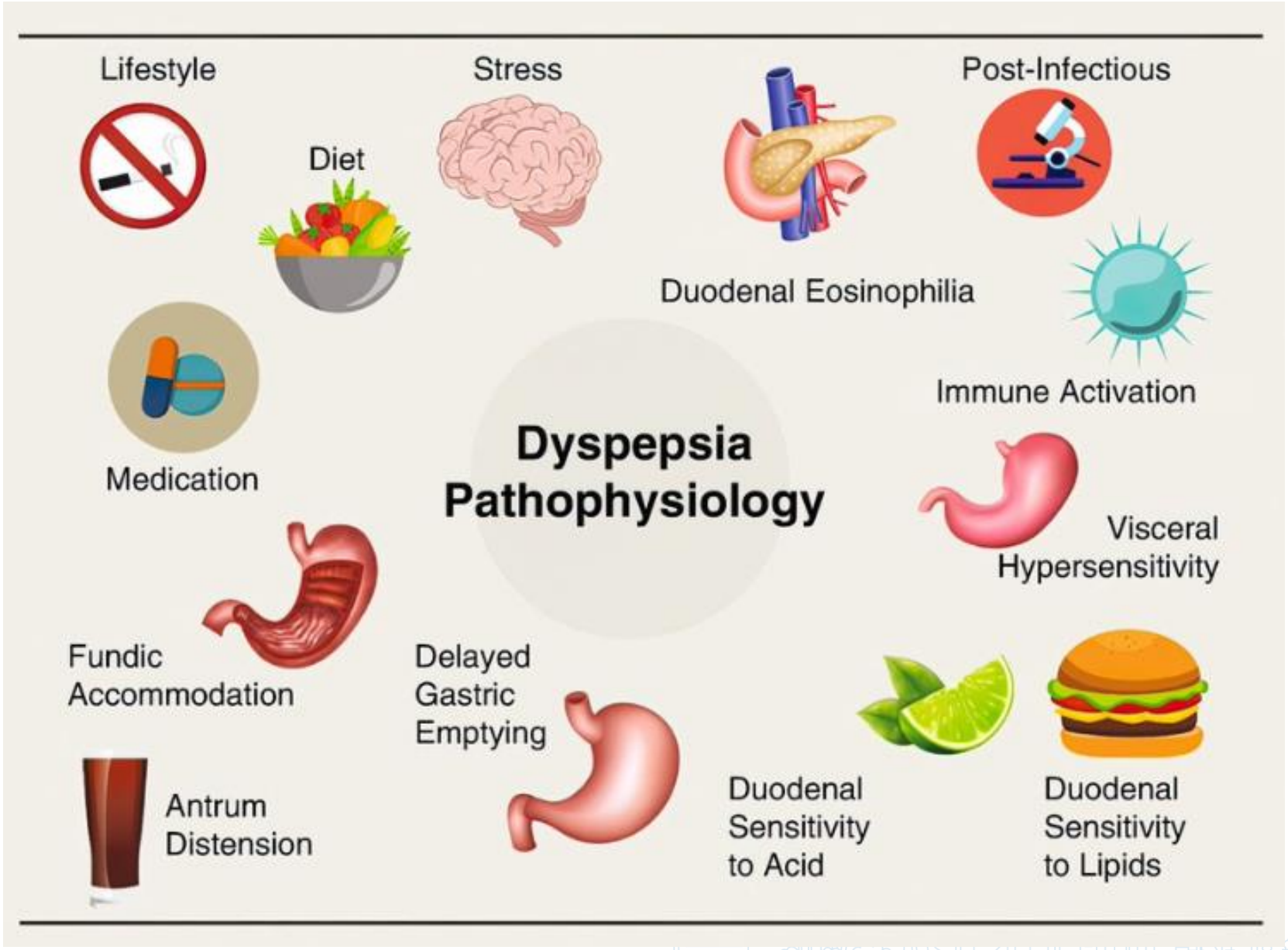
Drossman DA, et al. *Dig Dis Sci* 1993; AGA Teaching Unit in IBS, 1997

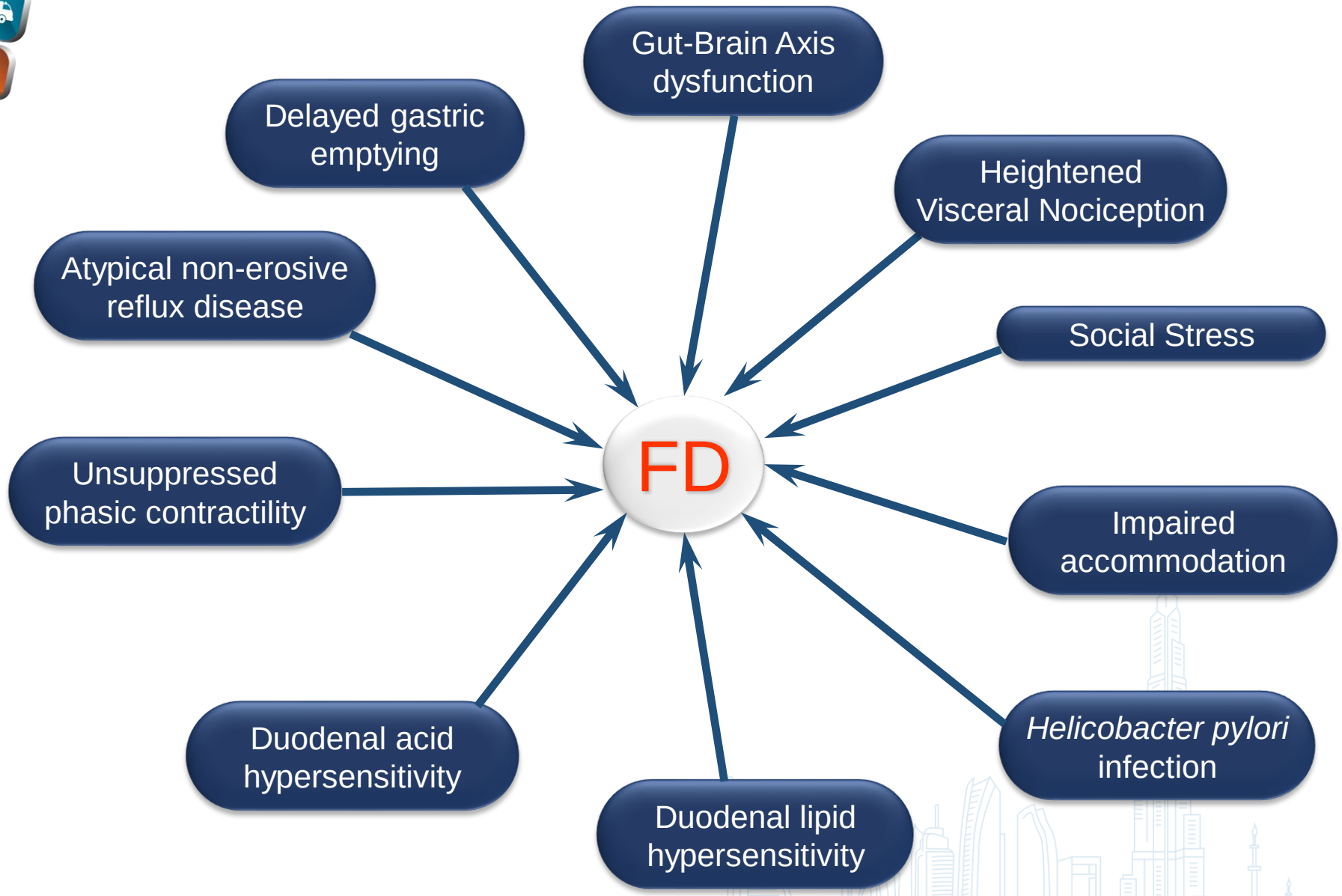
Impact of IBS on Quality of Life



Adapted from Wells et al. Aliment Pharmacol Ther 1997;11:1019-1030.


