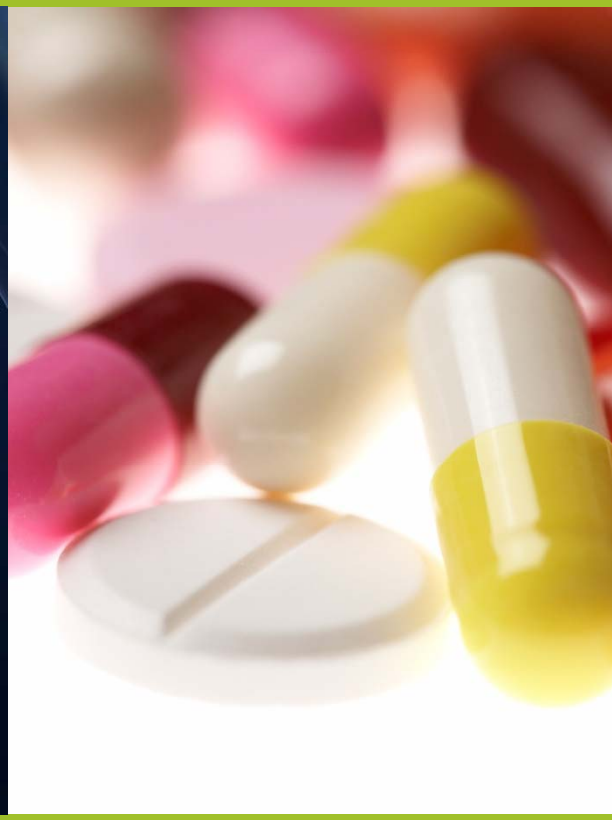
IRRITABLE BOWEL SYNDROME (IBS)
CHRONIC CONSTIPATION

Susan Lucak, MD



IBS: Definitions

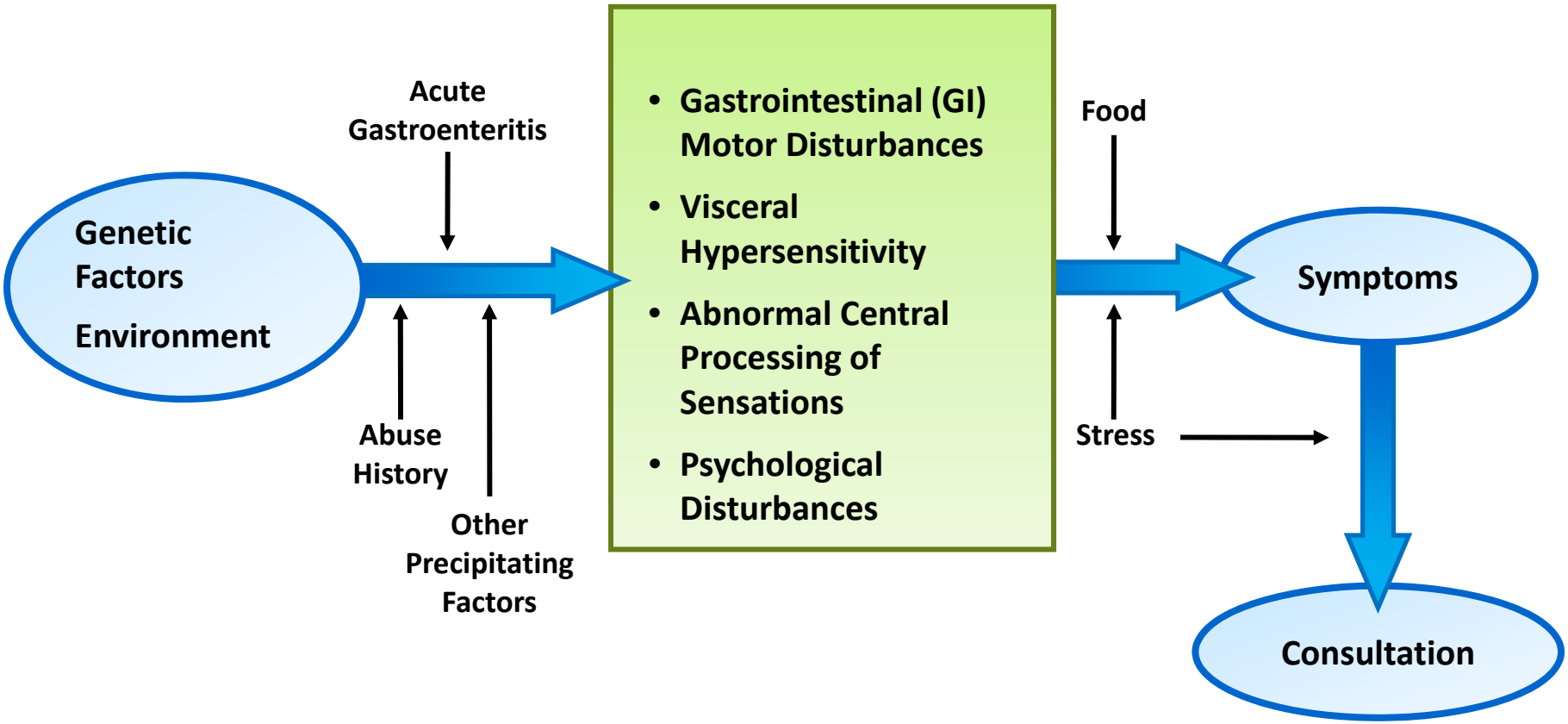
- **Functional** disorder=absence of organic abnormalities, i.e. no discernible biochemical or structural changes
- Syndrome **not** Disease
- A complex **biopsychosocial** disorder of unknown cause, characterized by abdominal pain/discomfort and bowel irregularities (C, D, C/D), gut interacts withCNS

IBS: Epidemiology

- Up to **22%** Americans report IBS Sxs
- ~70% IBS patients are **women**
- Age : less than 40
- Not directly lethal, associated with **suicidality** (SI, SA, suicides)
- Impacts on **Quality of Life** (~DM, depression)
- Reduces **productivity** (13.4 v. 4.9 days missed at work)

Pathophysiology of IBS

Proposed Pathophysiology of IBS



Adapted from Rome Foundation Functional GI Disorders Specialty Modules.

IBS: Pathophysiology, Predisposing Factors

Genetic Factors

- IBS aggregates in some families
- Gene polymorphisms: 5-HT, IL-10, COMT – pain sensitivity
- Twin studies : monozygotes – increased concordance

Environmental Factors – Early Life

- Children of adults with IBS, more health care visits, social learning of illness behavior
- Children with recurrent abdominal pain, higher levels of anxiety + depression, more Sxs

Abuse History

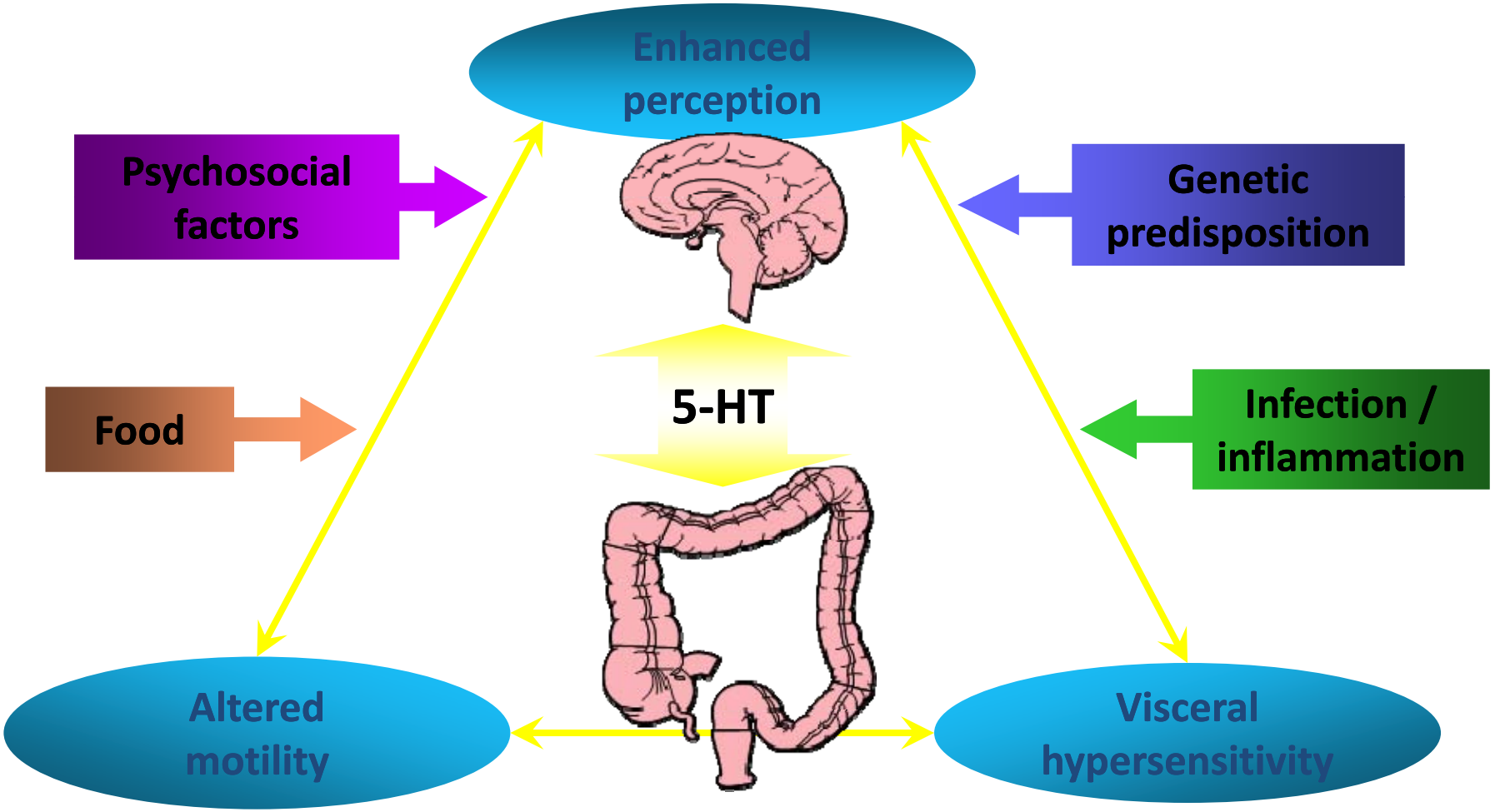
- Sexual, physical abuse (30-56% in referral centers in US + Europe, less frequent in primary care centers)
- Childhood abuse (~50%)
- Abuse affects health outcomes (more severe pain, greater impairment in functioning

Precipitating Factors – Adult Life

Breakup of a relationship

- Stressful life events (war, loss of loved one)
- Chronic life stress (unhappy marriage, war), more severe Sxs

IBS:Pathophysiology, Brain-Gut Interactions + Other Possible Modifying Factors



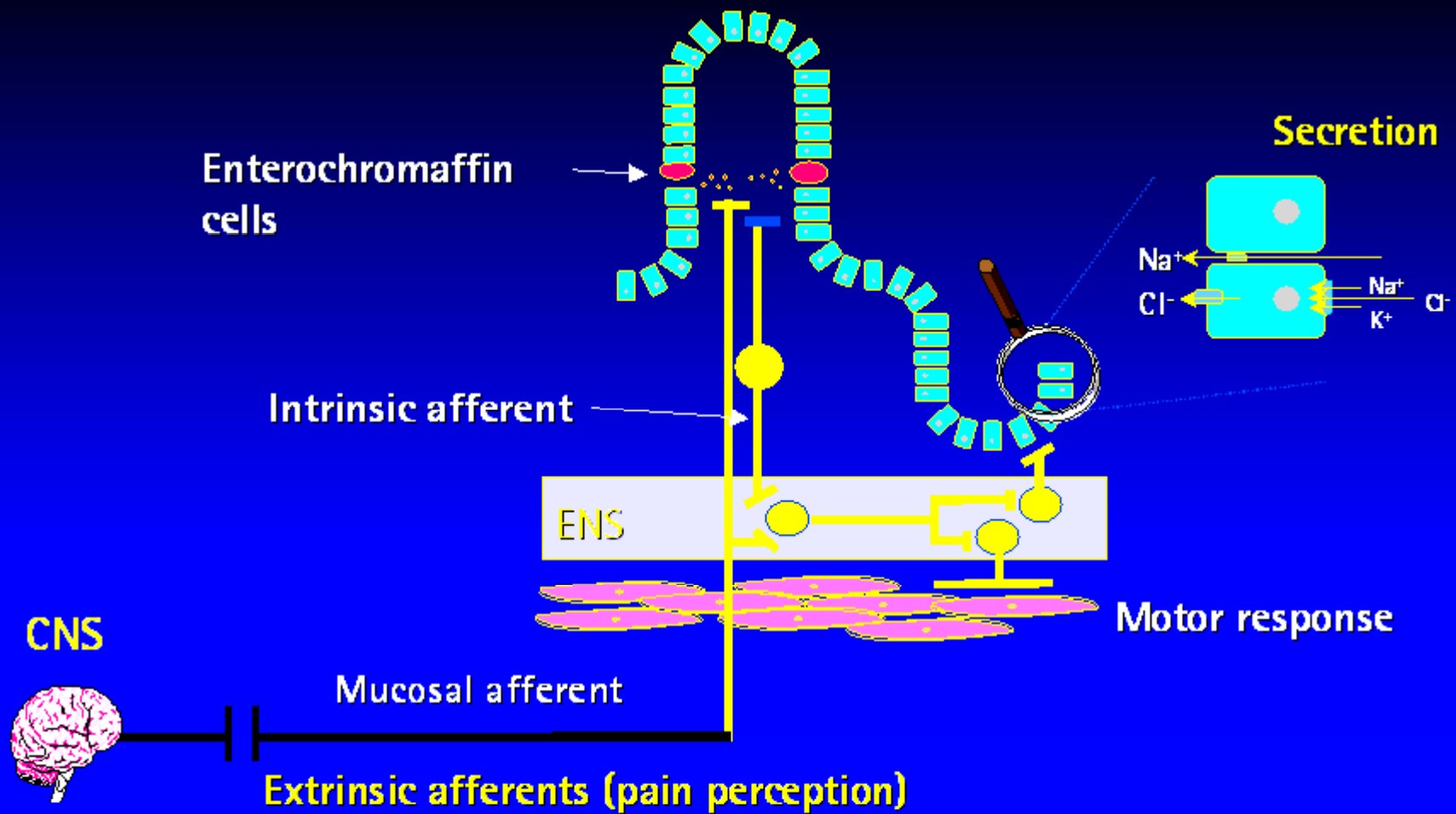
Adapted from Camilleri et al, Aliment Pharmacol Ther 1997; 11: 3

IBS: Functions of the GI tract-outline

Chemical/physical stimulation in the mucosa releases mediators, stimulate intrinsic neurons in ENS, afferent nerves synapse with:

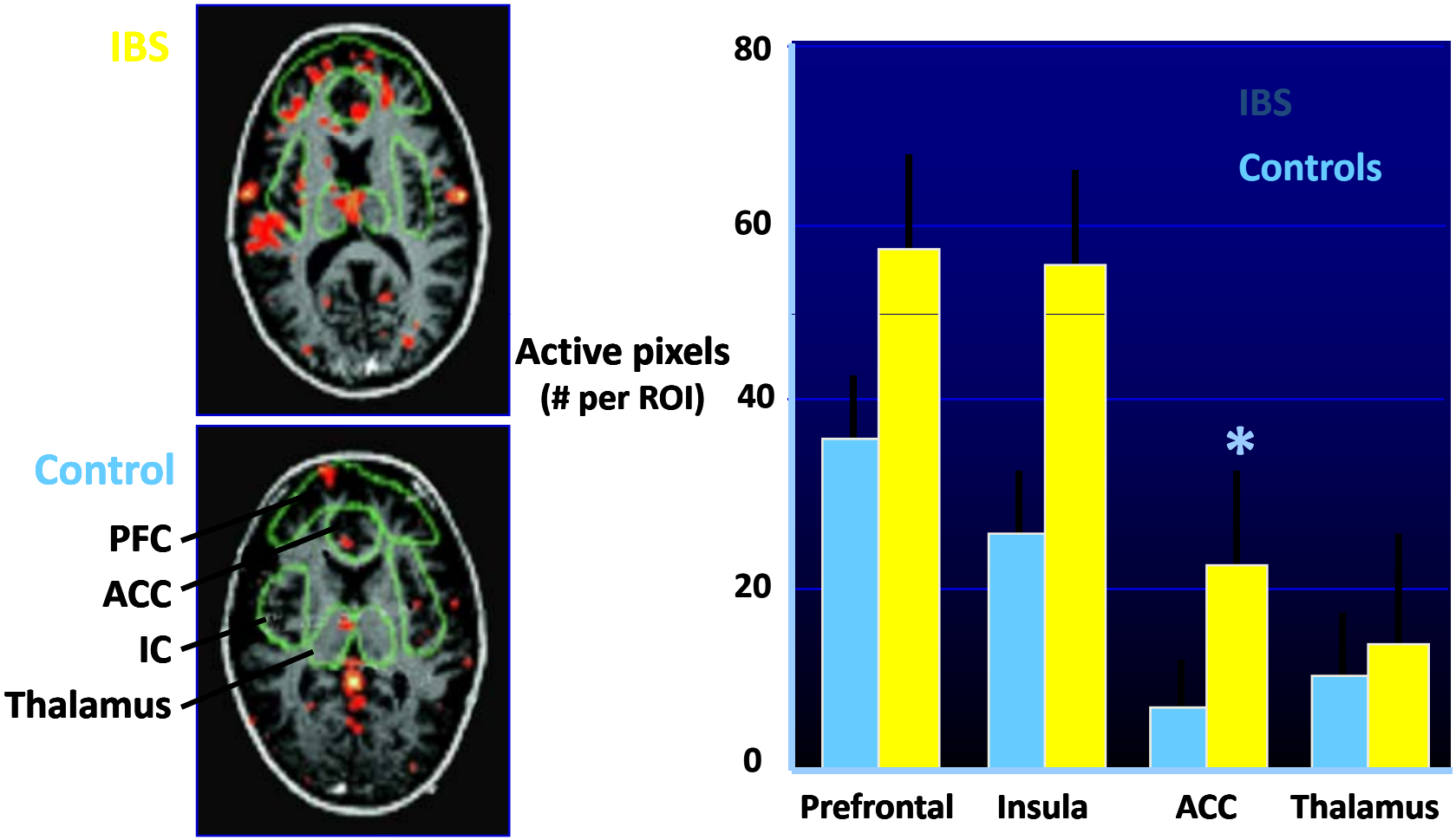
- **Sensory**: afferent neurons to spinal cord, to brain, descending inhibitory pathways back to ENS
- **Motor:** interneurons,in ENS, synapse with motor neurons in ENS, peristalsis (cycles of contraction+ relaxation)
- **Secretory:** interneurons, release of mediators stimulate chloride secretion
- **Mediators:** 5-HT, tachykinins, CGRP, enkephalins, Ach, NO, substance P, VIP, cholecystokinin

