EDUCATIONAL INITIATIVE ON CONSTIPATION

Focusing on IBS-C and Chronic Constipation

Collective Clinical Forum

JOHNS HOPKINS MEDICINE
CONTINUING MEDICAL EDUCATION

Presented by the Johns Hopkins University School of Medicine

American Academy of Nurse Practitioners

In collaboration with the American Academy of Nurse Practitioners

This educational initiative has been facilitated by Gullapalli & Associates, LLC.

CME Information

- **Presented by the Johns Hopkins University School of Medicine**
  - The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity
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- **Accreditation**
  - The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
- **CME Credit Designation**
  - The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

- This activity is supported by an educational grant from Sucampo Pharmaceuticals, Inc. and Takeda Pharmaceuticals North America, Inc.

Educational Initiative on Constipation

- Overview
  - Multi-disciplinary, multi-interventional performance improvement activity intended to measurably improve the management of patients with chronic constipation (CC) and irritable bowel syndrome with constipation (IBS-C)

- Multiple educational activities
  - Assessment webinar, satellite symposium during ACG, Performance Improvement (PI), satellite broadcasts of satellite symposium, publications, website and toolkit

The Performance Improvement Component of the EIC

What is Performance Improvement-CME?

- CME accredited, structured process where participant can
  - Learn about performance measures related to constipation;
  - Retrospectively assess their practice;
  - Apply these measures prospectively over a useful interval, and;
  - Reevaluate their practice performance

- An evidence-based participatory program with emphasis on quality of care and patient safety

- Ability to earn a total of 20 *AMA CME Credits* through participation

Why PI-CME in Constipation?

- Correct differential diagnosis can be difficult
- Appropriate treatment is essential
- Undiagnosed/untreated patients
  - Have greatly reduced quality of life
  - Have an increased delay before they are properly managed
  - Negatively impact health care provider's time and resources

PI-CME: Benefits of Participation

- Ease of implementation, no cost to participate
- First of its kind: Opportunity to participate in a national program leading to measurable change in patient care
  - Personal improvement and satisfaction with medical practice
- Alignment with Maintenance of Certification (MOC) requirements
  - Aligns your practice in accordance with American Board of Medical Specialties (ABSM) criteria
- Increase quality of care
  - Enhance "the feel good factor" about the care given at the end of every day

Educational Initiative on Constipation Award for Clinical Excellence™ Recognition Program

ACE™ Recognition Program

- Free, voluntary, non-financial, recognition program acknowledging healthcare providers participating in the EIC
- Co-sponsored by The Johns Hopkins School of Medicine in collaboration with the American Academy of Nurse Practioners
- Goals
  - Improve quality of care and outcomes in patients with constipation
  - Encourage physicians to seek optimal quality of care strategies and integrate the learning into their practice for improved clinical outcomes

ACE™ Recognition Award

- Provider Recognition
  - Through national and local PR campaign that includes print, new and live media
  - Through personalized certificate of acknowledgement of clinical excellence from the Dean of the Johns Hopkins School of Medicine
  - Listing on the Johns Hopkins School of Medicine Website for a period of 12 months

Collective Clinical Forum

- **Purpose: to measurably improve the management of chronic constipation by gastroenterologists**

1.Update on status of treating constipation (where are we?)

Adil E. Bharucha, MD

2. Pathophysiology, diagnosis, and management of patients with constipation (including quality of life issues)

Satish Rao, MD, PhD

3. Maximizing therapeutic strategies in patients with constipation

Jonathan Kaunitz, MD

4. Role of multidisciplinary care in constipation

Henry Parkman, MD

5. Panel Discussion

Faculty

Co-Chairs

Mark Donowitz, MD
Professor of Medicine and Physiology
Director of The Hopkins Center for Epithelial Disorders
LeBoff Professor for Research in Digestive Diseases
The Johns Hopkins University School of Medicine
Baltimore, MD