Altered autonomic nervous system
Altered serotonergic function
Gas retention
Food hypersensitivity
Colonic flora
Altered protease signaling
IBS
Small bowel bacterial overgrowth
Social stress
Gut-Brain axis dysfunction
Heightened visceral nociception
Post-Infectious IBS
Genetic polymorphism: SERT/Cytokines
Sleep dysfunction
Inflammation

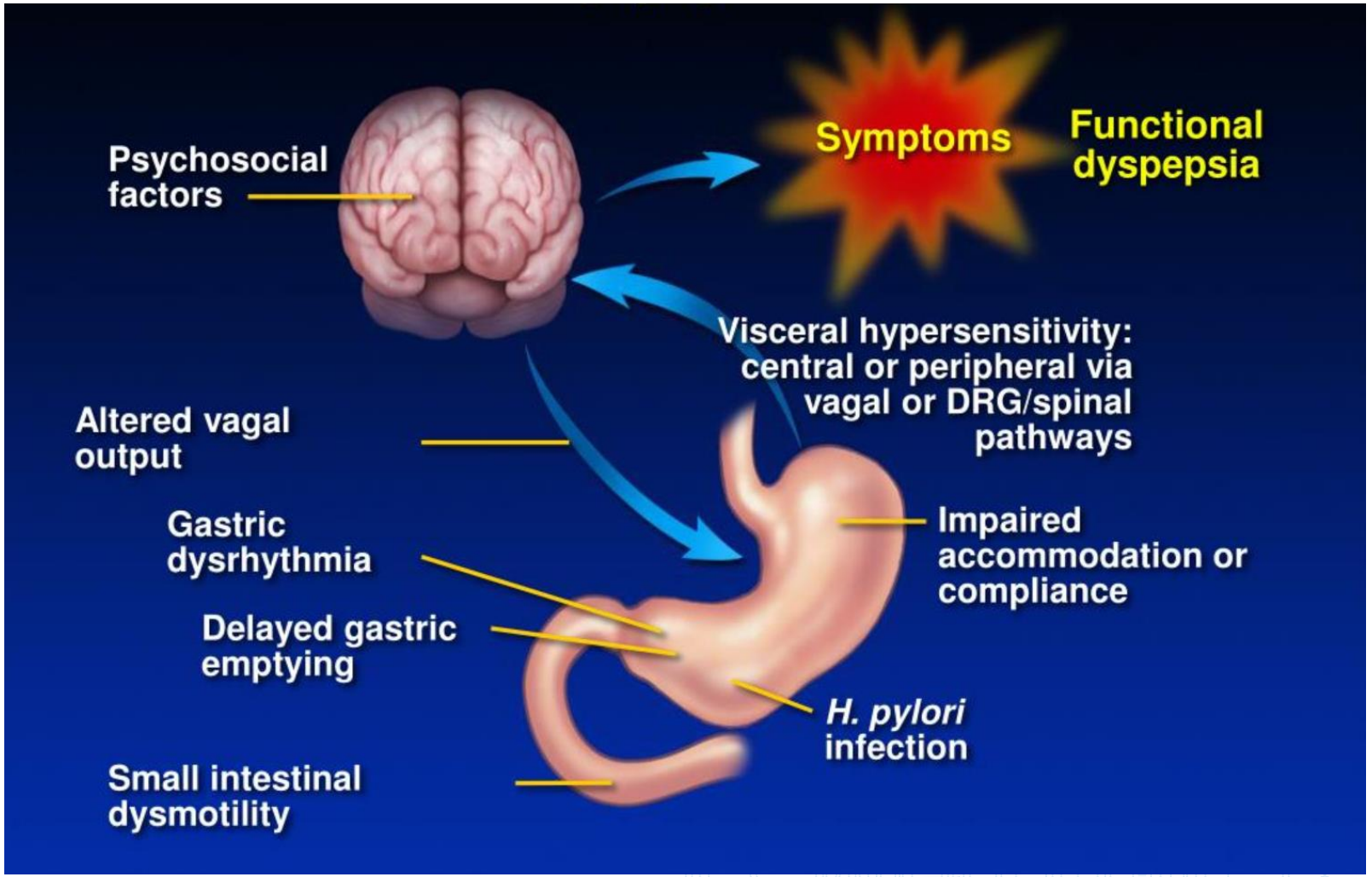

Lifestyle
Stress
Post-Infectious
Diet
Duodenal Eosinophilia
Immune Activation
Medication
Dyspepsia
Pathophysiology
Visceral
Hypersensitivity
Fundic
Accommodation
Delayed
Gastric
Emptying
Antrum
Distension
Duodenal
Sensitivity
to Acid
Duodenal
Sensitivity
to Lipids


Gut-Brain Axis dysfunction
Delayed gastric emptying
Heightened Visceral Nociception
Atypical non-erosive reflux disease
Social Stress
FD
Unsuppressed phasic contractility
Impaired accommodation
Duodenal acid hypersensitivity
Helicobacter pylori infection
Duodenal lipid hypersensitivity

Keys to Treatment of FD/IBS

- Education/reassurance
- Dietary modification
- Focus on health
- Set realistic goals
- Pharmacotherapy of GI symptoms
- Monitoring and modification
- Psychological treatments
- Referral to pain management

Pathophysiologic Factors in Functional Dyspepsia



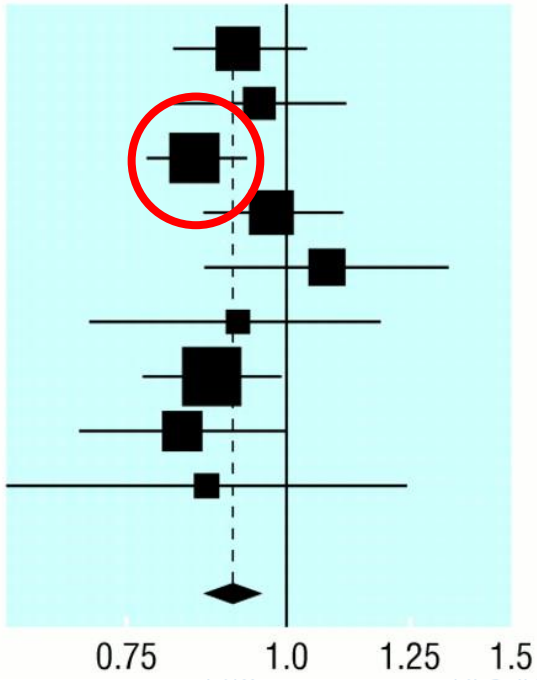
Therapy with PPI/ H2RA

- Several controlled trials but results have been generally disappointing
- Meta-analysis of randomized placebo-controlled trials, PPIs are superior to placebo particularly in ulcer-like & reflux-like dyspepsia subtypes
- Analysis performed on individual studies → trend for improvement in those with GER symptoms

Wang WH, et al. *Clin Gastroenterol Hepatol* 2007; 5:178-85.

H. pylori Eradication in FD

Study	No of patients still dyspeptic: Treatment	Placebo	Risk ratio (95% CI)	Risk ratio (95% CI)
Blum et al[18]	119/164	130/164		0.92 (0.81 to 1.03)
Koelz et al[19]	67/89	73/92		0.95 (0.81 to 1.11)
McColl et al[17]	121/154	143/154		0.85 (0.77 to 0.93)
Talley et al[20]	101/133	111/142		0.97 (0.85 to 1.11)
Talley et al[21]	81/150	72/143		1.07 (0.86 to 1.34)
Miwa et al[23]	33/48	28/37		0.91 (0.70 to 1.18)
Malfertheiner et al[24]	269/460	143/214		0.88 (0.77 to 0.99)
Bruley des Varannes et al[26]	74/129	86/124		0.83 (0.68 to 1.00)
Froehlich et al[25]	31/74	34/70		0.86 (0.60 to 1.24)
Total				0.91 (0.86 to 0.96) P=0.0002



NNT 18-50

Gisbert JP, et al. Med Clin (Barc) 2002; 118: 405–9.
Miwa H, et al. Am J Gastroenterol 2003; 98:2621-6.
Moayyedi et al. Cochrane Database Syst Rev 2005; 1: CD002096.