Some IBS Symptoms May Be Mediated by 5-HT Receptors in the Colon



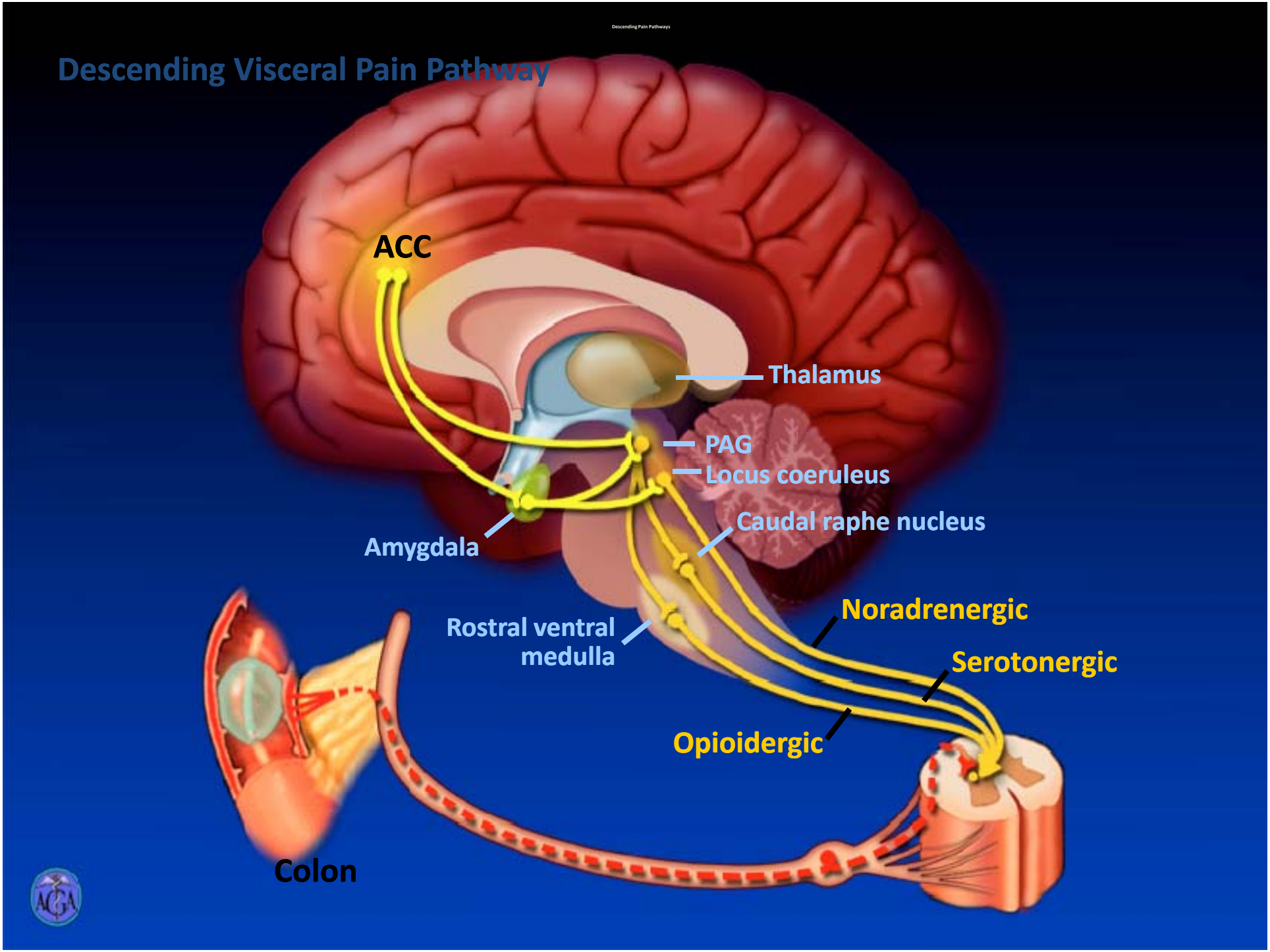
Adapted with permission from Professor David Grundy, Department of Biomedical Science, The University of Sheffield.

IBS: Brain functional MRI during rectal distention, differential activity in IBS v. C

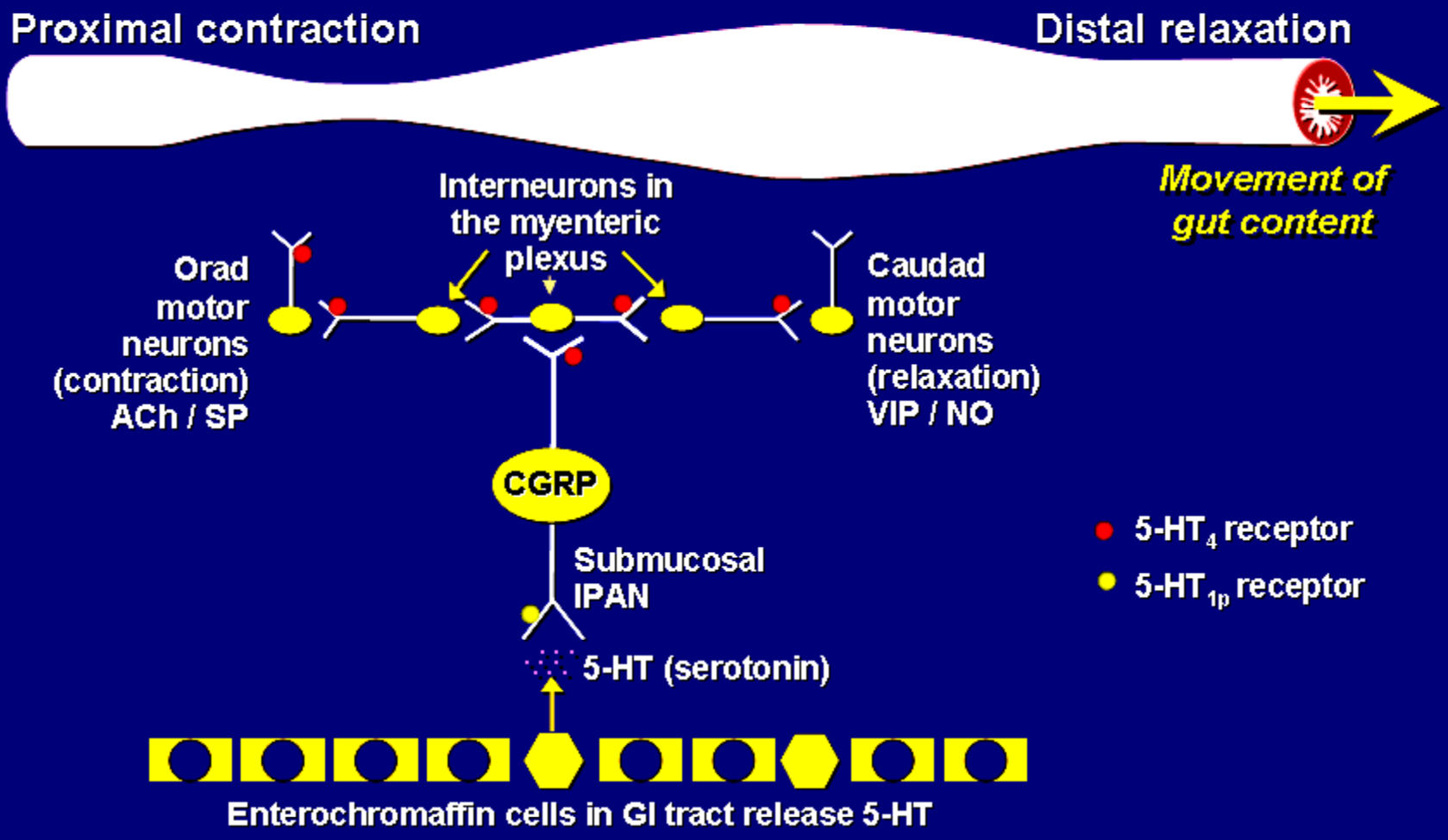


Mertz et. al., Gastroenterology 2000; 118:842

Descending Visceral Pain Pathway

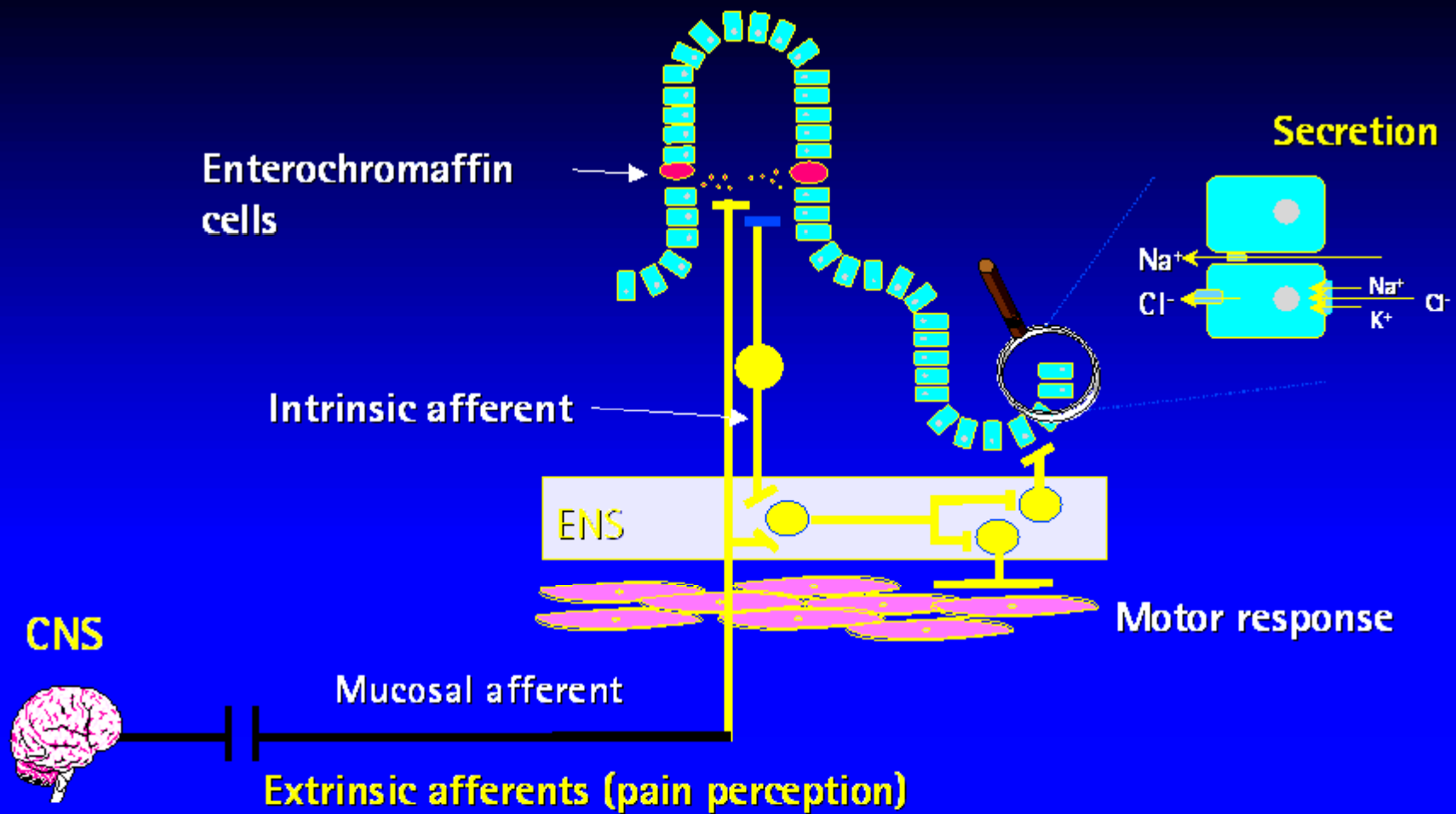


Serotonin (5-HT) and motor activity



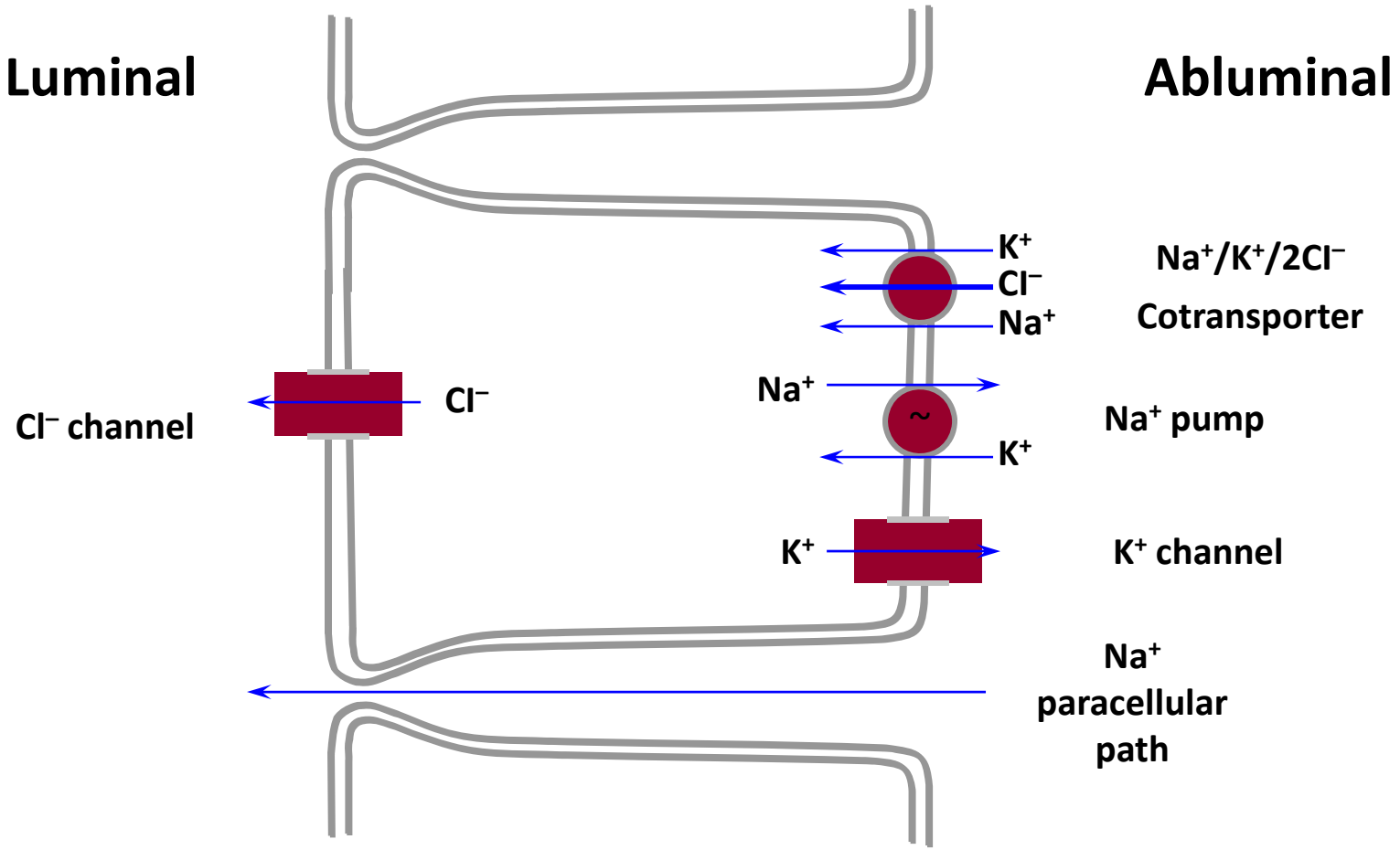
Adapted from Grider et al, Gastroenterology 1998; 115: 370
Adapted from Gershon, Rev Gastroenterol Disord 2003; 3: S25