Henry Parkman, MD
Director, Gastrointestinal Motility Laboratory
Director, Temple Clinical Research Unit
Chair, Research Committee, Department of Medicine
Professor of Medicine
Temple University School of Medicine
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David Geffen School of Medicine at UCLA
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Disclosures

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Disclosure Information

- Mark Donowitz, MD, reports receiving honoraria from Sucampo Pharmaceuticals, Inc; holding stock in Tranzmembrane, Inc (holder of NHE3 patent); and serving on the scientific advisory board for Institute for One World Health.
- Henry Parkman, MD, reports receiving grants/research support from Medtronic, Inc, SmartPill Corporation, and Tranzyme Pharma Inc; serving as a consultant for SmartPill Corporation and Tranzyme Pharma Inc; and serving on the speakers' bureau for SmartPill Corporation.
- Adil Bharucha, MD, reports having no financial or advisory relationships with corporate organizations related to this activity.
- Satish Rao, MD, PhD, reports receiving grants/research support from SmartPill Corporation; serving as a consultant for Boehringer Ingelheim, Forest Laboratories, Inc, Proctor & Gamble, SmartPill Corporation, and Takeda Pharmaceuticals North America, Inc; and serving on the speakers' bureau for AstraZeneca, Sucampo Pharmaceuticals, Inc, and Takeda Pharmaceuticals North America, Inc.
- Jonathan Kaunitz, MD, reports receiving grants/research support from Takeda Pharmaceuticals North America, Inc.
  Dr Kaunitz—discussing experimental drugs, non-FDA approved. –YES, we need unlabeled/unapproved drugs listed if they are going to be referenced.

Pathophysiology and Classification of Chronic Idiopathic Constipation

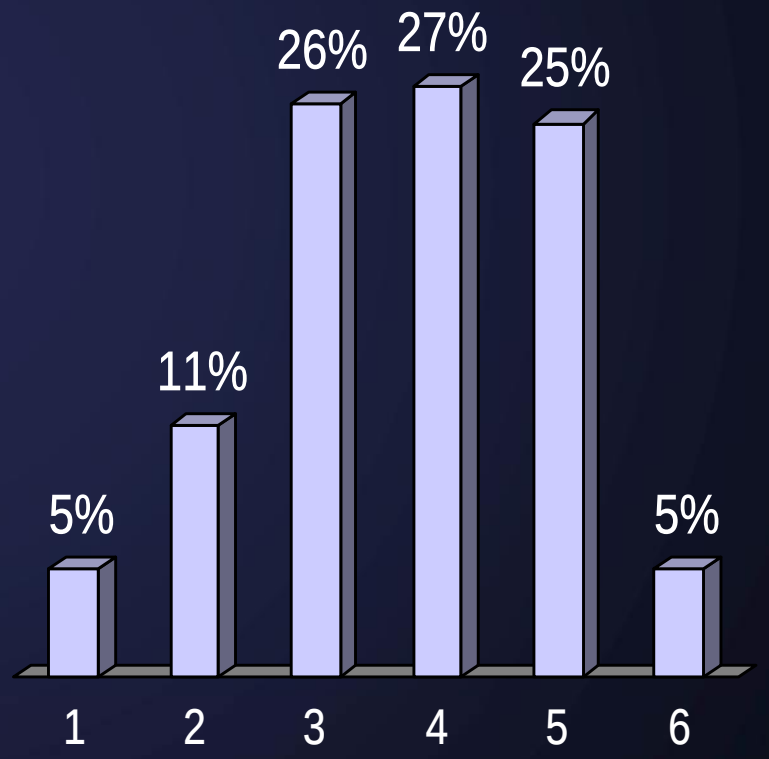
Adil Bharucha, MD
Professor of Medicine
Department of Gastroenterology
Mayo Clinic
Rochester, MN

The Educational Initiative on Constipation: Focus on IBS-C and CC

VIDEO CASE CHALLENGE

What is the most likely diagnosis?