Prokinetics in Functional Dyspepsia

- Several randomized controlled trials using cisapride, metoclopramide, mosapride and itopride → majority yielded positive results superior to placebo
- Meta-analyses suggest an added benefit of 30-50% over placebo
- Prokinetics may be considered particularly in the PPDS subtype of FD

Hiyama T, et al. *J Gastroenterol Hepatol* 2007; 22: 304–10.
Moayyedi P, et al. Cochrane Database Syst Rev 2002

Prokinetic agents are the mainstay of treatment of functional dyspepsia

Prokinetic agents are widely used for the therapy of FD worldwide[1]

They improve symptoms in patients with FD by stimulating gastric motility and stimulating gastric emptying [2]

Prokinetics release their effect through agonistic effect on

- 5HT receptors
- Motilin receptors
- Ghrelin receptors [3]

References:
1. Monkemuller K and Malfertheiner P. Drug treatment of functional dyspepsia. World J Gastroenterol 2006 May 7; 12(17): 2694-2700; 2. Ramesh R R and Tapas B K. Itopride: a prokinetic agent with dual mode of action and positive safety profile for the management of upper gastrointestinal dysmotility disorders. International Journal Of Current Medical And Pharmaceutical Research 2017;3(10):pp.2549-2558; 3. Dite P, Rydlo M, Dockal M et al. A prokinetic agent with a dual effect - itopride - in the treatment of dysmotility. Eur Med J Gastroenterology 2014;3:42–47

Itopride
Dual Effect on Gastric Motility

Itopride hydrochloride is a novel **prokinetic drug** for the treatment of disorders characterised by reduced gastric motility[1]

Has dual effect on gastric motility
- Dopamine D_2 receptor antagonism
- Acetylcholinesterase inhibition [1,2]

Promotes gastric motility, increases lower esophageal sphincter pressure, accelerates gastric emptying, improves gastro duodenal co-ordination

It has been widely used clinically for the symptomatic management of FD [1,2]

Minimal crrossing of blood-brain barrier
Devoid of cardiac side effects

References:
1. Ramesh R R and Tapas B K. Itopride: a prokinetic agent with dual mode of action and positive safety profile for the management of upper gastrointestinal dysmotility disorders. International Journal Of Current Medical And Pharmaceutical Research 2017;3(10):pp.2549-2558; 2. Dite P, Rydlo M, Dockal M et al. A prokinetic agent with a dual effect - itopride - in the treatment of dysmotility. Eur Med J Gastroenterology 2014;3:42–47

Meta-analysis of 6 RCT articles showed that Itopride significantly improved GPA compared to controls

Study	Number of patients, N	Treatment duration, w	Itopride, %	Control, %	p value	
Amarapurkar and Rane 2004[2]	58	2	93.3[a]	63.3[a]	<0.05	Mosapride-controlled
Zhou et al. 2000[3]	201	2	79.0[a]	73.3[a]	>0.05	Domperidone-controlled
Li et al. 2005[4]	200	4	89.0[b]	89.0[b]	>0.05	
Zhu et al. 2005[5]	236	4	78.3[c]	75.1[c]	0.325	
Talley et al. 2008[6] (North America)	620	8	37.8[d]	35.4[d]	>0.05	Placebo-controlled
Talley et al. 2008[6] (international)	509	8	45.2[d]	45.6[d]	>0.05	
Holtmann et al. 2006[7]	523	8	59.9[d]	41.2[d]	<0.001	

[a]Patient global efficacy was reported as excellent to good; [b]Effective rate was calculated from patients reporting as cured to markedly effective – the total score also included effective, ineffective and aggravated scores; [c]Efficacy effective rate was calculated from patients reporting treatment as effective to good – the total also included moderate and poor scores; [d]Responders were defined as either symptom free or markedly improved

Itopride significantly improved the GPA of patients with functional dyspepsia compared to that in the control groups (RR 1.11 [95% CI 1.03, 1.19]; p=0.006)[1-4]

References:
1. Huang X, Lv B, Zhang S, et al. Itopride therapy for functional dyspepsia: A meta-analysis. World J Gastroenterol 2012;18(48):7371–7377. 2. Amarapurkar DN, Rane P. Randomised, double-blind, comparative study to evaluate the efficacy and safety of ganaton (itopride hydrochloride) and mosapride citrate in the management of functional dyspepsia. J Indian Med Assoc 2004;102(12):735–737; 3. Zhou et al. 2000; 5. Zhu CQ, Mao YM, Zeng MD, et al. A clinical study of hydrochloride itopride in the treatment of functional dyspepsia. Zhonggou Yaoke Daxue Xuebao 2005;6:580–583; 6. Talley NJ, Tack J, Ptak T, et al. Itopride in functional dyspepsia: Results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. Gut 2008;57(6):740–746; 7. Holtmann G, Talley NJ, Liebregts T, et al. A placebo-controlled trial of itopride in functional dyspepsia. N Engl J Med 2006;354(8):832–840

Meta-analysis of 4 studies showed that Itopride improved postprandial fullness compared to Domperidone

Improvement in postprandial fullness

Study	Number of patients, N	Treatment duration, w	Itopride (50 mg tid), %	Domperidone (10 mg tid), %	p value
Mo et al. 2003[2]	79	2	97.4[a]	72.5[a]	<0.05
Sun et al. 2003[3]	232	2	50.4[b]	53.0[b]	>0.05
Chen et al. 2004[4]	40	4	85.0[c]	70.0[c]	>0.05
Li et al. 2005[5]	200	4	78.7[d]	58.9[d]	<0.01

[a]Improvement was graded as marked or good; [b]Improvement was assessed as change in symptom score after treatment as a percentage of baseline symptom score; [c]Improvement in postprandial fullness was defined as improvement in patient-reported upper abdominal distention; [d]Improvement was assessed as patients reporting disappearance of symptoms after treatment

CI, confidence interval; RR, risk ratio; tid, three-times daily

Itopride significantly improved postprandial fullness in patients with functional dyspepsia compared to domperidone (RR 1.21 [95% CI 1.03, 1.44]; p=0.02)1

References:
1. Huang et al. 2012; 2. Mo et al. 2003; 3. Sun et al. 2003; 4. Chen et al. 2004; 5. Li et al. 2005

Meta-analysis of 3 RCTs showed that Itopride improved LDQ scores when compared with placebo

Mean change from baseline in LDQ score for patients treated with Itopride or placebo

Study	Number of patients, N	Treatment duration, w	Itopride	Placebo	p value
Talley et al. 2008 [2] (North America)	620	8	-5.6	-4.8	>0.05
Talley et al. 2008 [2] (international)	509	8	-6.2	-6.3	0.04[a]
Holtmann et al. 2006 [3]	523	8	-6.2[b]	-4.5[b]	0.02

[a]At the primary endpoint, based on LDQ improvement by 2 or more points in questions 1 and 8 and no deterioration in the other questions, there was a significant difference in the international trial Itopride [62%] *vs* placebo [52.7%]; p=0.04);
[b]The Holtmann *et al*. 2006 study included three doses (50, 100 and 200 mg tid) of Itopride, but the meta-analysis only included two doses (50 and 100 mg tid); the results presented in the table above are for all three doses pooled[3]

Itopride significantly improved the LDQ scores of patients with functional dyspepsia compared to placebo (WMD -1.38 [95% CI -1.75, -1.01]; p<0.01)