Some IBS Symptoms May Be Mediated by 5-HT Receptors in the Colon



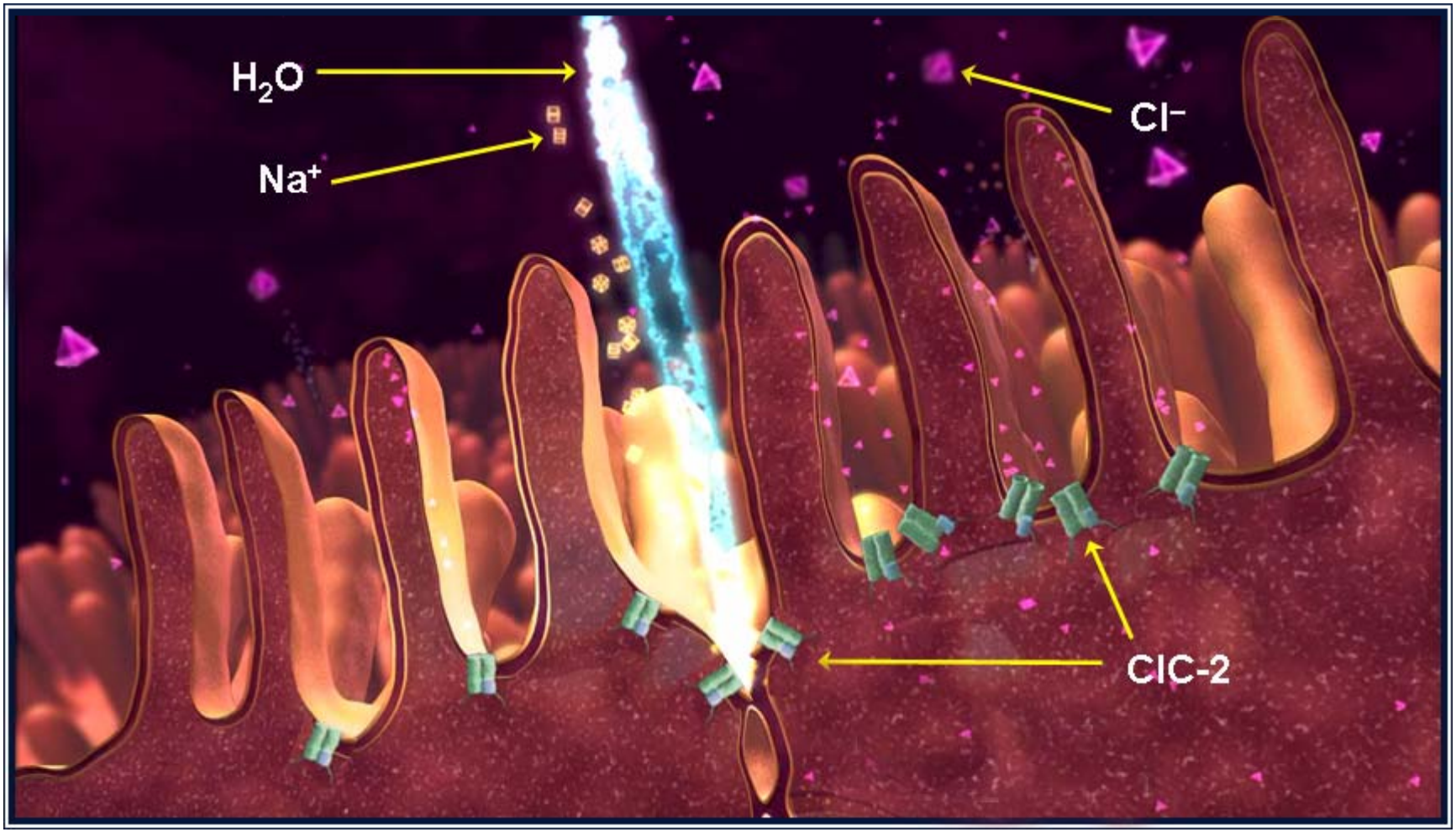
Adapted with permission from Professor David Grundy, Department of Biomedical Science, The University of Sheffield.

IBS: Pathophysiology
Secretion via Chloride Channels



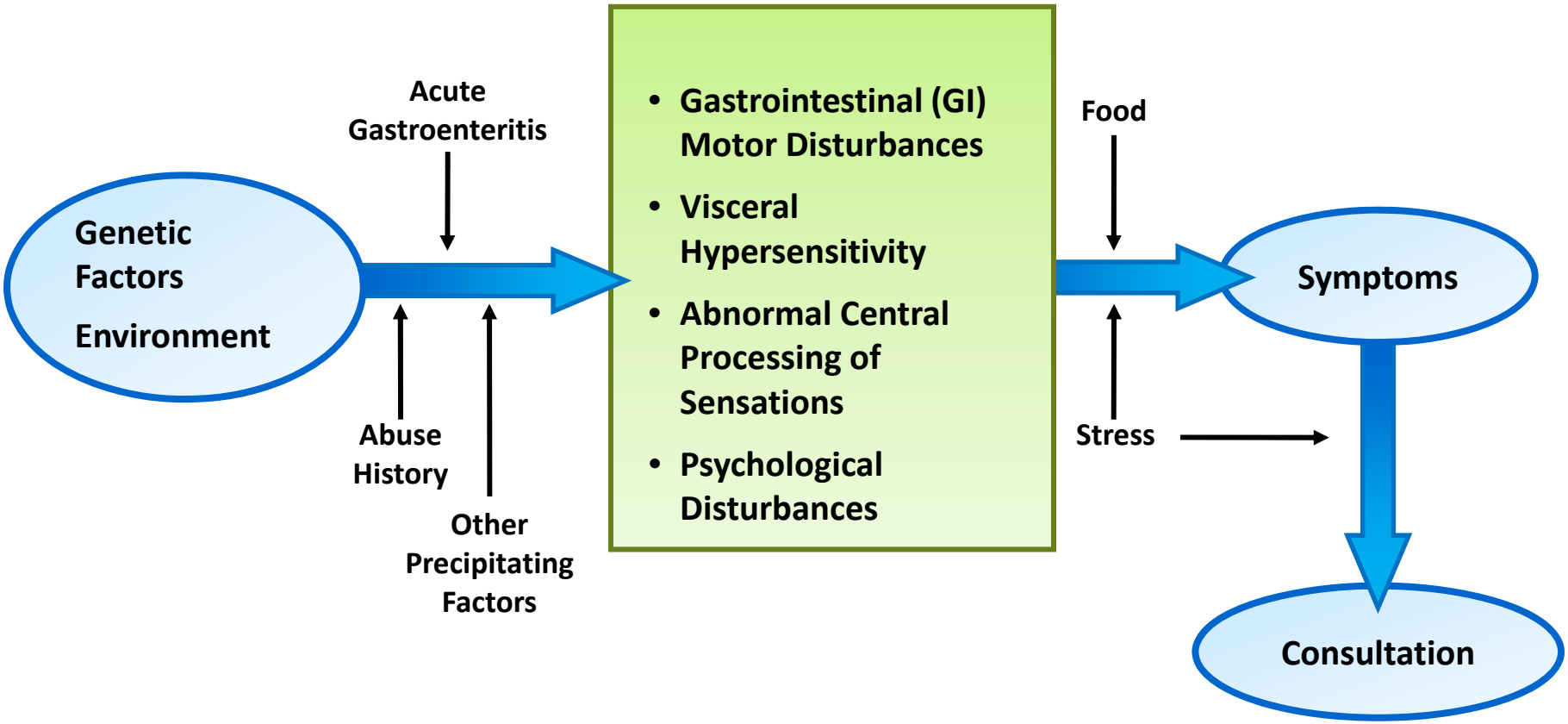
Adapted from Cuppoletti J, et al. *Am J Physiol Cell Physiol*. 2004;287:C1173-C1183.

IBS: Pathophysiology, Secretion via Chloride Channels (ClC-2)



Pathophysiology of IBS

Proposed Pathophysiology of IBS

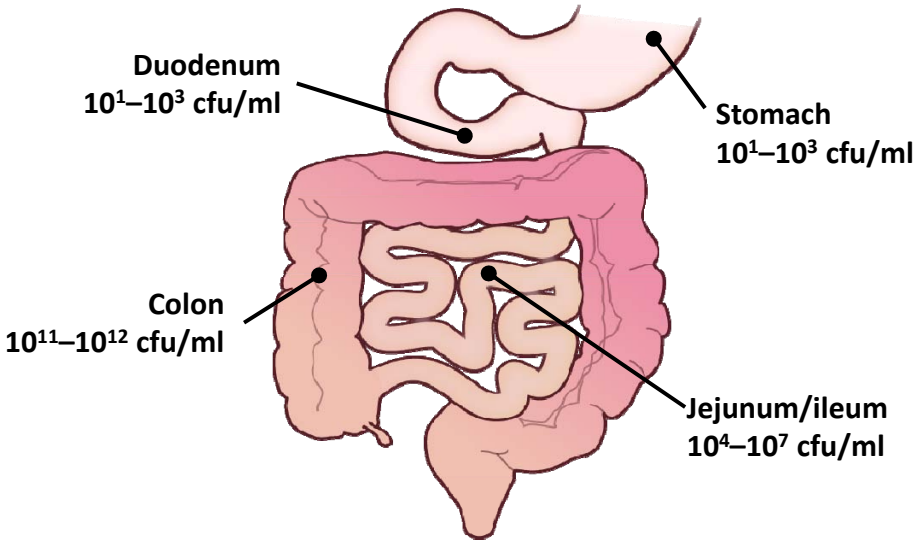


Adapted from Rome Foundation Functional GI Disorders Specialty Modules.

Gut Flora in IBS

- Postinfectious IBS (PI-IBS)
- SIBO

Normal Intestinal Microflora

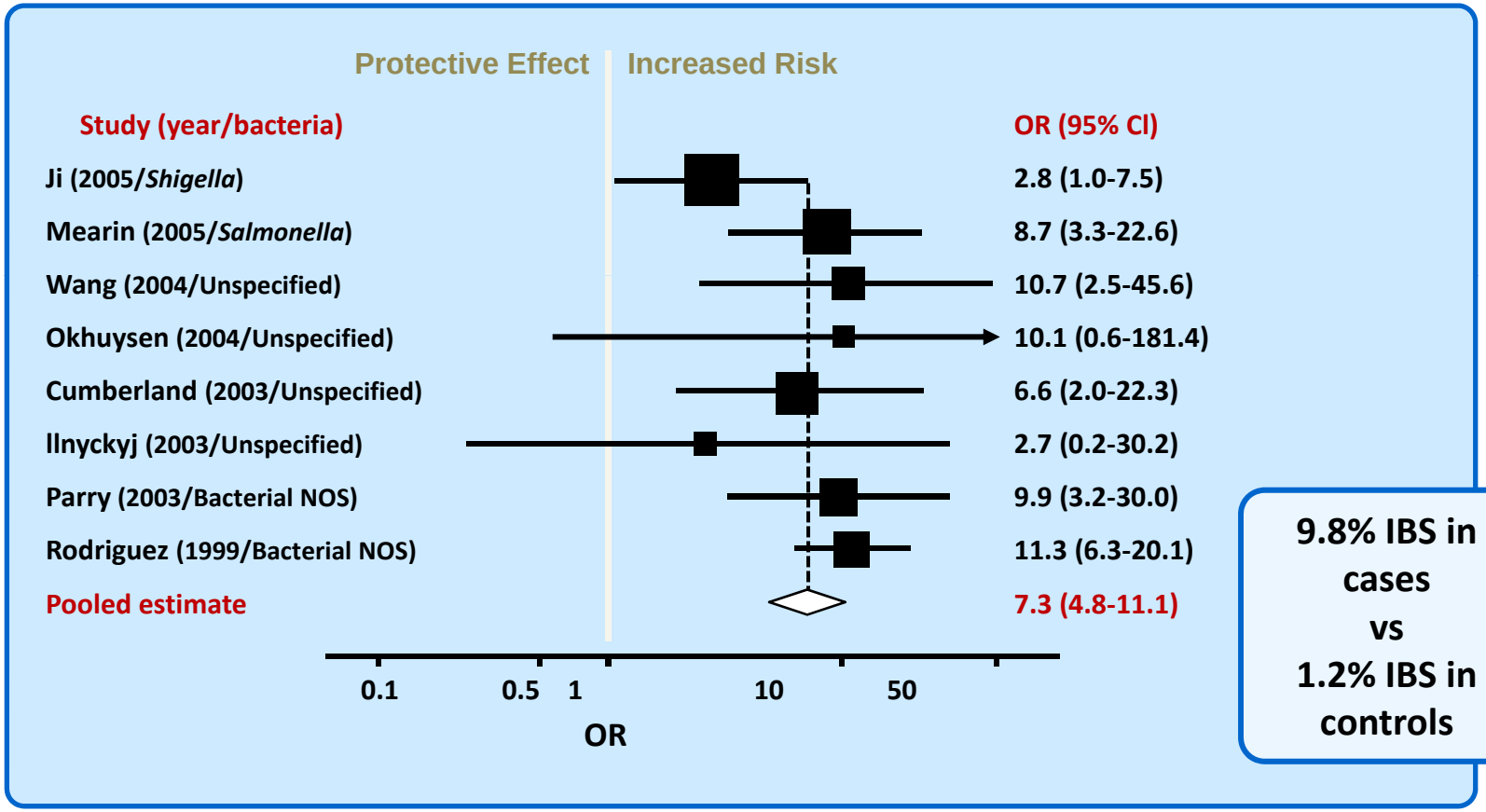


Most common bacteria	
Anaerobic genera	**Aerobic genera**
Bifidobacterium	***Escherichia***
Clostridium	***Enterococcus***
Bacteroides	***Streptococcus***
Eubacterium	***Klebsiella***

- 10 trillion **nonpathogenic** bacteria in the GI tract (1-2 kg)
- Exert protective function by creating a barrier against **pathogenic** by producing various anti-microbial factors
- Influence the development and function of the mucosal immune system

O'Hara AM. *EMBO Rep*. 2006;7:688-693.

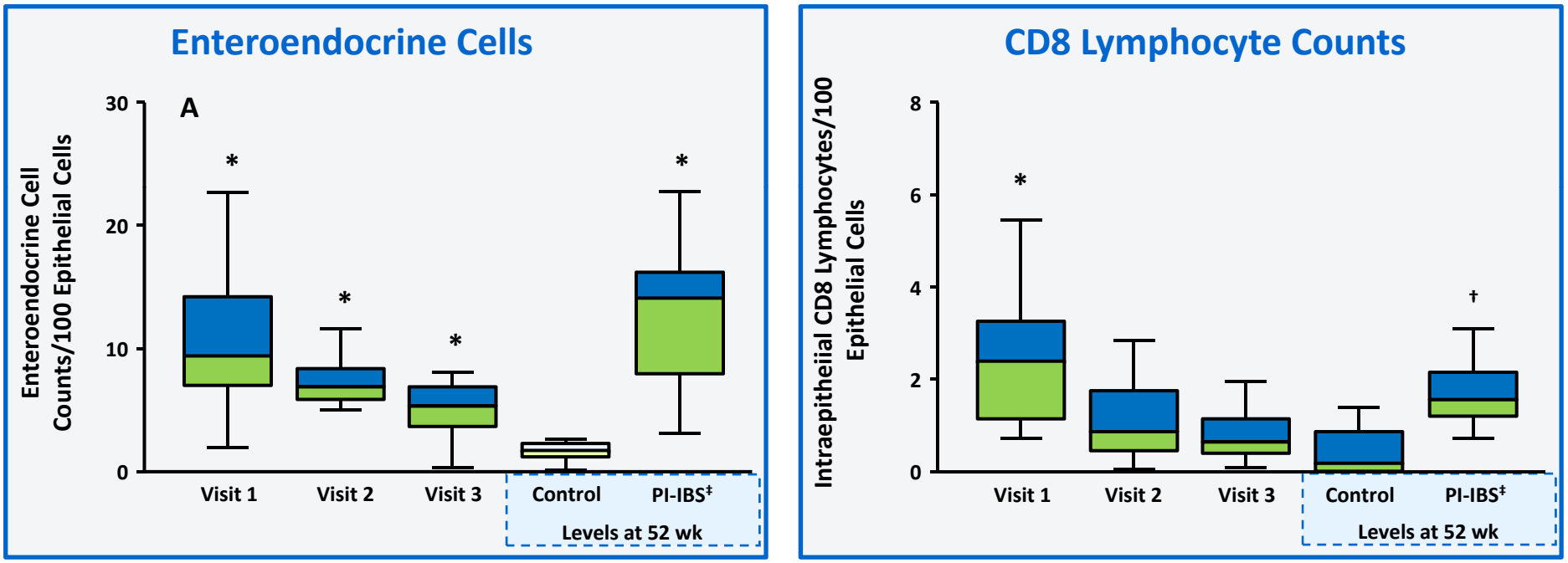
Risk of PI-IBS Increases 7-fold After Infectious Gastroenteritis*



*Systematic review of 8 studies involving 588,061 subjects; follow-up ranged from 3 to 12 months.

Halvorsen HA et al. *Am J Gastroenterol*. 2006;101:1894-1899.