- Hemorrhoids
- Normal transit constipation
- Slow transit constipation
- Dyssynergic defecation
- IBS-C
- Colon cancer



Objectives

- Mechanisms of normal colonic motor functions and defecation
- Epidemiology of chronic constipation (CC)
- Classification of chronic constipation
- Pathophysiology of chronic constipation

HAPC = high amplitude propagated contraction.

Rao. *Gastroenterol Clin North Am.* 2007;36:687-711.
Cook and Brookes. In: *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2006.

Colonic Motor Activity

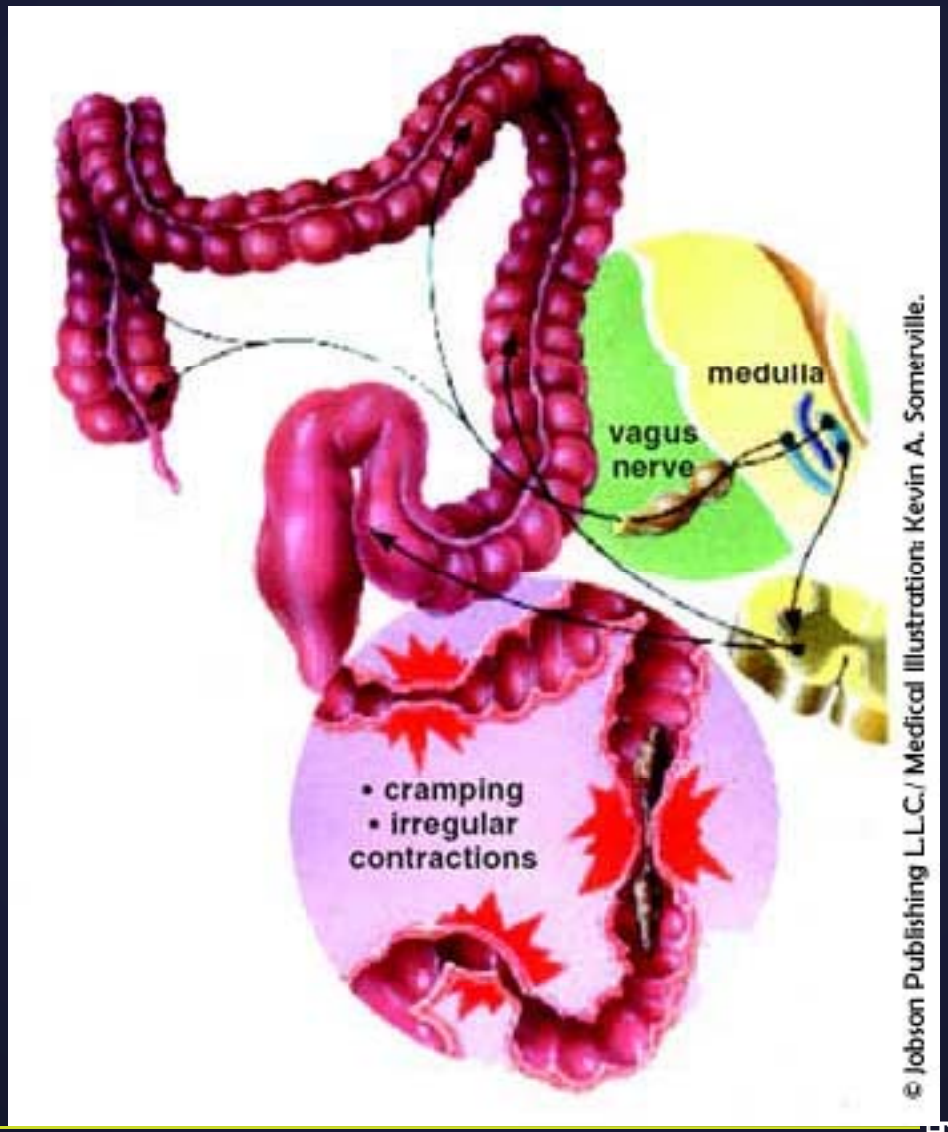
Salient Features

- Mostly irregular
- Increases upon awakening, decreases at night
- Increases after meals—gastrocolonic reflex
- Most activity is non-propagated and facilitates mixing
- HAPCs occur infrequently (~5/day) and move contents rapidly; often precede defecation