1

References:
1. Huang X, Lv B, Zhang S, et al. Itopride therapy for functional dyspepsia: A meta-analysis. World J Gastroenterol 2012;18(48):7371–7377; 2. Talley NJ, Tack J, Ptak T, et al. Itopride in functional dyspepsia: Results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. Gut 2008;57(6):740–746; 3. Holtmann G, Talley NJ, Liebregts T, et al. A placebo-controlled trial of itopride in functional dyspepsia. N Engl J Med 2006;354(8):832–840

Itopride – Safety Profile

Safety of Itopride vs. Placebo in Functional Dyspepsia [1]

- N= 554 (randomized), 523 had outcome data
- Itopride vs. placebo
- Randomised Placebo controlled trial
- Patients with FD received 50, 100 & 200 mg of itopride three times daily or placebo for 8 weeks
- Adverse events were recorded during the treatment period

	Itopride 50	Itopride 100	Itopride 150	Placebo
Adverse events during the treatment	35.6%	40.0%	39%	37.3%
GIT adverse events	12.6%	11.1%	7.4%	14.1%

Frequently reported adverse events were abdominal pain, nausea, constipation and diarrhoea with most adverse events being mild to moderate in intensity. [1]

References:
1. Holtmann G, Tallyey N J, Liebregts T et al. A Placebo-Controlled Trial of Itopride in Functional Dyspepsia. N Engl J Med 2006;354:832-40

Anti-anxiety or Anti-depressants for FD: A systematic review

- 9 RCTs (871 patients)
- 5/9 showed benefit
- For the statistical quantitative analyses, 3/9 studies were selected
- Funnel plot was assymetrical → publication bias?

	Anti-depressants or Anxiolytics	Anti-depressants
RR (95% CI)	0.72 (0.55-0.99)	0.63 (0.38-1.03)*

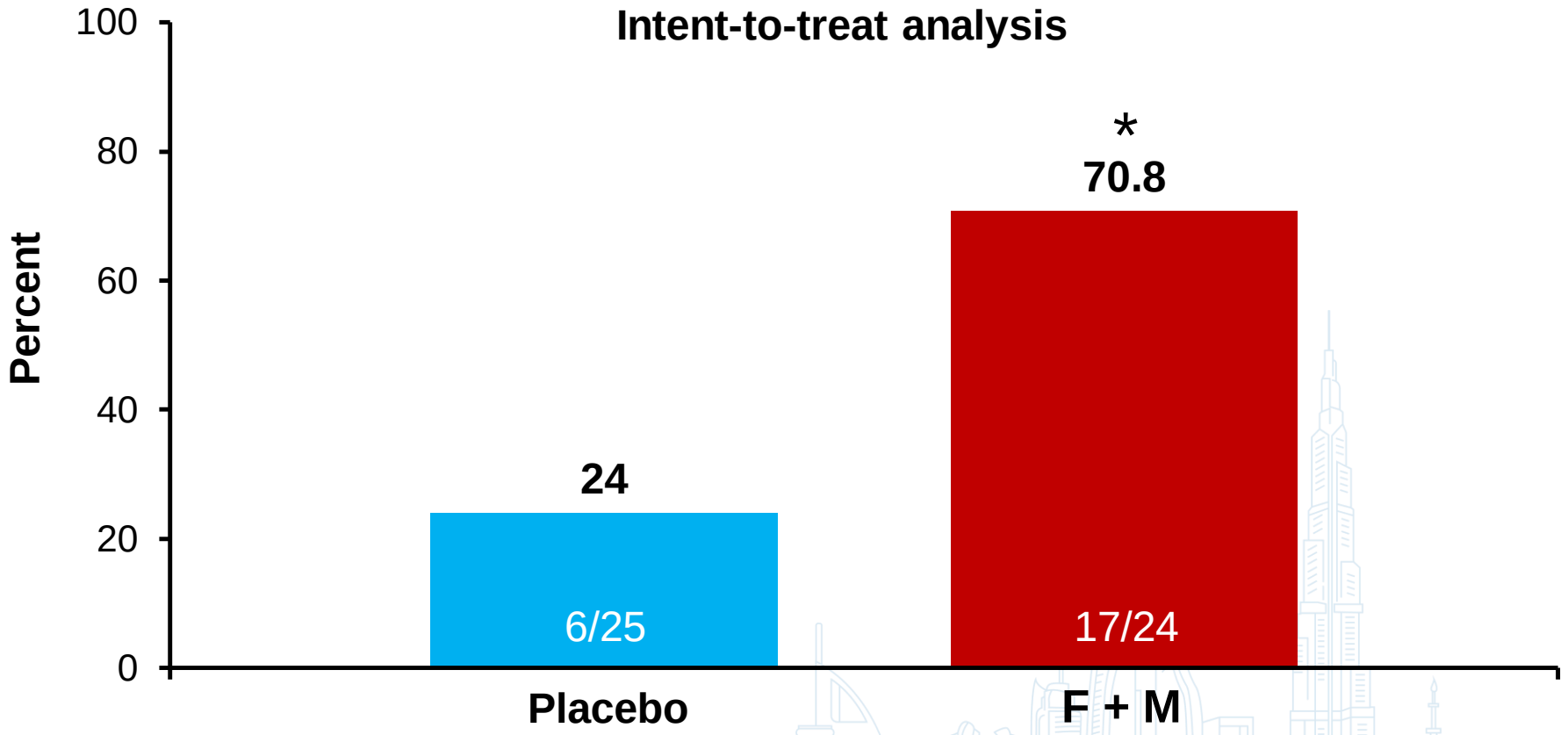
*NS

Hojo M, et al. *Intern Med* 2017;56:3127-3133.

Flupenthixol + Melitracen

- 0.5mg flupenthixol & 10mg of melitracen
- Flupenthixol is a typical antipsychotic, with dopamine D1 and D2 receptor antagonist properties; melitracen is a bipolar thymoleptic with activating properties
- Anxiolytic & antidepressant properties at small doses (‘anti-stress’), non-habituating with rare AE
- Approved in Europe for anxiety, depression, and apathy but available only in few restricted markets

RCT with Cross-over Design: Subjective Global Symptom Relief



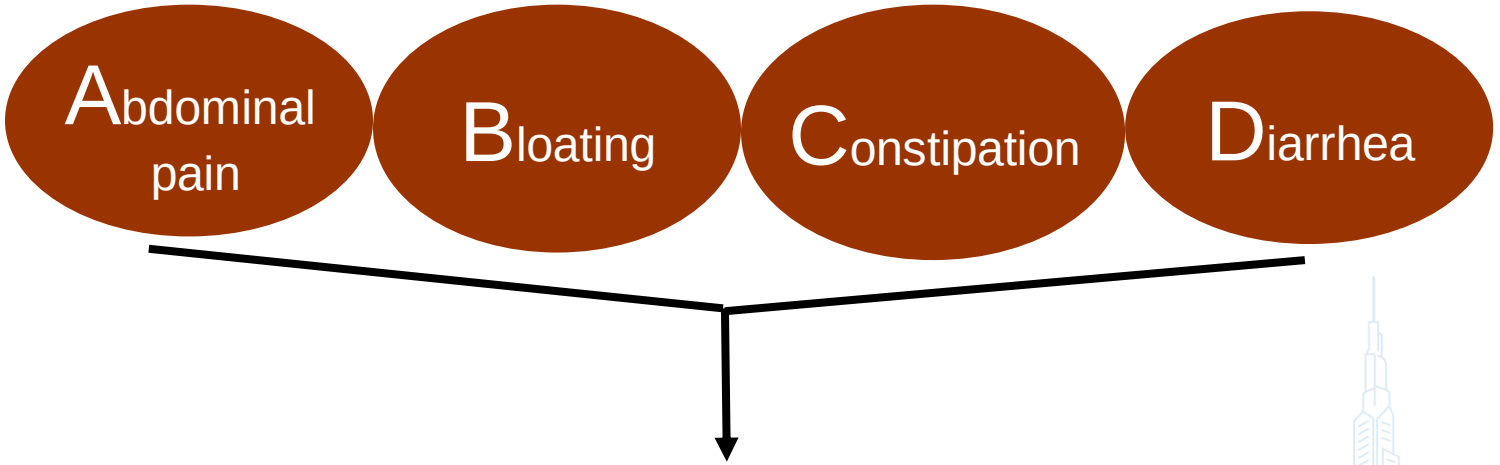
Hashash JG, et al, and Sharara AI. *Aliment Pharmacol Ther* 2008;27:1148–1155.