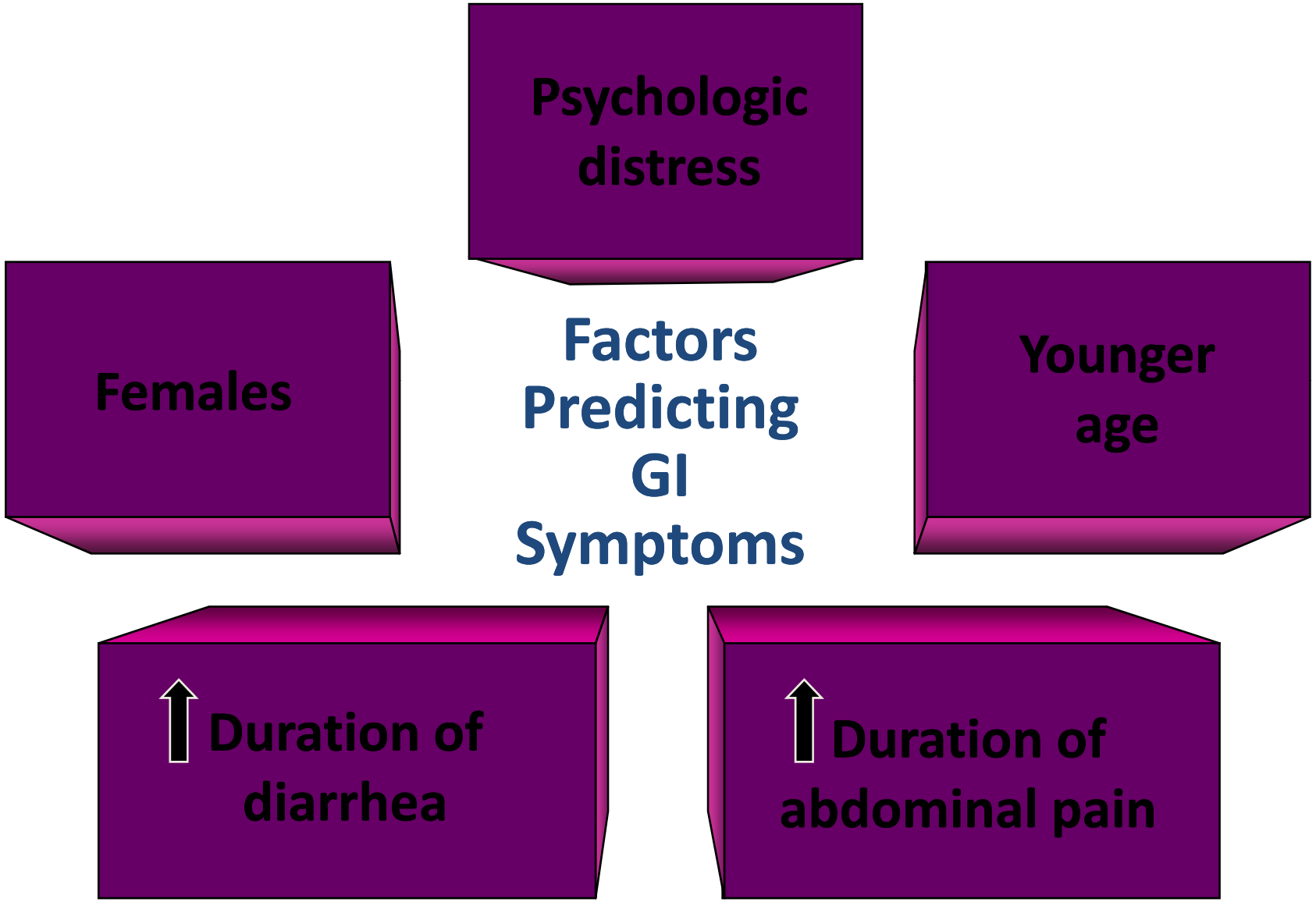
Increased Inflammatory Cells Found in PI-IBS Rectal Biopsies



*P<.001 vs controls; †Significantly elevated compared with controls.
‡Experienced gastroenteritis in previous 8 to 12 months.

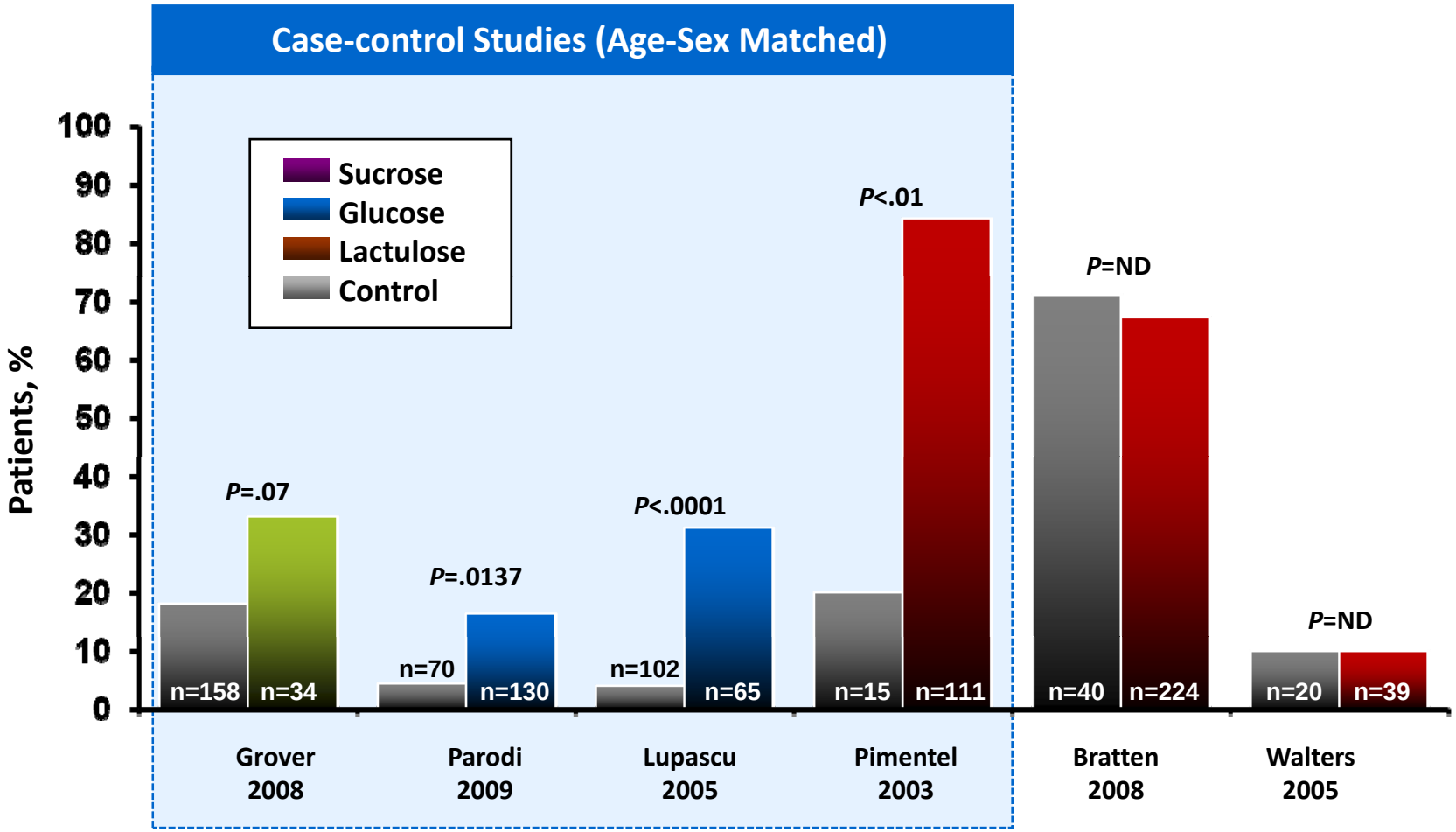
Spiller RC et al. *Gut*. 2000;47:804-811.

IBS - Post Infectious



Neal R, BMJ, 1997; 314:779
Gwee et al, Gut 1999; 44:400

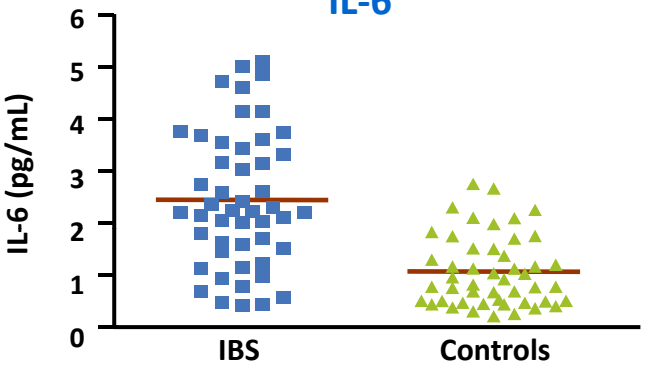
Prevalence of SIBO in IBS in Case-control Studies

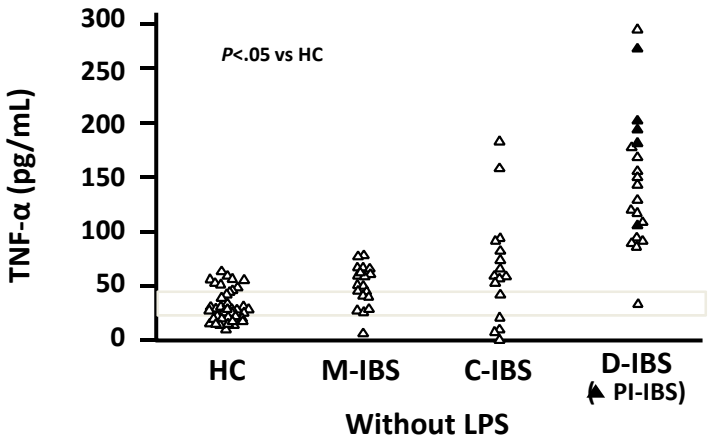


Grover M et al. *Neurogastroenterol Motil.* 2008;20:998-1008.
Parodi A et al. *J Clin Gastroenterol.* 2009. Epub ahead of print.
Lupascu A et al. *Aliment Pharmacol Ther.* 2005;22:1157-1160.
Pimentel M et al. *Am J Gastroenterol.* 2000;95:3503-3506.
Bratten JR et al. *Am J Gastroenterol.* 2008;103:958-963.
Walters B et al. *Am J Gastroenterol.* 2005;100:1566-1570.

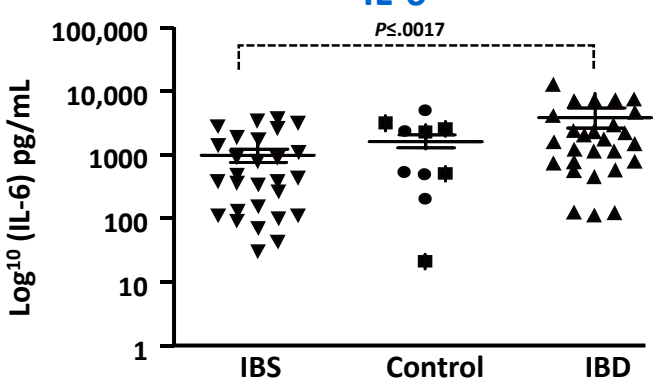
Elevated Serum But Low to Normal Mucosal Cytokines in IBS

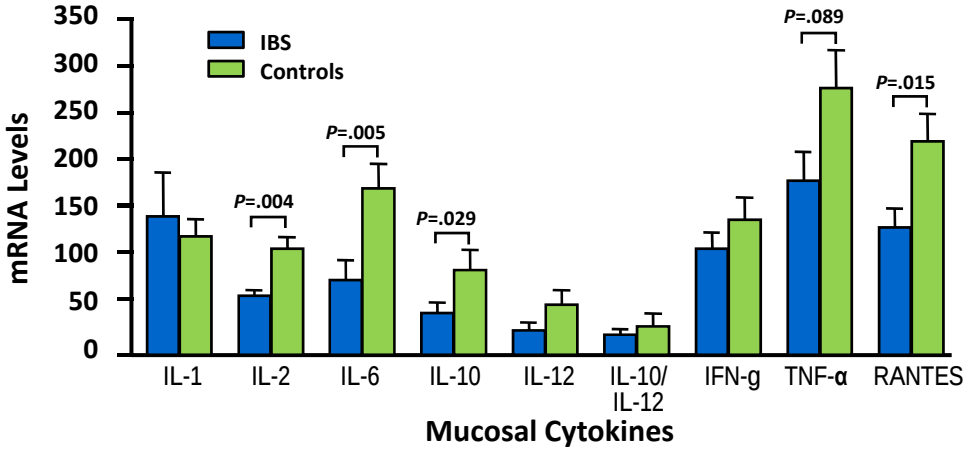
Serum[1,2]





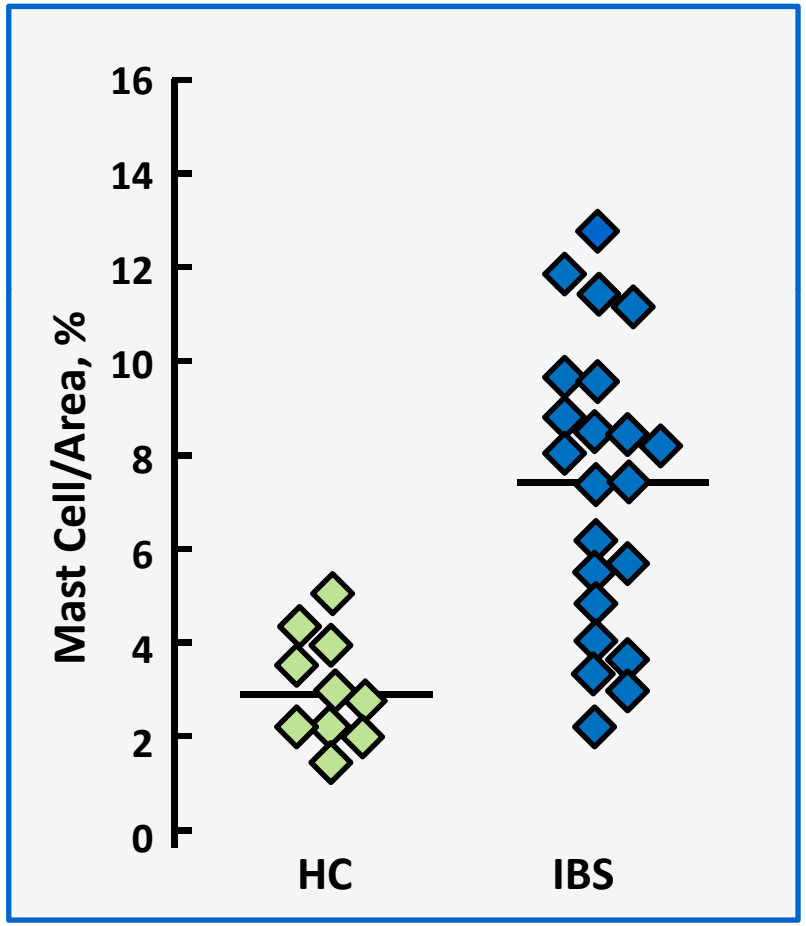
Colonic Mucosa[3,4]

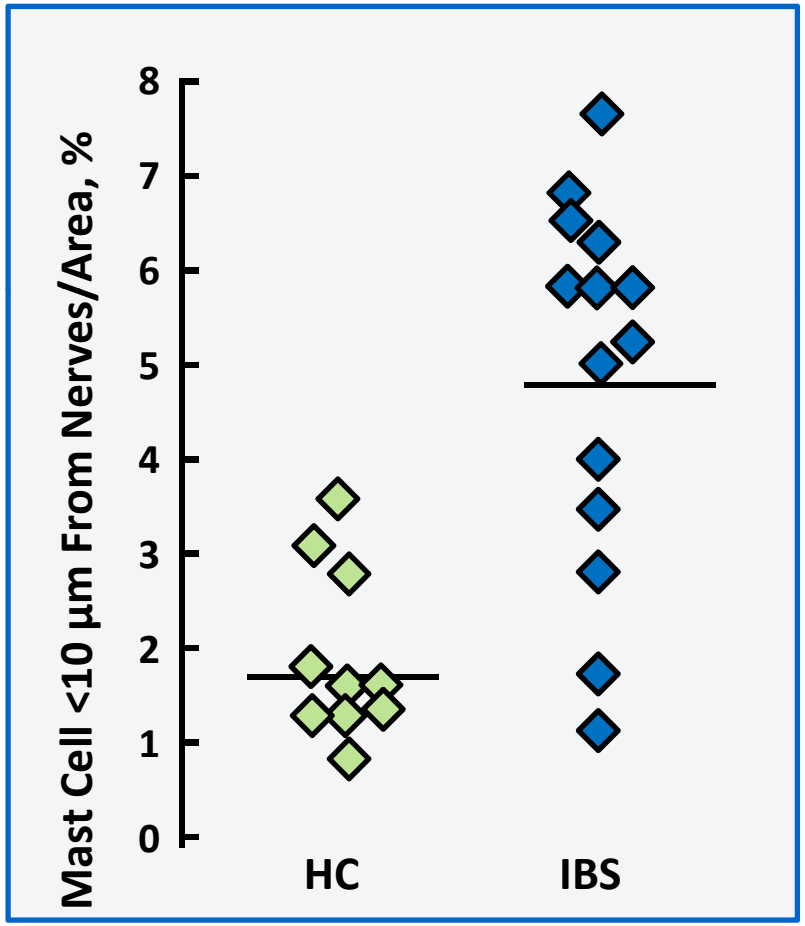




1. Dinan TG et al. *Gastroenterology*. 2006;130:304-311.
2. Liebregts T et al. *Gastroenterology*. 2007;132:913-920.
3. Macsharry J et al. *Scand J Gastroenterol*. 2008;43:1467-1476.
4. Chang L et al. *Neurogastroenterol Motil*. 2009;21:149-159.