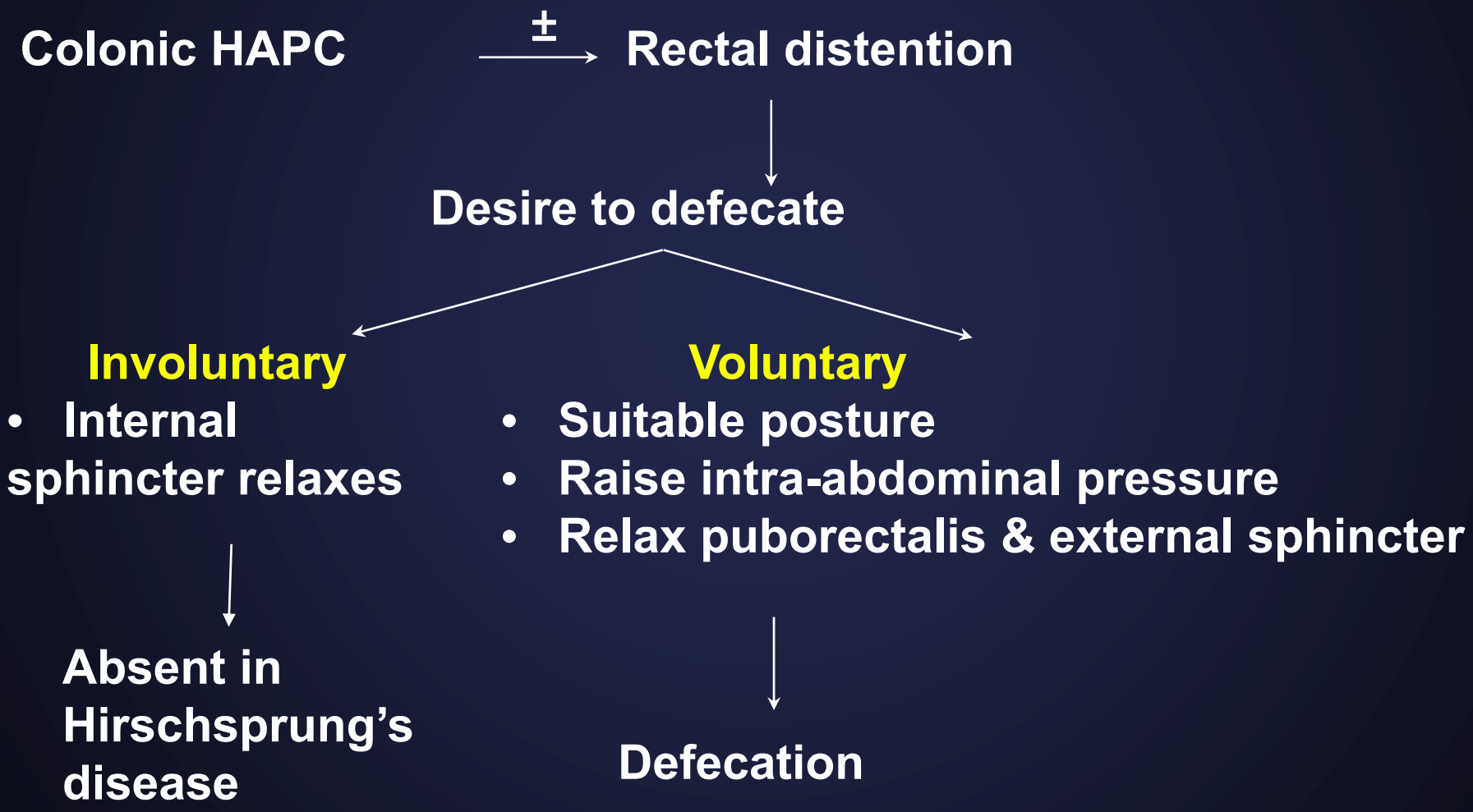
HAPC = high amplitude propagated contraction.