Venlafaxine (SSRI) in FD

- Multicenter, randomized, double-blind, placebo-controlled trial in patients with persistent dyspeptic symptoms and a negative EGD
- 160 pts → 8 wks of placebo or venlafaxine XR
- 44% drop-outs on venlafaxine vs. 27% placebo
- No difference in response even on per-protocol analysis: 38% vs. 39%

Van Kerkhoven LA, et al. *Clin Gastroenterol Hepatol* 2008; 6:746-52.

IBS: Dominant Symptoms



Management of IBS

CLINICAL GUIDELINES

ACG Clinical Guideline: Management of Irritable Bowel Syndrome

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Am J Gastroenterol 2021;116:17–44.

Emerging Pharmacologic Therapies for IBS

Atypical benzodiazepine
Modulates autonomic responses
- Dextofisopam

K-Opioid receptor agonist
Activates opioid receptors, which may ↓ visceral sensation
- Asimadoline

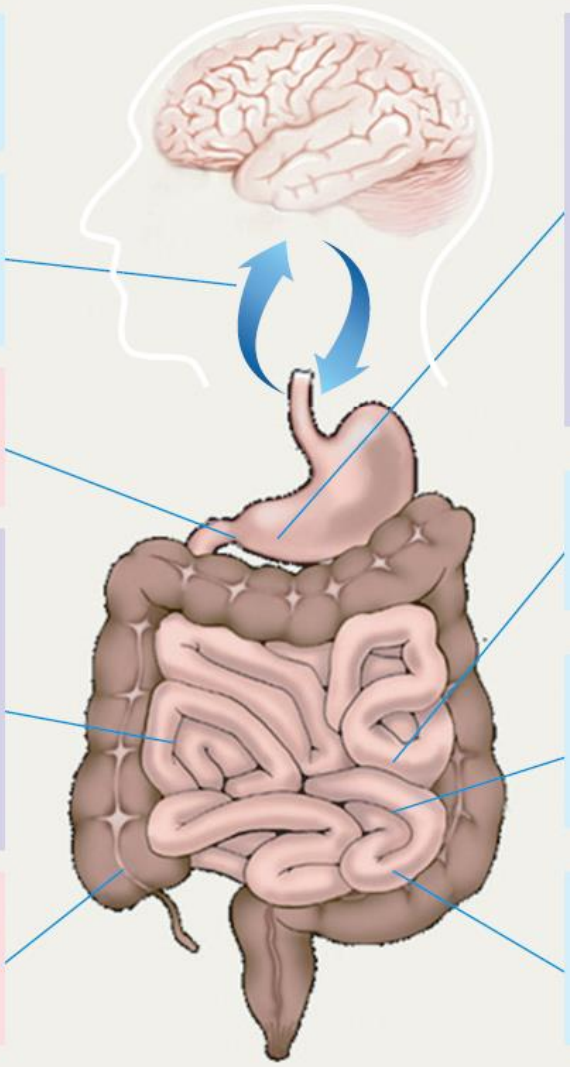
Dopaminergic antagonist
Leads to prokinetic effects
- Itopride

CFTR and chloride channel modulator
IBS-C: GC-C receptor agonists
- Linaclotide
- Plecanatide

IBS-C: chloride channel activator
- Lubuprostone

IBS-D: chloride secretion inhibitors
- Crofelemer

Bile acid modulators
Bile acids accelerate CTT, ↑MI & secretion
- Chenodeoxycholic acid
- IBAT inhibitor, A3309



Serotonin receptor modulator
Agonist for IBS-C: accelerate GI transit & alter visceral sensation
- $5HT_4$ agonist: prucalopride, mosapride
- Selective $5HT_4$ partial agonist: tegaserod
- Partial $5HT_3$ agonist: pumosetrag

Antagonist for IBS-D: slow GI transit and ↓ visceral sensation
- $5HT_3$ antagonist: alosetron, ramosetron

Tryptophan hydroxylase-1 inhibitor
↓ GI level of serotonin
- LX1031

CRF antagonist
↓ GI motility and visceral sensation
- Pexacerfont
- GW 876008

Oral carbon adsorbant
Adsorbs luminal substances including serotonin and bile acids
- AST-120

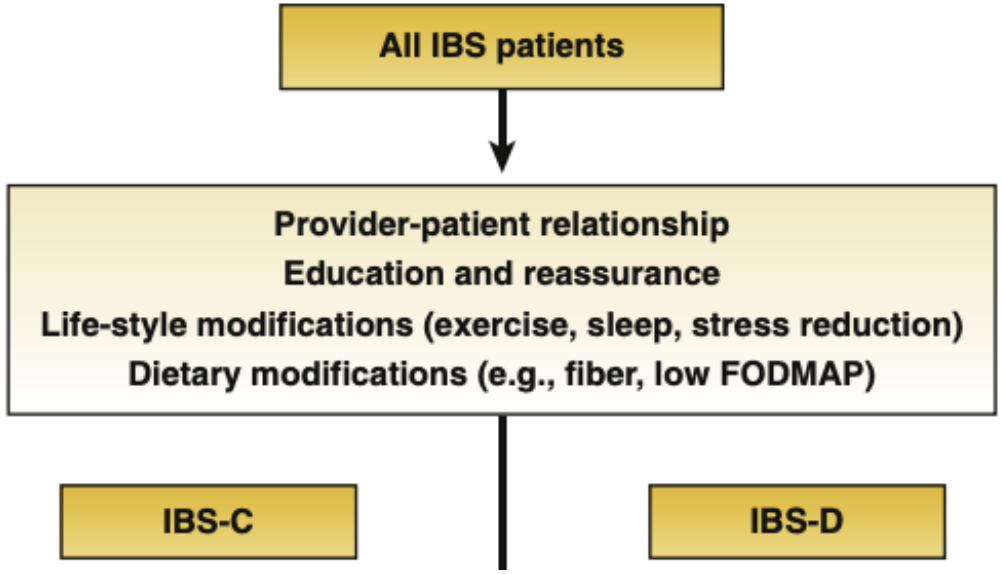
Chey WD, et al. *Gut and Liver*, Vol. 5, No. 3, September 2011, pp. 1-14

Current FDA-approved Therapy for IBS

Drug Mechanism	FDA-Approved Drug	Indication	Percentage Response Drug	Percentage Response Placebo	Number Needed to Treat (NNT)
Microbiome	Rifaximin	IBS-D	43	34	11
Hypersensitivity and motility	Eluxadoline	IBS-D	27	17	10
Motility	Alosetron	IBS-D	51	36	7
Gut Secretion	Lubiprostone Linaclotide Plecanatide	IBS-C IBS-C IBS-C	18 34 30	10 14 18	12.5 5 8
Gut secretion	Tenapanor *NHE3 Inhibitor*	IBS-C	27 37	18 24	11 7.7