Mast Cells Are Increased and Are Closer to Nerve Fibers in Colonic Mucosa in IBS

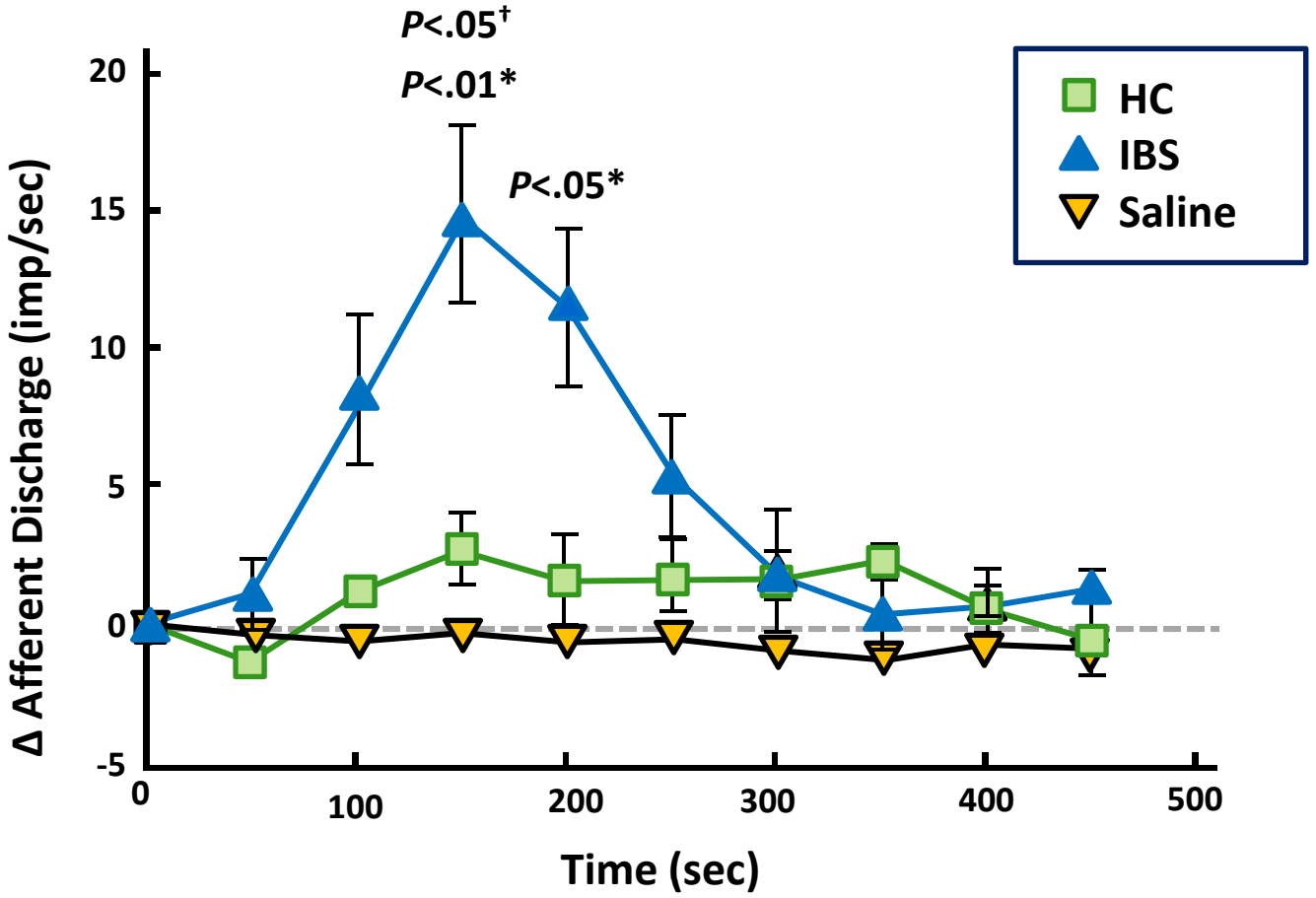




HC=healthy controls

Barbara G et al. *Gastroenterology*. 2007;132:26-37.

Mast Cell Mediators Excite Visceral Sensory Neurons



HC=healthy controls; *vs buffer; †IBS vs HC.

Barbara G et al. *Gastroenterology*. 2007;132:26-37.

IBS: Pathophysiology
The Role of Inflammation and Altered Gut Flora - Summary

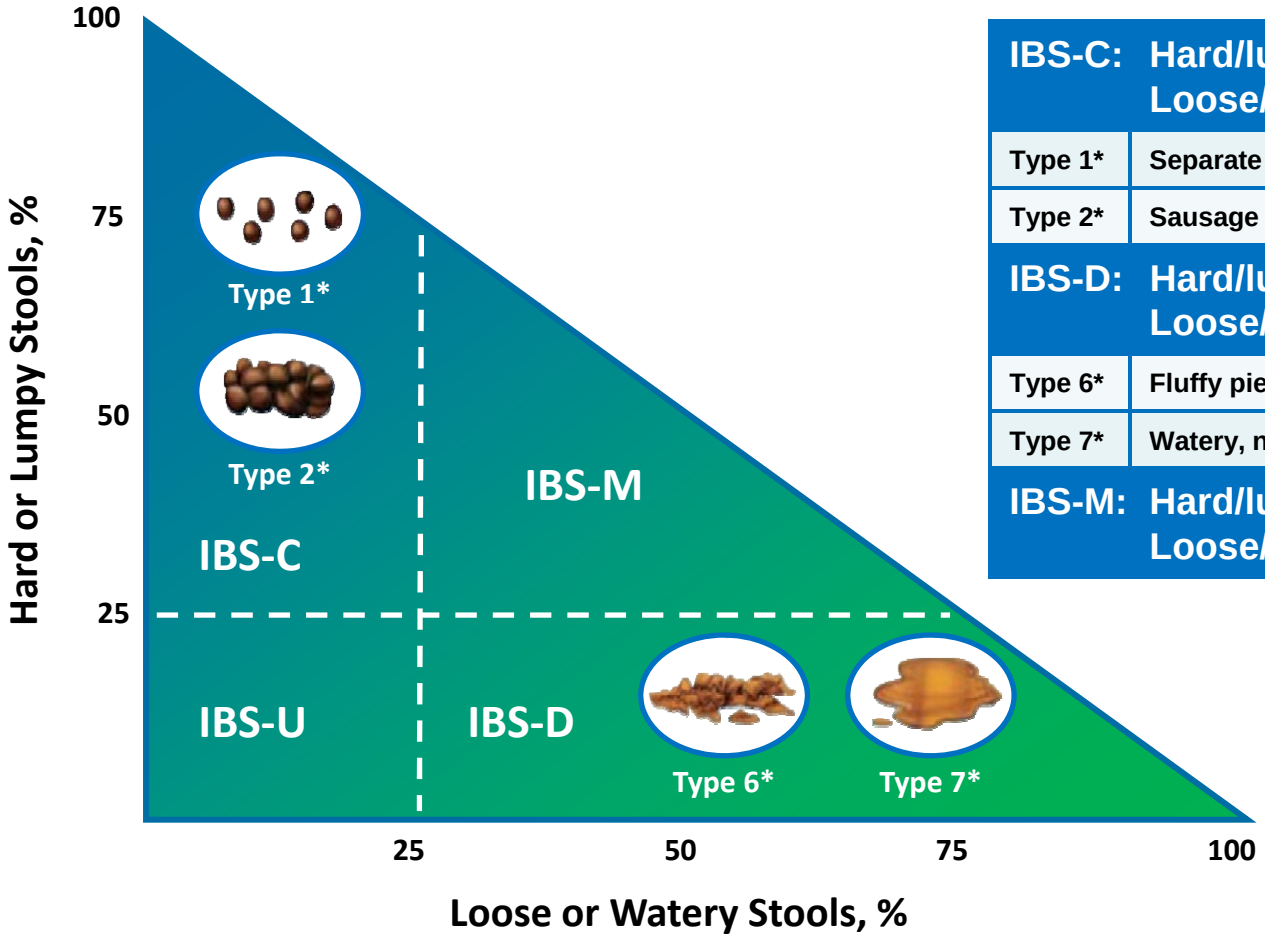
- Infectious gastroenteritis significantly increases the risk of developing IBS
  - Severity of gastroenteritis symptomsandare predictive for PI-IBS
  - Stress and other psychological factors are associated with PI-IBS
- Gut microfloramay play a role in IBS (SIBO)
- The role of inflammation is an emerging area of research in IBS

IBS: DIAGNOSIS
Rome III Diagnostic Criteria

- **Recurrent abdominal pain or discomfort for ≥3 days per month in the last 3 months associated with ≥2 of the following:**
  - **Improvement with defecation**
  - **Onset associated with a change in stool frequency**
  - **Onset associated with a change in stool form (appearance)**
- **Diagnostic criteria fulfilled for the last 3 months with symptom onset ≥6 months prior to diagnosis**

Longstreth GF et al. *Gastroenterology.* 2006;130:1480-1491.

IBS Subtypes Based on Bowel Form



IBS-C:	**Hard/lumpy stools ≥25% Loose/watery stools <25%**
Type 1*	Separate hard lumps like nuts (difficult to pass)
Type 2*	Sausage shaped but lumpy
IBS-D:	**Hard/lumpy stools <25% Loose/watery stools ≥25%**
Type 6*	Fluffy pieces with ragged edges, a mushy stool
Type 7*	Watery, no solid pieces, entirely liquid
IBS-M:	**Hard/lumpy stools ≥25% Loose/watery stools ≥25%**

*Bristol Stool Form Scale

IBS-C=constipation-predominant IBS; IBS-D=diarrhea-predominant IBS; IBS-M=mixed IBS; IBS-U=unsubtyped IBS.

Longstreth GF et al. *Gastroenterology.* 2006;130:1480-1491.

Diagnostic Investigation Recommended in Patients With Alarm Features

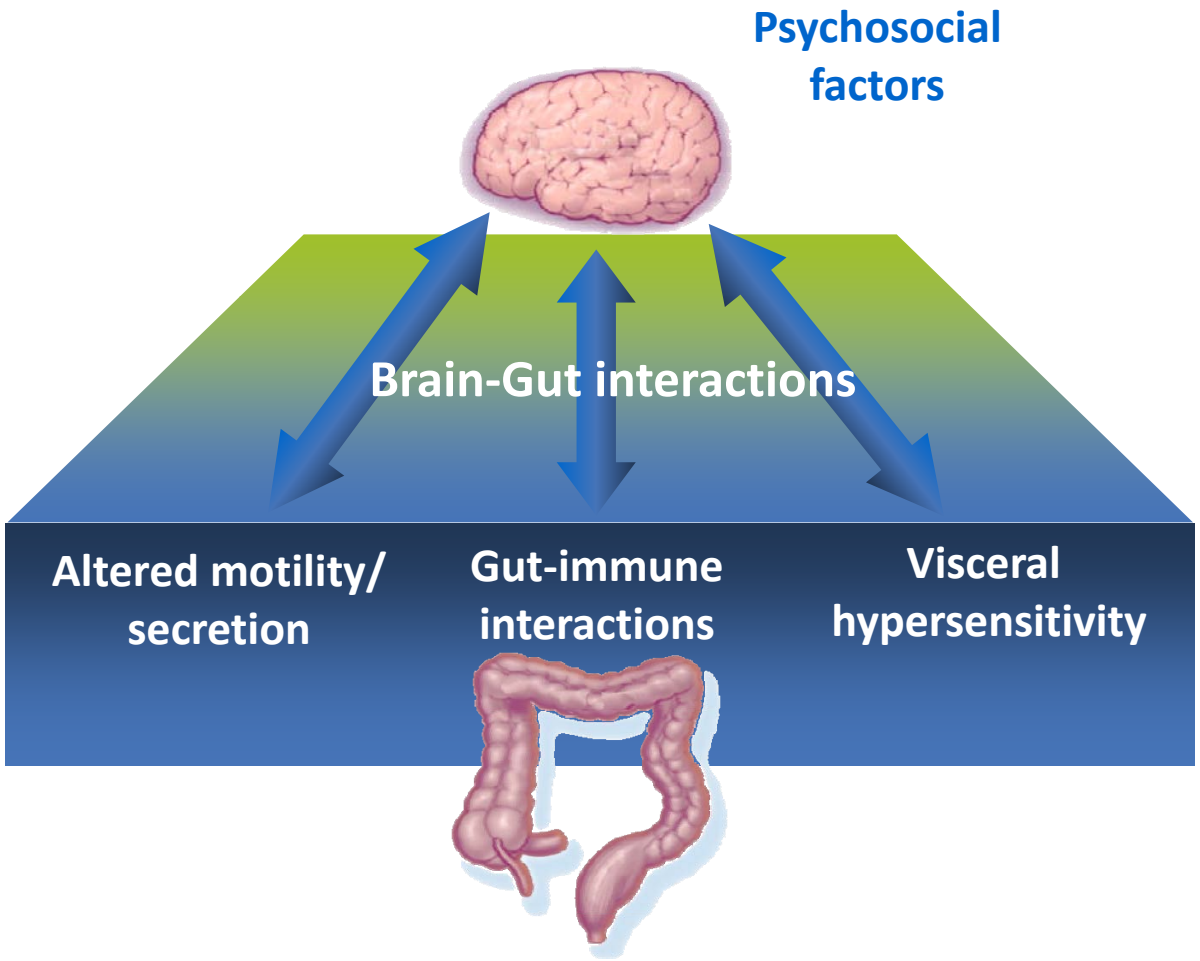
- Onset of symptoms after age 50
- GI bleeding
- Nocturnal diarrhea
- Weight loss
- Iron-deficiency anemia
- Family history of organic GI disease (colorectal cancer, inflammatory bowel disease [IBD], celiac sprue)

ACG Task Force on IBS. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.

Diagnosis of IBS: Summary

- **Patients with typical symptoms and no alarm features can be confidently diagnosed with IBS**
- **Patients with alarm features such as anemia, weight loss, a family history of colorectal cancer, IBD, or celiac disease, or symptom onset after age 50 warrant a more detailed evaluation (colon cancer screening)**
- **Patients with IBS-D or M should be screened for celiac sprue**
- **When patients with IBS-D undergo colonoscopy, random biopsies should be obtained to rule out microscopic colitis**

IBS: Therapeutic Strategies



Agents acting in CNS and peripherally

- Antidepressants
- Serotonin modulators

Peripherally-acting drugs

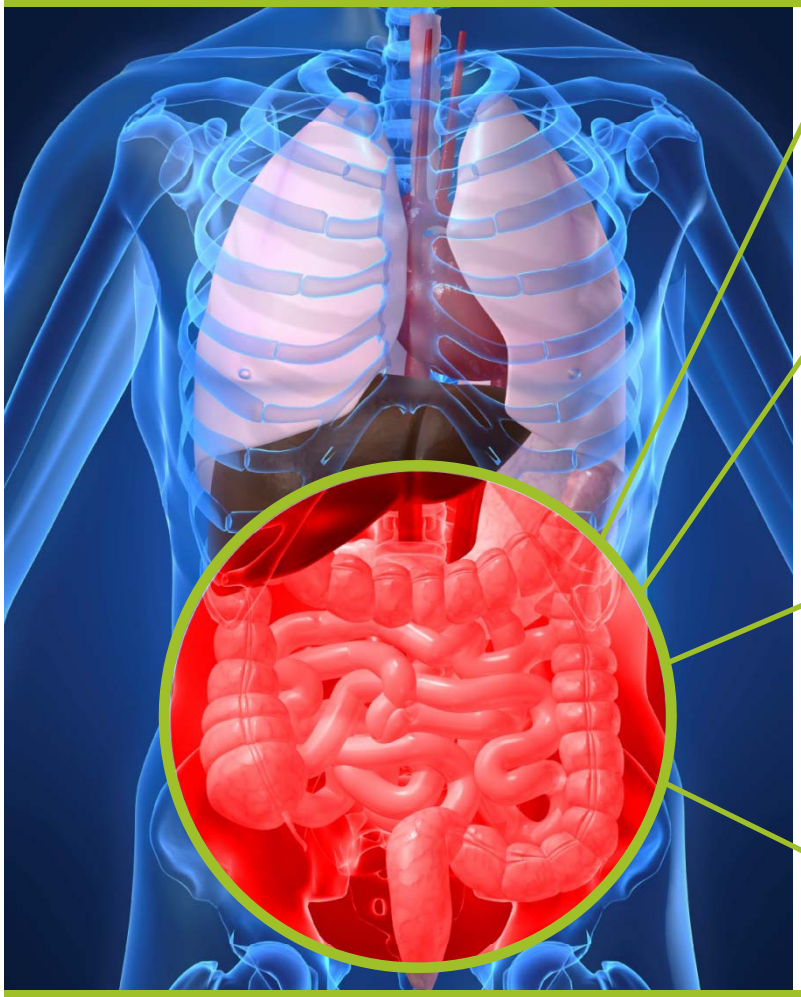
- Chloride channel modulators
- Antibiotics
- Probiotics
- Antidiarrheals
- Fiber/bulking agents
- Laxatives
- Antispasmodics

CNS=central nervous system; ANS=autonomic nervous system; CRF=corticotrophin-releasing factor; NK=neurokinin.

Adapted from Rome Foundation Functional GI Disorders Specialty Modules.