Rao. *Gastroenterol Clin North Am.* 2007;36:687-711.
Cook and Brookes. In: *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2006.

Gastrocolonic Response



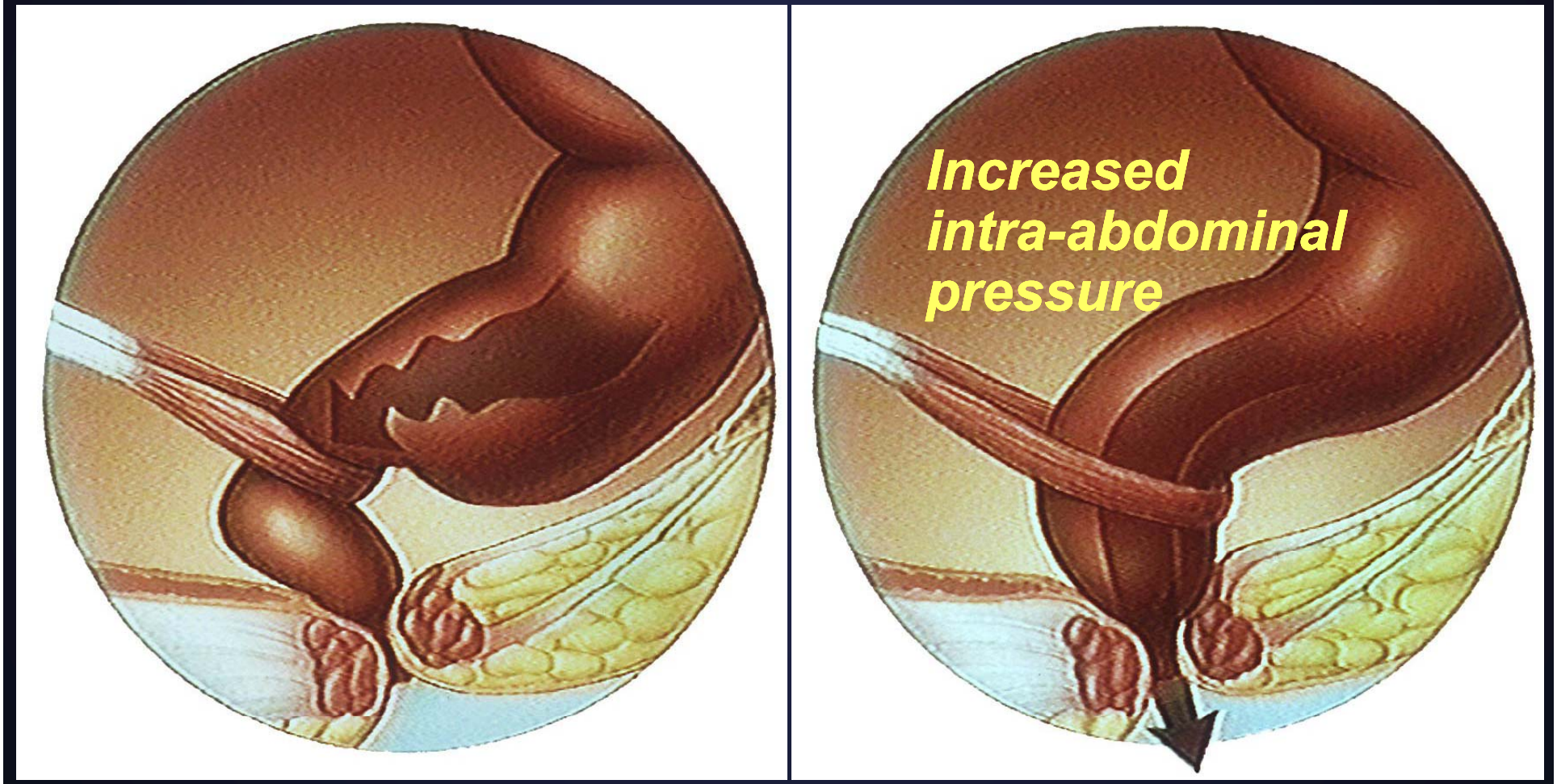
Mechanisms of Defecation



Mechanisms of Normal Defecation

Rest

Defecation



Surprise, Surprise . . .