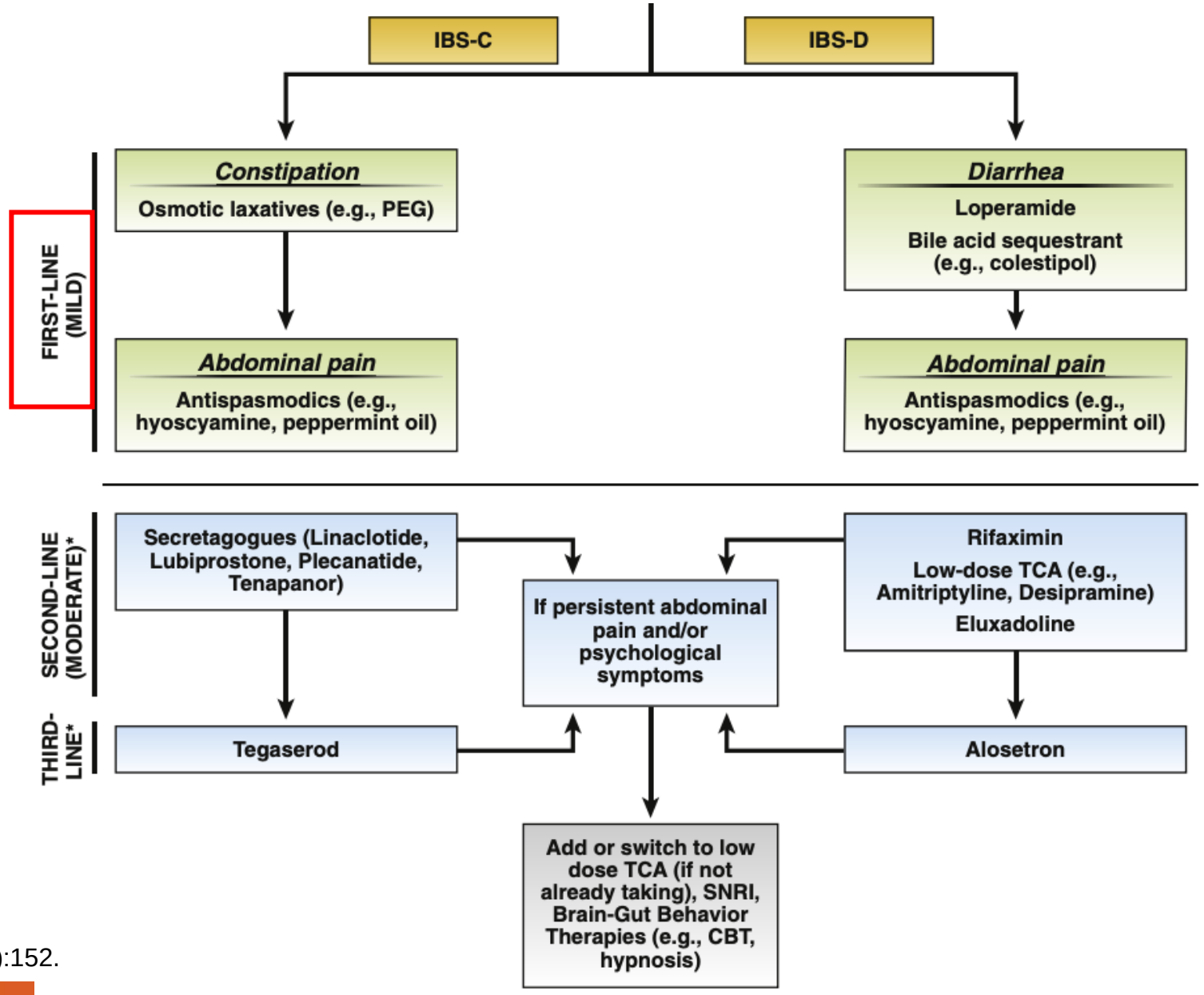
Patel NV. *Clin Exp Gastroenterol* 2021:14:377-384.
Sinagra E. et al. Exp Review Clin Pharmacol 2020 May;13(5):473-479.

AGA: Clinical Decision Tool for IBS



Gastroenterology 2022; 163 (1):152.

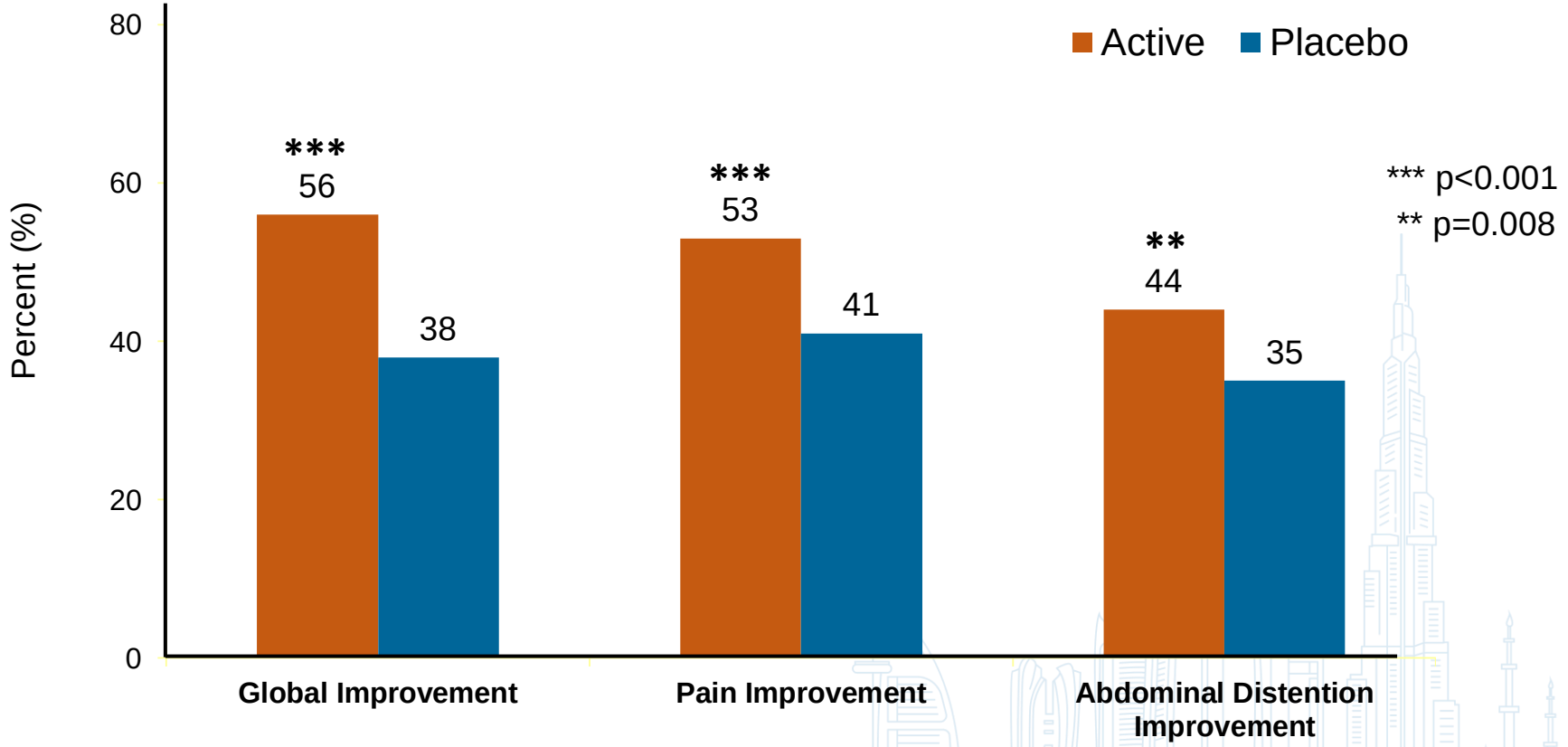
AGA: Clinical Decision Tool for IBS



Gastroenterology 2022; 163 (1):152.