IBS: PERIPHERAL MANAGEMENT

Pharmacologic RxIs Directed at Dominant Sxs



Diarrhea
- Loperamide
- Diphenoxylate
- Alosetron

Constipation
- Fiber
- Osmotic and stimulant laxatives
- Lubiprostone

Abdominal pain/ discomfort
- Antispasmodics
- Antidepressants
- Alosetron
- Lubiprostone

Bloating
- Antibiotics
- Probiotics

Adapted from Rome Foundation Functional GI Disorders Specialty Modules.

Evidence-based Summary of Medical Therapies for IBS-D Symptoms

	Improvements in Symptoms					Grading Recommendations*	
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency	Recommendation	Evidence
Fiber (psyllium)						Insufficient evidence	
Loperamide			+	+		2	C
Antidepressants	+	+				1	B
Antispasmodics	±	+				2	C
Alosetron	+	+	+	+		2/1	A/B
Rifaximin	+	+			+	1	B
Probiotics (*bifidobacterial* some combos)	+					2	C

*Recommendations – based on the balance of benefits, risks, burdens, and sometimes cost: Grade 1=strong, Grade 2=weak; Assessment of Quality of evidence – according to the quality of study design, consistency of results among studies, directness and applicability of study endpoints: Grade A=high, Grade B=moderate, Grade C=low

ACG Task Force on IBS. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.

Adapted from Rome Foundation Functional GI Disorders Specialty Modules.

Evidence-based Summary of Medical Therapies for IBS-C Symptoms

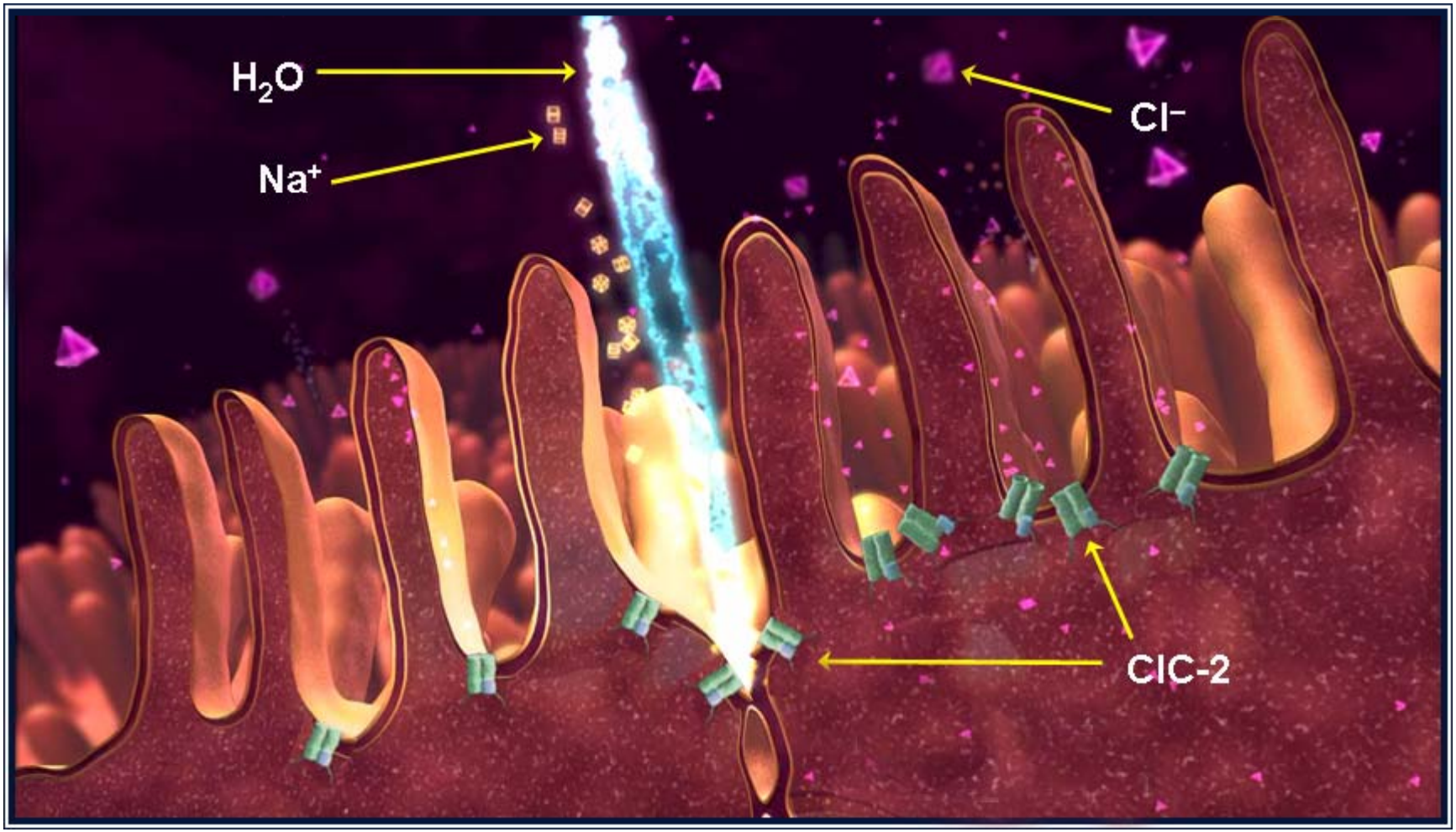
	Improvements in Symptoms					Grading Recommendations*	
	Global Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency	Recommendation	Evidence
Fiber (psyllium)				+	+	2	C
Laxatives (PEG)				+		2	C
Lubiprostone	+	+			+	1	B
Antidepressants	+	+				1	B
Tegaserod†	+	±	+	+	+	2	A

*Recommendations – based on the balance of benefits, risks, burdens, and sometimes cost: Grade 1=strong, Grade 2=weak; Assessment of Quality of evidence – according to the quality of study design, consistency of results among studies, directness and applicability of study endpoints: Grade A=high, Grade B=moderate, Grade C=low

† Available only under Emergency IND program. PEG=polyethylene glycol.

Adapted from ACG Task Force on IBS. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.
Adapted from Rome Foundation Functional GI Disorders Specialty Modules.

Lubiprostone activates ClC-2 Stimulates Gut Secretion



AMITIZA™ (lubiprostone) Activates ClC-2 Chloride Channels

- Specific chloride channel-2 (ClC-2) activator
- Promotes fluid secretion
- Enhances intestinal fluid secretion to facilitate increased motility
- Dose for IBS-C: 8ucg PO BID with meals

Ueno R, et al. *Gastroenterology*. 2004;126(suppl 2):A298. Abstract M1109.

IBS: Treatment with Antibiotics

Rifaximin = non-absorbable ABX derived from rifamycin

- < 0.4% systemic absorption
- Delivered in high concentrations to GI tract
- Inhibits RNA synthesis of targets microorganisms
  - In-vitro activity against Gm+ and Gm- aerobic and anaerobic bacteria
- Improves IBS Sxs for up to 10 weeks beyond RX
- Improves gas-related Sxs (bloating, flatulence) in pts without SIBO

Probiotics - Definitions

Probiotics: live, viable microorganisms that when ingested in adequate amounts, exert a health benefit on the host[1]

Single-organism probiotics[1-3]

E. coli 1917 *Nissle*
L. salivarius UCC4331
L. reuteri
L. casei
L. plantarus 299v
L. rhamnosus GG
B. infantis 35624
B. animalis DN-173010
Saccharomyces boulardii

Composite probiotics[1-3]

VSL #3 (*Bifidobacterium, Lactobaciluus, Streptococcus salivarius thermophilus*)

Lacteol Fort (*L.acidophilus* LB, lactose monohydrate, calcium carbohydrate, silicic acid, talc, magnesium stearate, anhydrous lactose)

Prebiotics: food ingredients that influence the composition of the commensal flora[2]

Symbiotics: combination of probiotic and prebiotic[2]

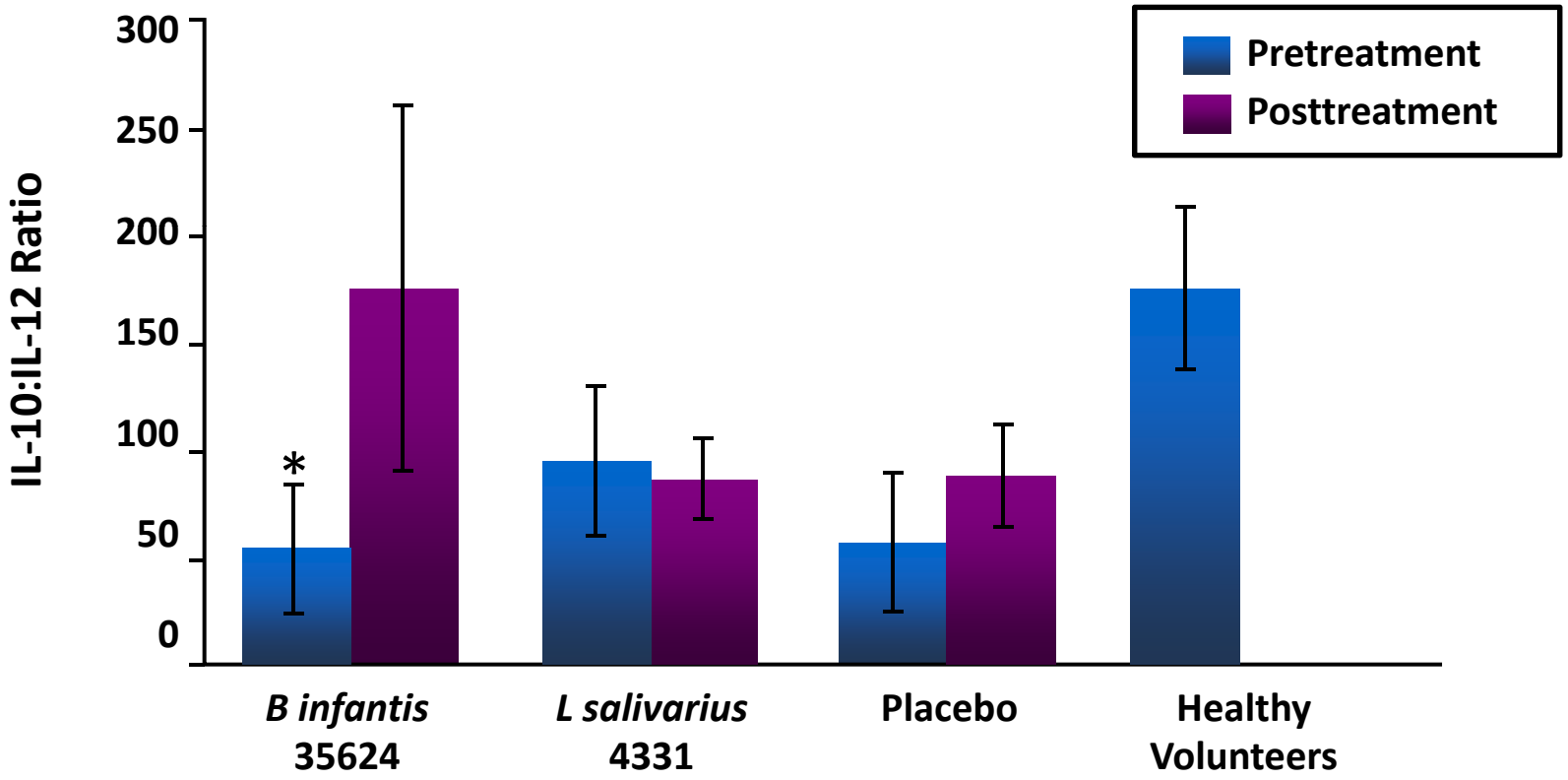
1. Quigley EMM, Flourie B. *Neurogastroenterol Motil*. 2007;19:166-172.
2. Brenner DM et al. *Am J Gastroenterol*. 2009;104:1033-1039.
3. Shanahan F. *Am J Physiol Gastrointest Liver Physiol*. 2005;288:417-421.

Potential Mechanisms of Probiotics in IBS

- Displace gas-producing, bile salt-deconjugating bacterial species
  - Inhibit pathogenic bacterial adherence
- Immunomodulatoryproperties
- Acidification of the colon by nutrient fermentation
- Secretion of bacteriocins that inhibit pathogenic bacteria
- Enhance epithelial barrier function

Quigley EMM. *Curr Opin Pharmacol*. 2008;8:704-708.
Spiller R. *Aliment Pharmacol Ther*. 2008;28:385-396.

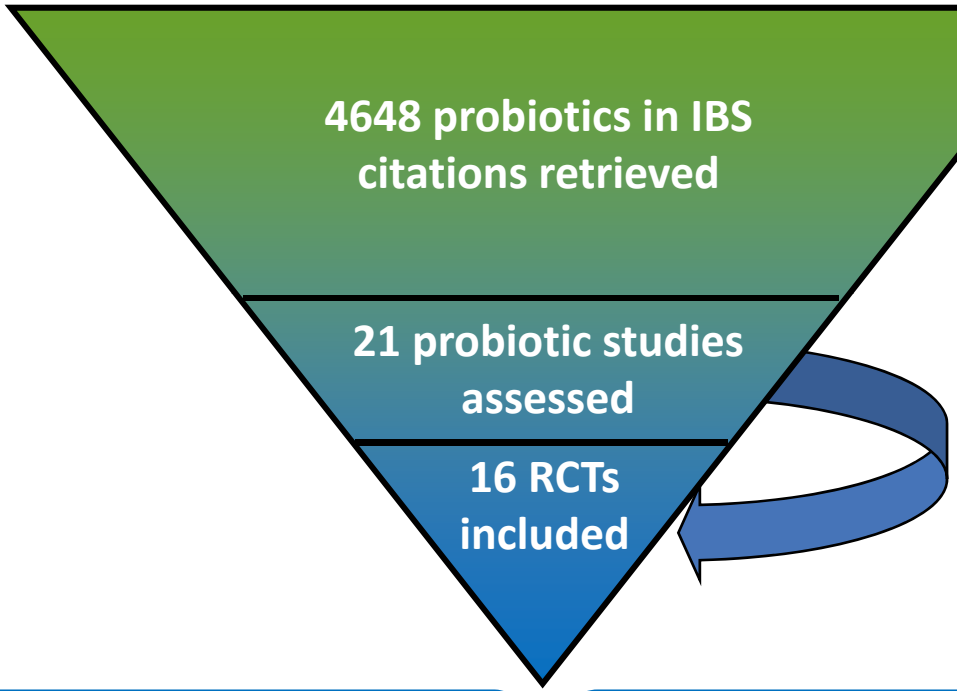
Bifidobacterium infantis Affects Cytokine Levels in IBS



**P*=.001.

O'Mahony L et al. *Gastroenterology*. 2005;128:541-551.

B infantis Improves IBS Symptoms But Insufficient Evidence for Other Probiotics



RCTs

- Adults with IBS defined by Manning or Rome II criteria
- Single or combination probiotic vs placebo
- Improvement in IBS symptoms and/or decrease in frequency of AEs reported

No other probiotic showed significant improvement in IBS symptoms in appropriately designed RCTs
(7 RCTs with isolated *Lactobacillus* species)

B infantis 35624 demonstrated efficacy in 2 appropriately designed RCTs

RCTs=randomized, controlled trials.

Brenner DM et al. *Am J Gastroenterol*. 2009;104:1033-1049.

Antibiotics and Probiotics for IBS: Unanswered Questions/Issues

	Antibiotics	Probiotics
Optimal dose, and duration of therapy	?	?
Long-term safety and effectiveness (eg, durability of response)	?	?
Potential contribution of widespread use to bacterial resistance	?	
Benefits and timing of sequential strategies (eg, probiotic use after antibiotics)	?	?
Lack of quality control ensuring purity, viability, and safety		?

Saad RJ, Chey WD. *Expert Opin Invest Drugs*. 2008;17:117-130.
ACG Task Force on IBS. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.
Pimentel M et al. *Ann Intern Med*. 2006;145:557-563.