Efficacy of Antispasmodic Agents in IBS

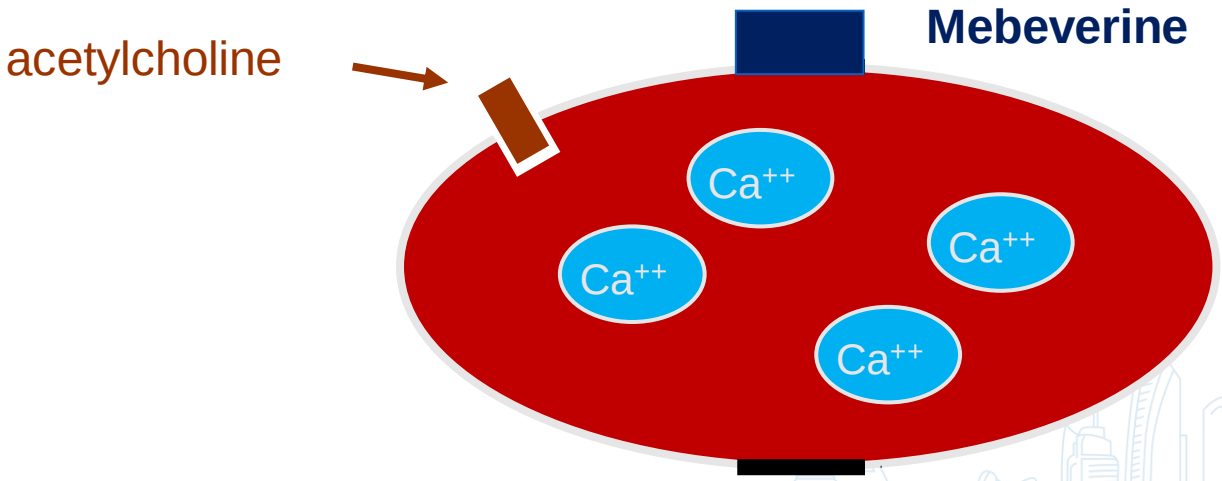
- Meta-analysis of 23 RCTs with comparable outcomes (1888 pts)
- 5 superior to placebo: **mebeverine** , pinaverium, otilium, trimebutine, cimetropium



Poynard et al. *Aliment Pharmacol Ther* 2001;15:355-61.

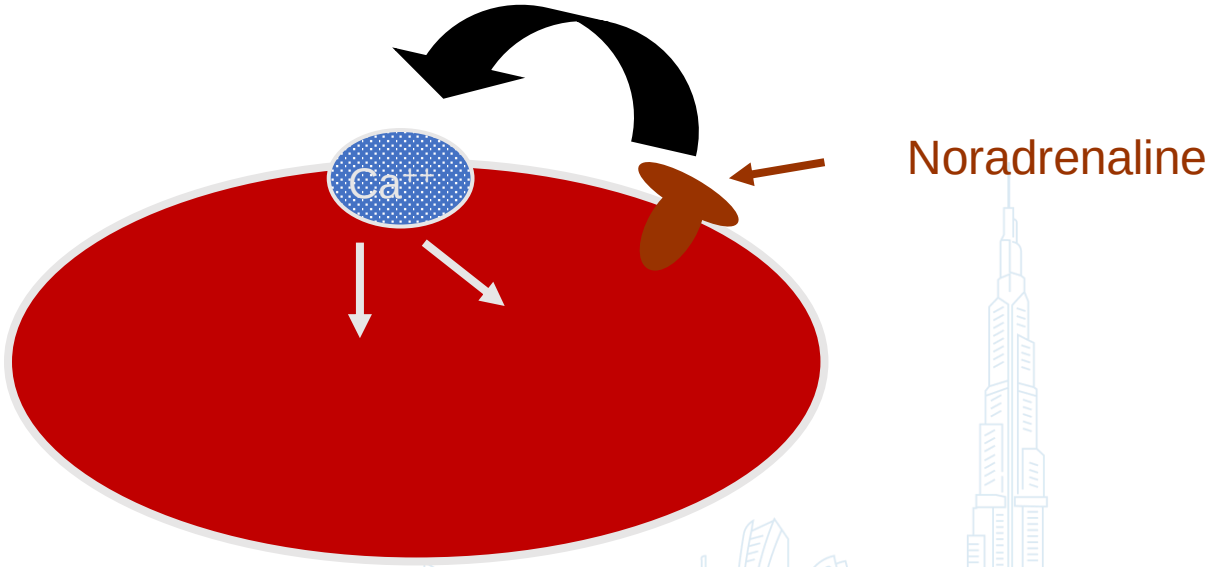
Mebeverine HCl : Mode of Action
Antispasmodic effect

- blocks Na+ channels → no depolarization → no Ca++ accumulation → muscle relaxation



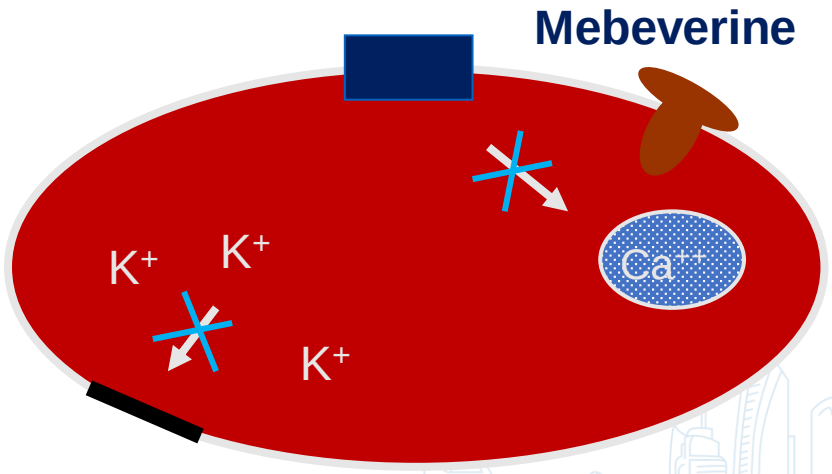
Mebeverine HCl (Duspatalin®): Mode of Action
Musculotropic effect

- Avoids extreme muscle relaxation or hypotony stimulated by noradrenaline



Mebeverine HCl : Mode of Action
Musculotropic effect

- Prevents replenishment of Ca++ reservoir → Stops K+ flow → Avoids hypotony



Mebeverine HCl : Mode of Action

smooth muscle tone

Fully relaxed — Fully contracted

HYPOTONY — NORMAL RANGE — SPASM (Pain)

Range with mebeverine

does not cause hypotony

reduces spasm

Other Antispasmodics / Anticholinergics

Act by blocking the receptor site of acetylcholine

Side effects:

- Urine retention
- Blurred vision
- Constipation
- Dry mouth
- Increased heart rate
- Drowsiness/ sedation