Peripheral Mgmt of IBS Symptoms: Summary

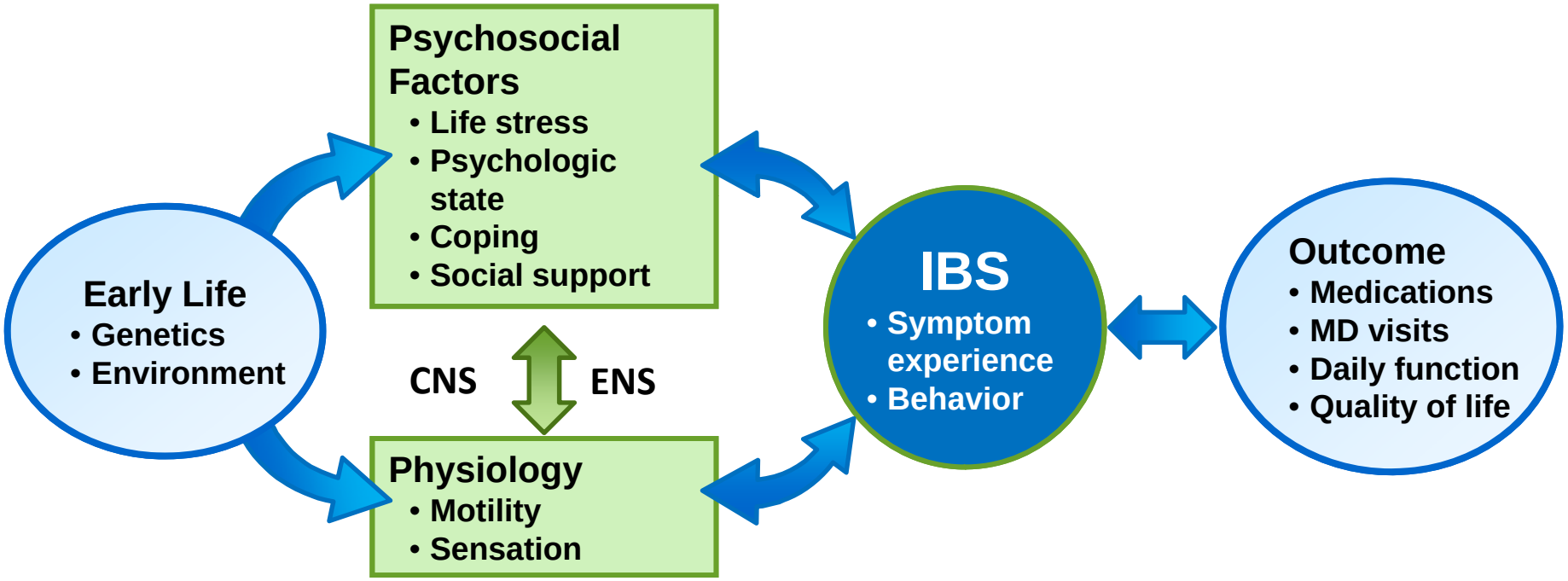
- Current therapeutic strategies are largely directed against predominant symptoms
- Evidence-based treatments
  - IBS-D: TCAs, alosetron, non-absorbable ABX,
  - IBS-C: lubiprostone, SSRIs
- Rifaximin appears effective for global improvement of IBS symptoms
- Many probiotics studied in IBS
  - Efficacy demonstrated with B.infantis

  (More data needed to determine the role + characterize optimal RX)

*** Restricted use through the alosetron prescribing program; † Available only under an Emergency IND program.**

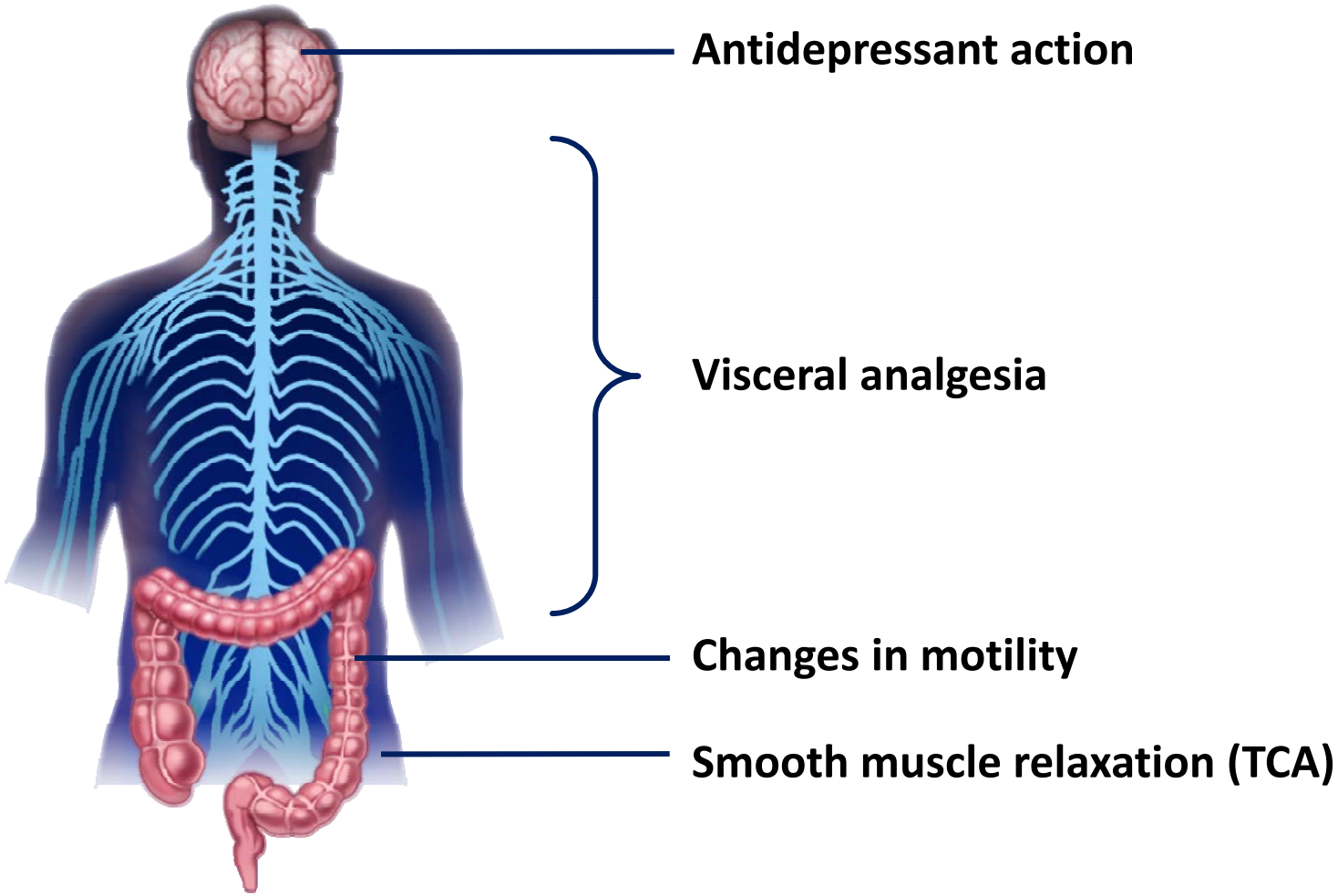
Central Management of IBS Symptoms

IBS Conceptual Model



Drossman DA et al. *Gastroenterology*. 2002;123:2108-2131.

Antidepressants: Mechanism of Action

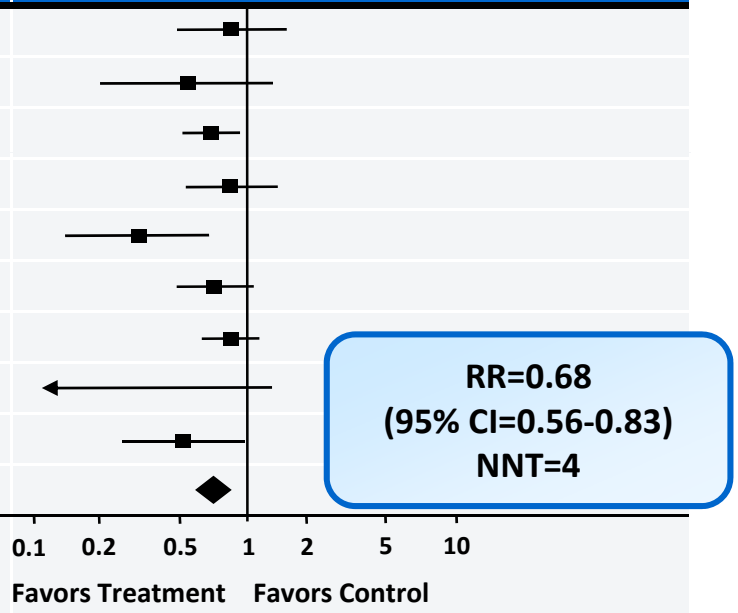


TCA=tricyclic antidepressant.

Adapted from Rome Foundation Functional GI Disorders Specialty Modules.

Efficacy of TCAs in Relieving Global IBS Symptoms*

Study (yr, drug dose)	Treatment n/N	Control n/N	RR (Random) 95% CI
Heefner (1978, desipramine 150 qd)	10/22	12/22	
Myren (1982, trimipramine 50 qd)	5/30	10/31	
Nigam (1984. amitriptyline 12.5 qd)	14/21	21/21	
Boerner (1988, doxepin 50 qd)	16/42	19/41	
Bergmann (1991, trimipramine 50 qd)	5/19	14/16	
Vij (1991, doxepin 75 qd)	14/25	20/25	
Drossman (2003, desipramine 50-150 qd)	60/115	26/57	
Talley (2008, imipramine 50 qd)	0/18	5/16	
Vahedi (2008, amitriptyline 10 qd)	8/27	16/27	
Subtotal (95% CI)	319	256	

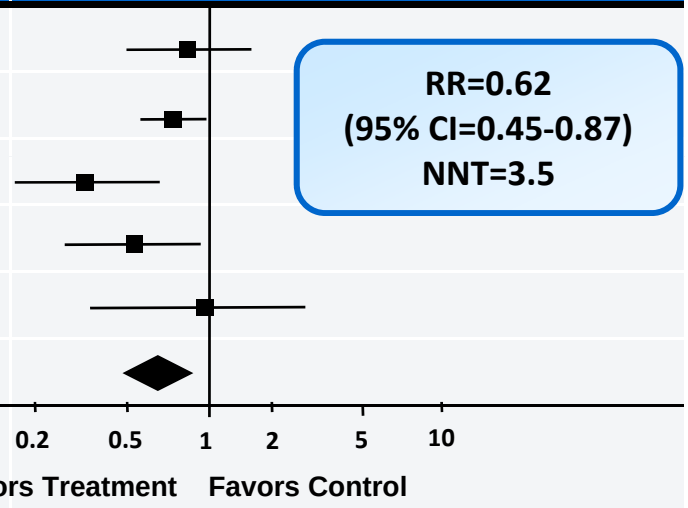


*Significant heterogeneity among studies may limit conclusions.
Study duration ranged from 4 weeks to 3 months.

Ford AC et al. *Gut*. 2009;58:367-378.

Efficacy of SSRIs in Relieving Global IBS Symptoms*

Study (yr, drug dose)	Treatment n/N	Control n/N	RR (Random)95% CI
Kuiken (2003, fluoxetine 20 qd)	9/19	12/21	
Tabas (2004, paroxetine 10-40 qd)	25/44	36/46	
Vahedi (2005, fluoxetine 20 qd)	6/22	19/22	
Tack (2006, citalopram 20-40 qd)	5/11	11/12	
Talley (2008, citalopram 40 qd)	5/17	5/16	
Subtotal (95% CI)	113	117	



*Significant heterogeneity among studies may limit conclusions.
Study duration ranged from 6 weeks to 12 weeks.

Ford AC et al. *Gut*. 2009;58:367-378.

IBS–Psychological Treatments

- Cognitive–behavior therapy (CBT)
  - Uses diaries and exercises to reframe maladaptive thoughts and increase control over symptoms
- Interpersonal psychodynamic therapy (“talk therapy”)
  - Identify and address difficulties in relationships
- Hypnotherapy (HT)
  - Suggestion used to reduce gut sensations
- Relaxation training (stress reduction)
  - Uses imagery and relaxation techniques to reduce autonomic arousal and stimulate muscular relaxation

Drossman DA et al. *Gut*. 1999;45:II25-II30.

Psychosocial Therapies Are More Effective Than Usual Care at Relieving Global IBS Symptoms

Treatment Modality	Studies (n)	N		RR (95% CI)
		Patients	Controls	
Cognitive behavioral therapy (CBT)	7	279	212	0.60 (0.42-0.87)
Hypnotherapy	2	20	20	0.48 (0.26-0.87)
Multicomponent psychological therapy	4	106	105	0.69 (0.56-0.86)
Dynamic psychotherapy	2	138	135	0.60 (0.39-0.93)

Ford AC et al. *Gut*. 2009;58:367-378.

Summary: Central Management of IBS

- Psychotropic agents and psychological/behavioral therapies can effectively relieve IBS symptoms
- Antidepressants (TCAs, SSRIs) exert their beneficial effects in IBS via central and peripheral actions, which can be independent of their effect on mood
- Efficacious psychological therapies for IBS include cognitive behavioral therapy, hypnosis, psychotherapy and stress management

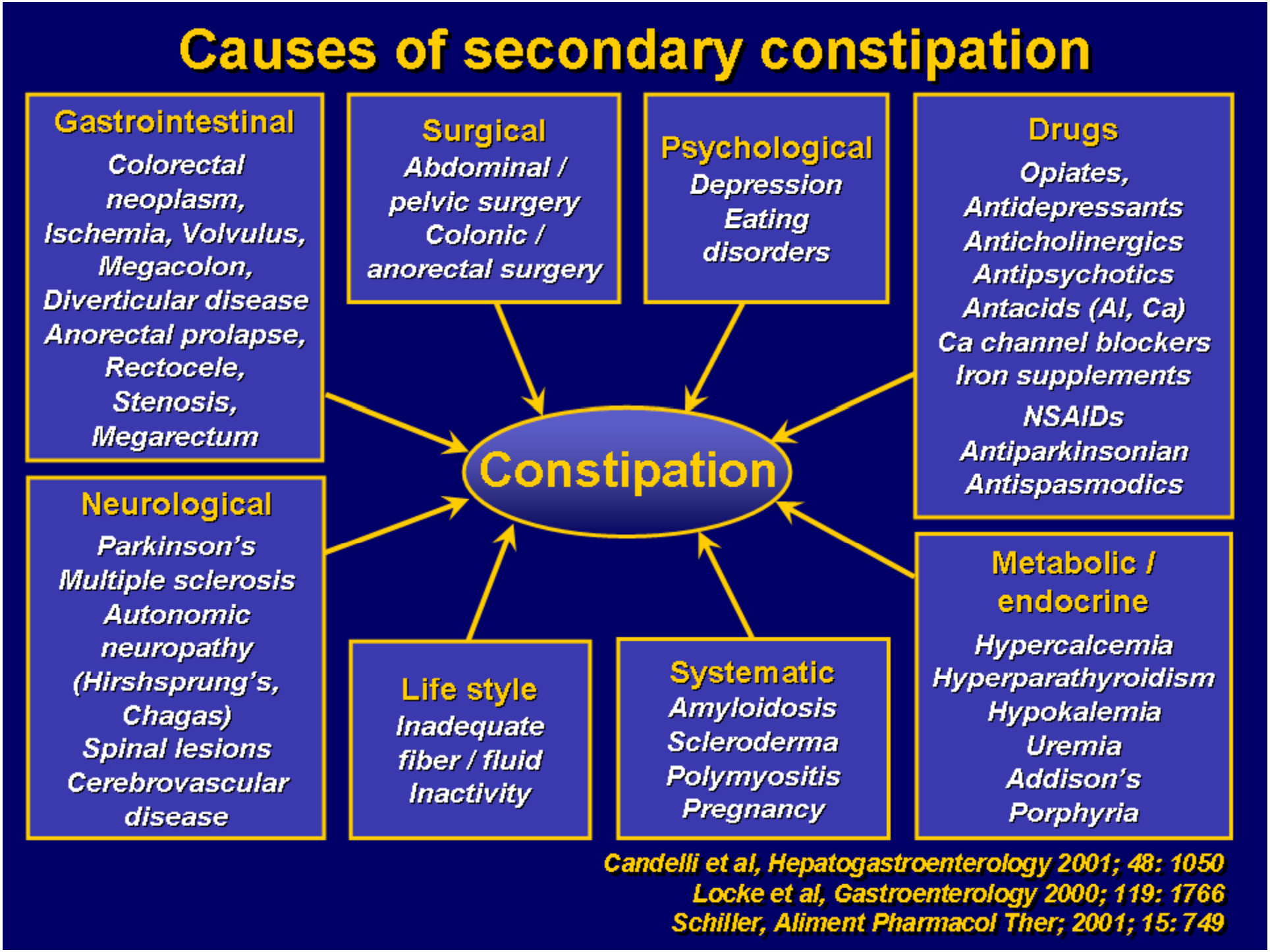
IBS: CONCLUSIONS

- IBS is a complex biopsychosocial disorder
- Pathophysiologic mechanisms include an interplay between genetic, early life, environmental factors with gut physiology (hypersensitivity, dysmotility) and different central processing+ psych. co-morbidities
- Low-grade inflammation + altered gut flora may play a role in pathophysiology of IBS
- Current pharmacotherapies are largely directed at the predominant symptoms (peripheraly directed Rxs)
- Non-absorbable ABX + B. infantis PBX appear effective for global improvement in IBS symptoms
- Centrally directed Rxs may reduce global IBS symptoms + improve well-being in selected patients

CHRONIC CONSTIPATION

- **PRIMARY (IDIOPATHIC)**
  - SLOW TRANSIT
  - PELVIC FLOOR DYSSYNERGIA
- **SECONDARY**
  - RELATED TO A VARIETY OF CAUSES

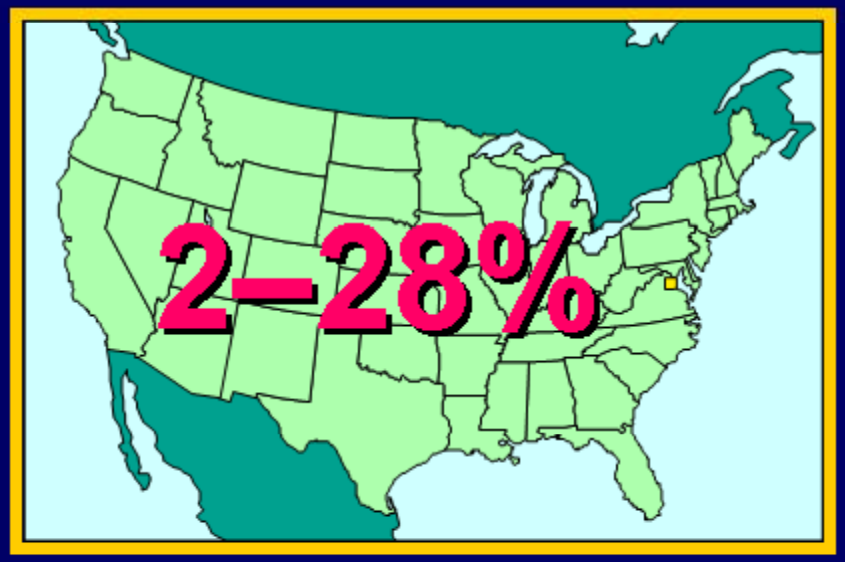
Causes of secondary constipation



Candelli et al, Hepatogastroenterology 2001; 48: 1050
Locke et al, Gastroenterology 2000; 119: 1766
Schiller, Aliment Pharmacol Ther; 2001; 15: 749