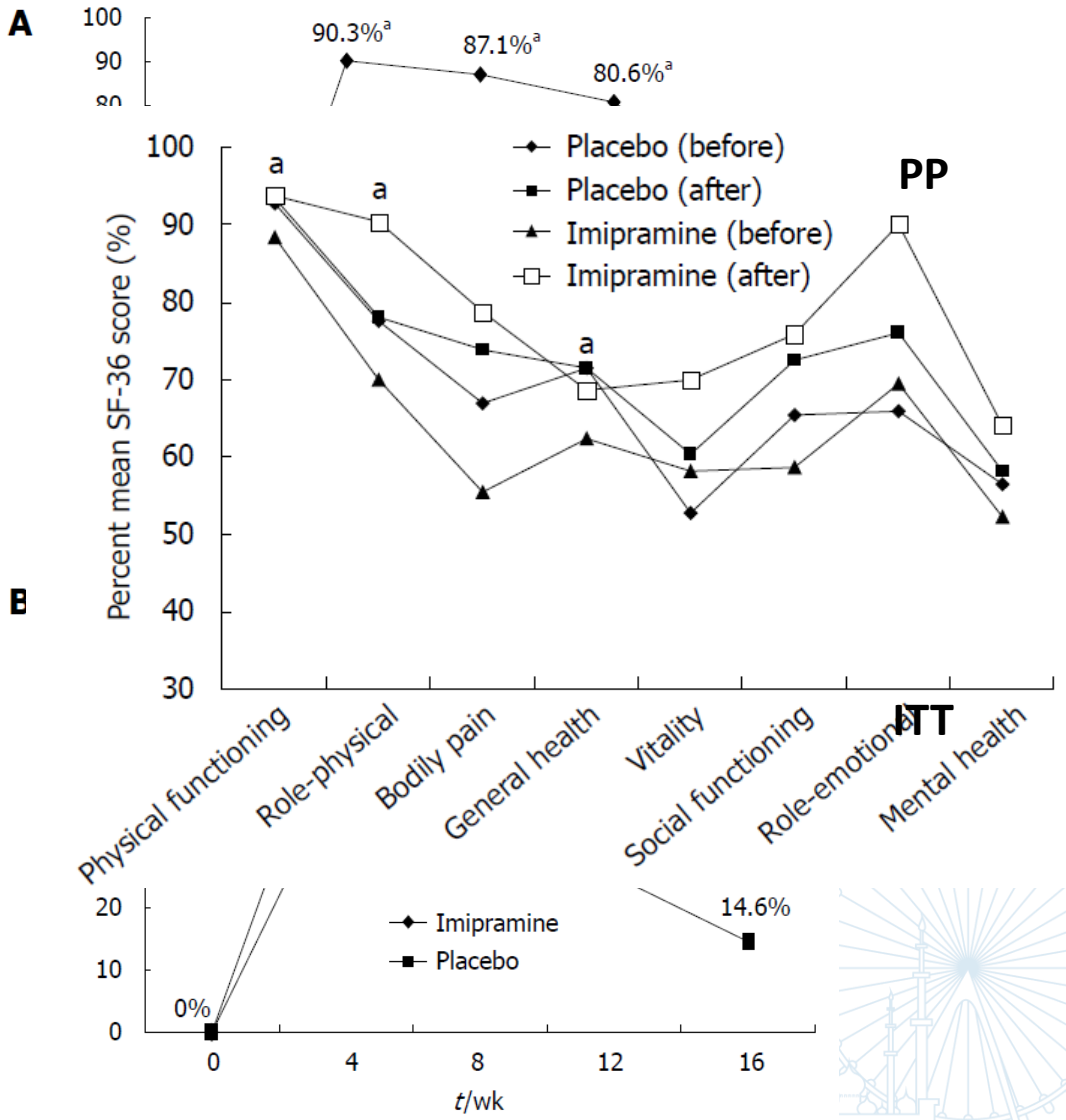
Contra-indications:

- Prostatic hypertrophy
- Glaucoma
- Hypertension
- Cardiac problems

Tricyclic Antidepressants in IBS

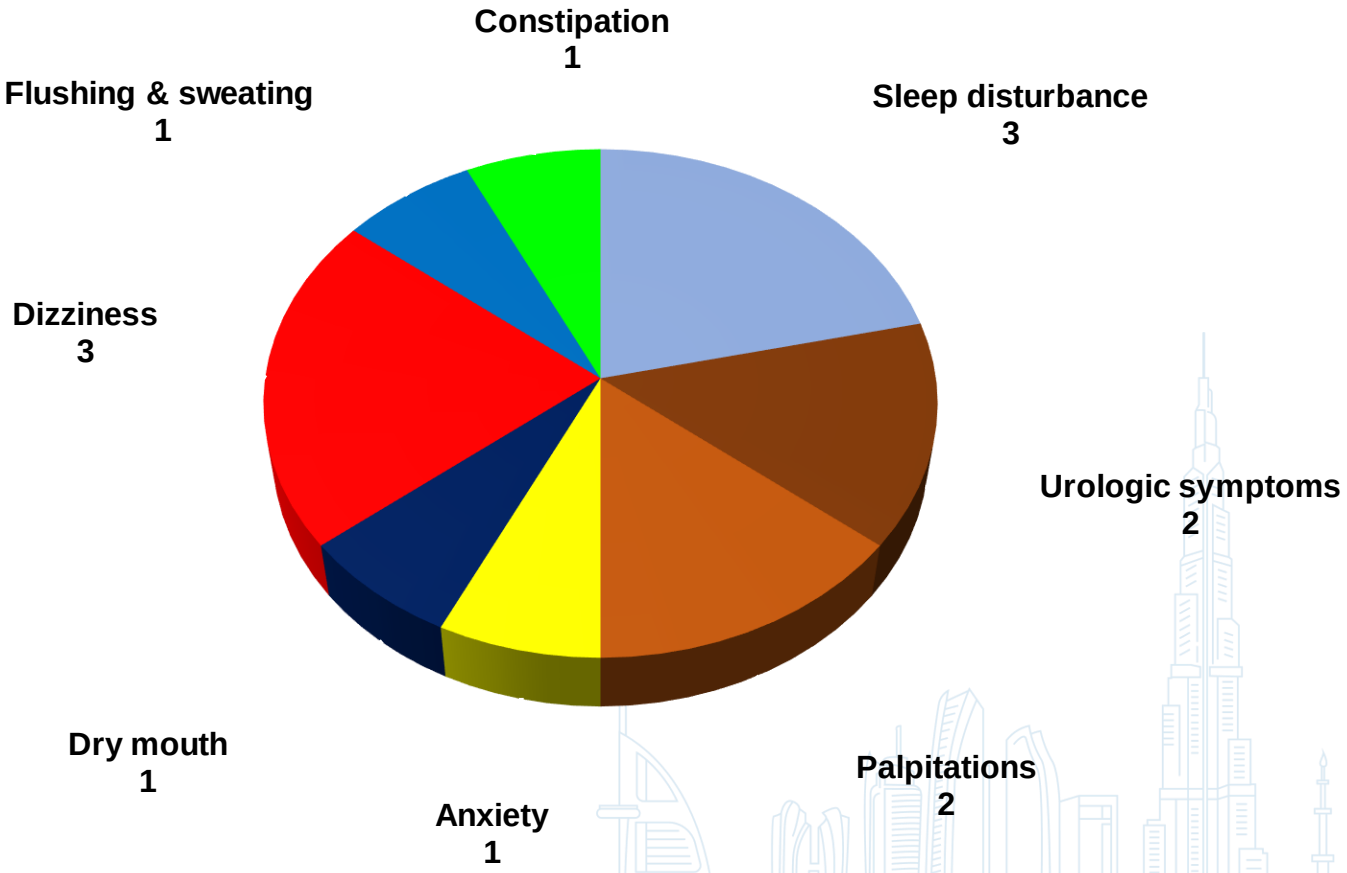
Table 1 Baseline patient characteristics *n* (%)

	Imipramine (*n* = 59)	Placebo (*n* = 48)
Mean age (yr)	42.6 ± 12.4	45.3 ± 13.8
Male sex	33 (55.9)	29 (60.4)
Type of recruitment	38 (64.4) referrals	29 (60.4) referrals
Bloating/distention	57 (96.6)	46 (95.8)
Abdominal pain	58 (98.3)	47 (97.9)
Flatulence	45 (76.3)	40 (83.3)
Constipation	17 (28.8)	15 (31.3)
Diarrhea	11 (18.6)	7 (14.6)
Mixed pattern	14 (23.7)	15 (31.3)
Mean baseline SF-36 score	98.6 ± 21.3	102.8 ± 16.6



Abdul-Baki Heitham, et al, Sharara AI. *World J Gastroenterol* 2009;15:3636-42.

Imipramine-Associated Side-effects Leading to Drop-out in 25% of patients (n=14)



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Take Home Message

- Functional GI disorders are prevalent biopsychological disorders with significant overlap
- Pathophysiology is complex and involves multiple factors
- Treatment should be based on a holistic strategy involving diet, psychosocial management and targeted therapies depending on the clinical syndrome
- Prokinetics and antispasmodics remain first-line therapies in patients with functional dyspepsia and IBS respectively