Prevalence and incidence of constipation in the US

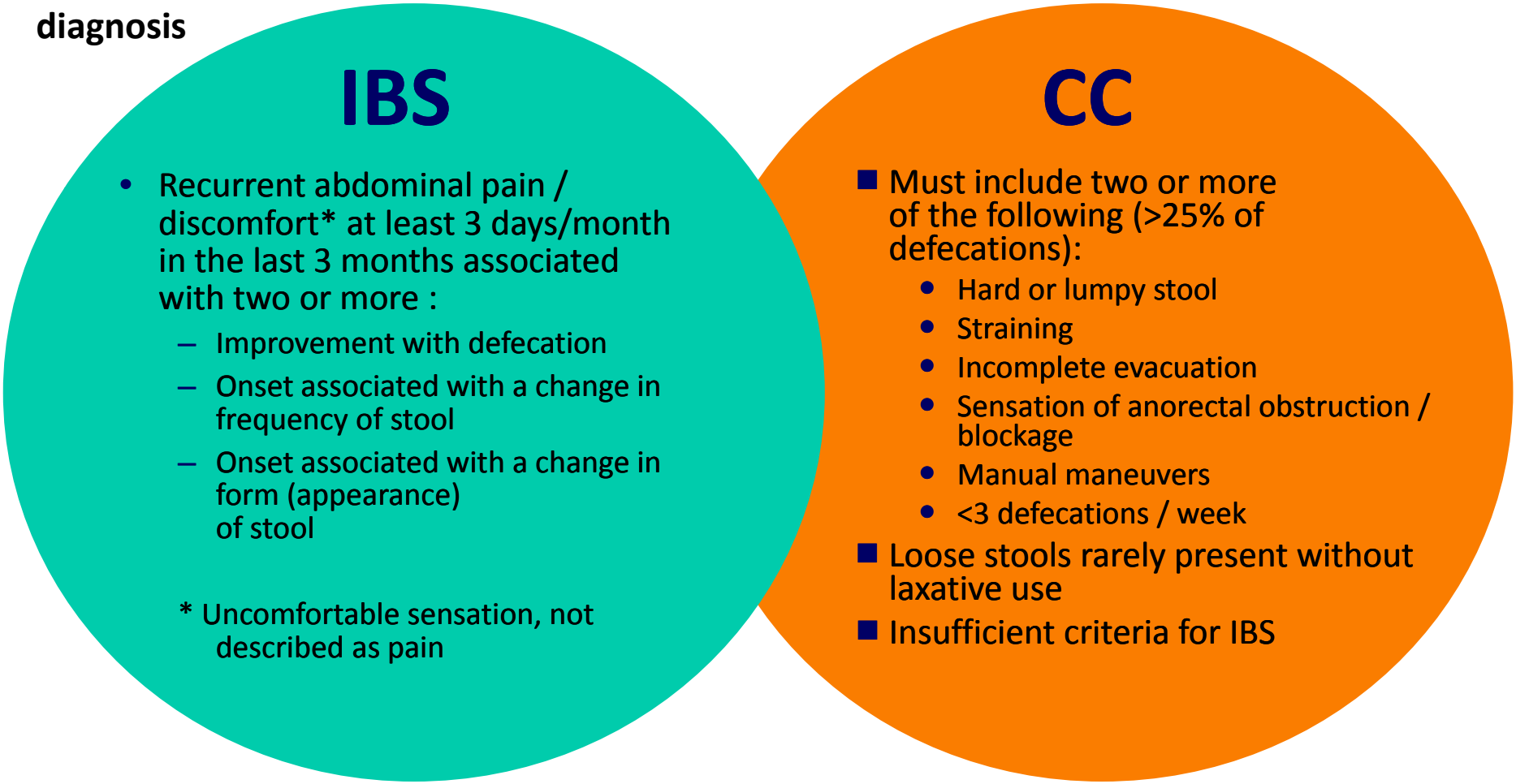
- **Prevalence:**
  - estimated 55 million Americans (prevalence 28%)[1]
    - men 12%[2]
    - women 16%[2]
    - elderly individuals 40%[3]
- **Onset rate 40 / 1000 person-years[4]**



[1]Locke et al, Gastroenterology 2000; 119: 1766
[2]Stewart et al, Am J Gastroenterol 1999; 94(12): 3530
[3]Talley et al, Am J Gastroenterol 1996; 91: 19
[4]Talley et al, Am J Epidemiol 1992; 136: 165

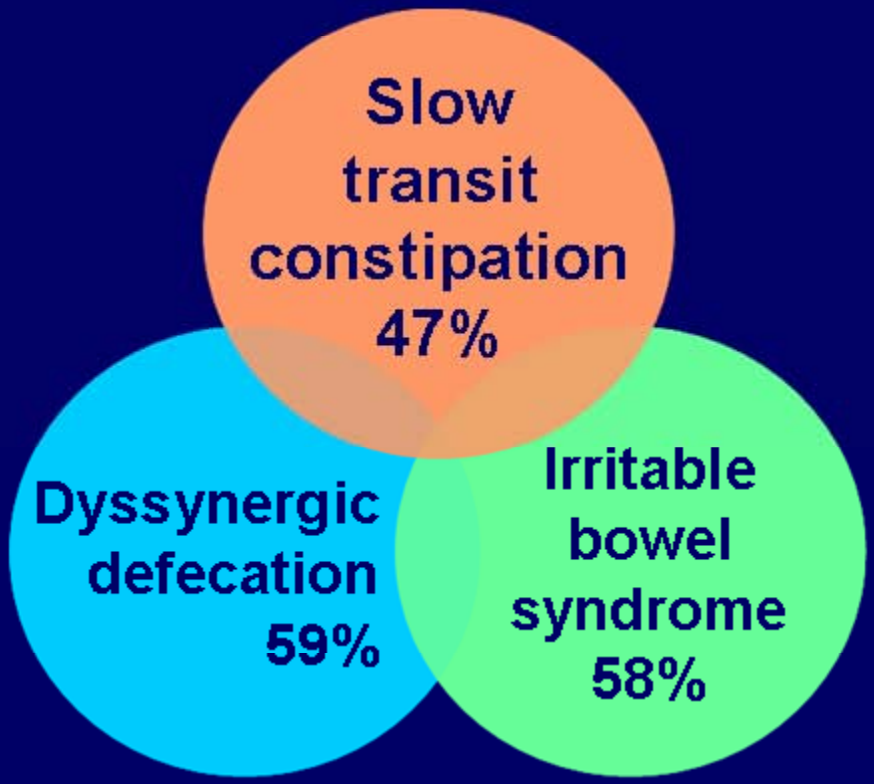
Overlap in IBS-C and CC – The ROME III criteria

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



Longstreth et al. *Gastroenterology* 2006;130(5):1480–91

Functional subtypes of idiopathic constipation

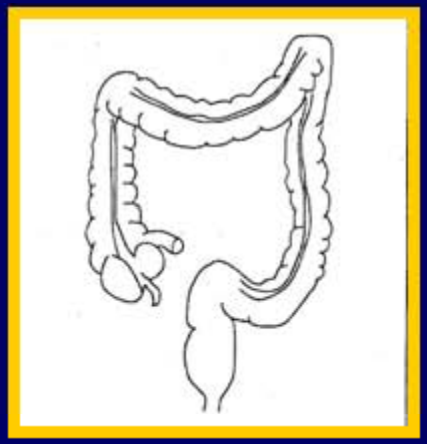


- Slow-transit and IBS-C overlap in half of each group

Rao et al, Gastroenterol Clin North Am 2003; 32: 659
Mertz et al, Am J Gastroenterol 1999; 94: 609

Measurement of colonic transit: Distribution of radiographic markers

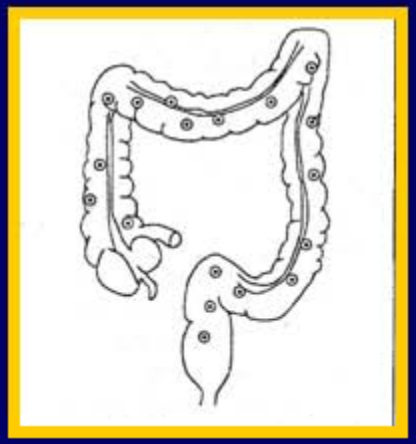
A



Normal

≤5 markers remain

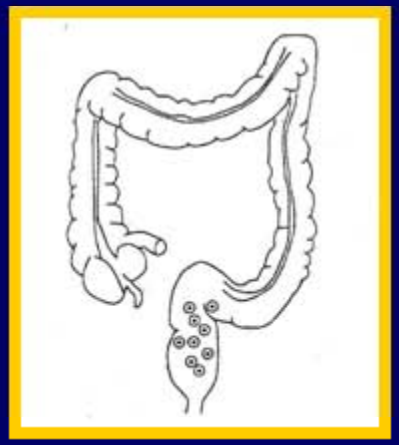
B



Slow-transit

Rings are scattered throughout the colon

C

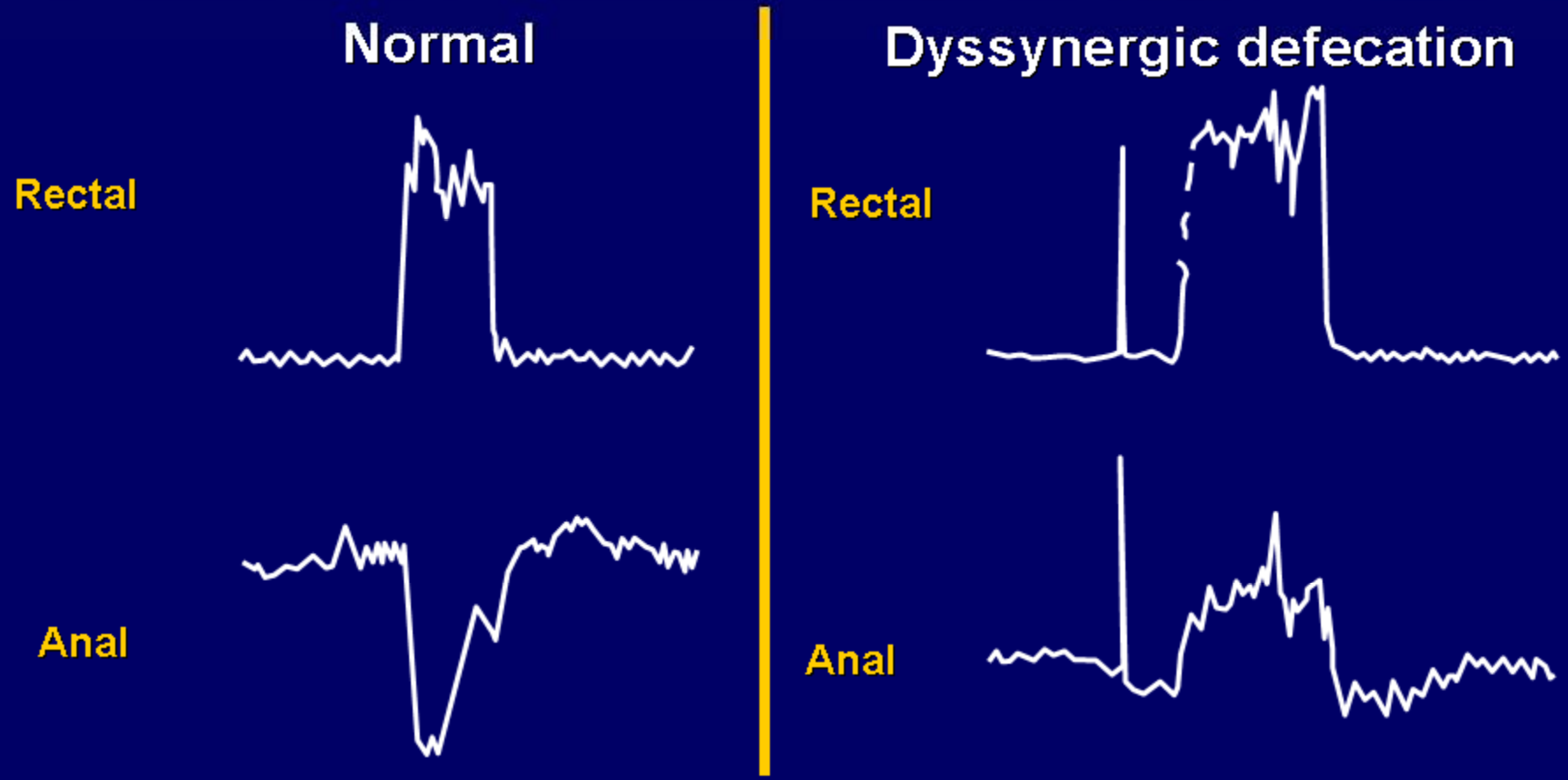


Functional outlet obstruction

Rings are gathered in the rectosigmoid

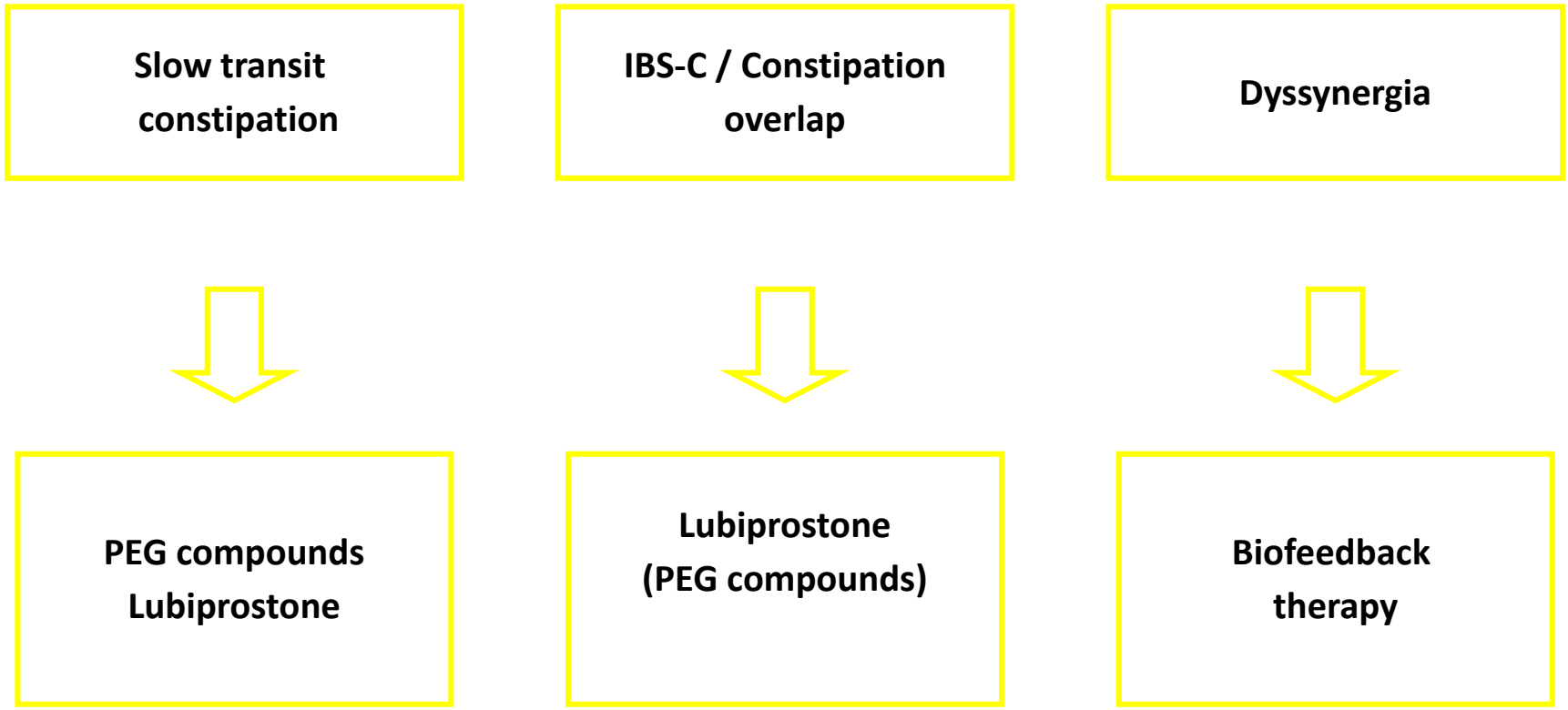
Faigel et al, Clin Cornerstone 2002; 4: 11

Manometry in patients with dyssynergia



Rao, Gastroenterol Clin North Am 2003; 32: 659

Pathophysiologic-based treatment approach for chronic constipation



CHRONIC CONSTIPATION: CONCLUSIONS

- Determine if CC is primary or secondary
- Differentiate between CC and IBS-C (Rome III)
- Sitzmark study + anorectal motility studies can distinguish between STC (slow-transit) v. PFD (dyssynergic or pelvic floor dyssynergia)
- STC responds to laxatives + prokinetic meds
- PFD treated with meds as STC + biofeedback