Constipation Is Common!

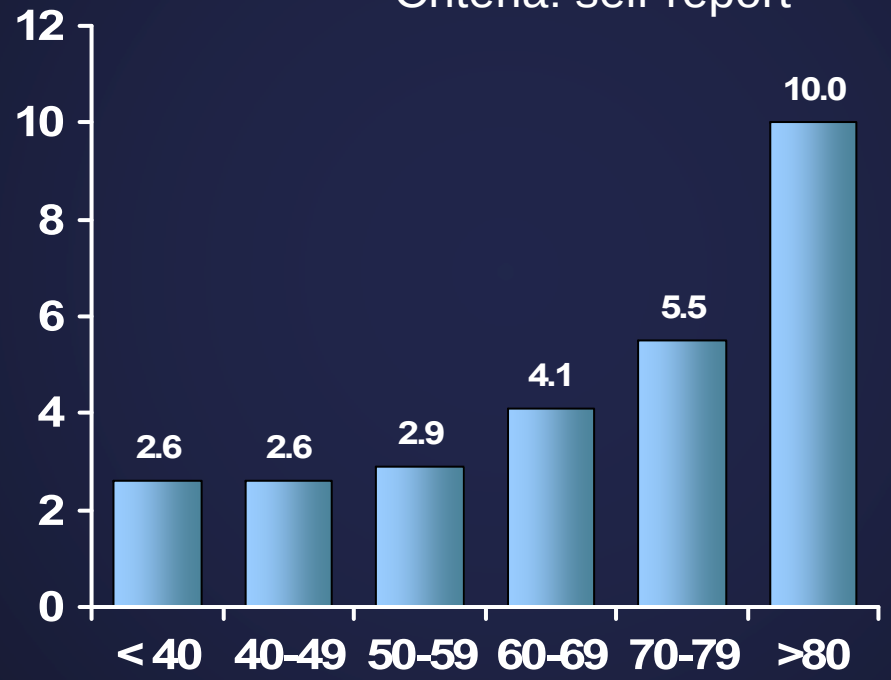
- Prevalence 12% to 19%; more common in:
  - Women (2:1)
  - Elderly—particularly after 70 years
  - Lower income
- Substantial healthcare utilization
  - ~8 million visits annually, $2752 per patient (tertiary evaluation)
  - Reduced primary care visits, GI visits stable[2]
- Probably impairs quality of life
- Natural history unclear

GI = gastrointestinal.

Higgins and Johanson. *Am J Gastroenterol.* 2004;99:750-759[1]; Shah ND et al. *Am J Gastroenterol*. 2008;103:1746-1753.[2]

Prevalence by Age: CC

N = 42 375[1]
Population: National Health Interview Survey 1987
Criteria: self-report



63 million North Americans meet Rome definition of constipation[2]

Reprinted with permission from Higgins and Johanson. *Am J Gastroenterol*. 2004;99:750-759.[1]
Harari et al. *Arch Intern Med*. 1996;156:315-320.[2]

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Definition of Constipation

What's In A Name?

May be identified by:

- **Self-report ("Doc, I'm constipated")**
- **Laxative use**
- **Symptom criteria[1]**
  - **Infrequent bowel movements**
  - **Hard stools**
  - **Excessive straining during defecation**
  - **Anal digitation during defecation**
  - **Sense of anorectal blockage during defecation**
  - **Sense of incomplete evacuation after defecation**

Longstreth et al. *Gastroenterology*. 2006;130:1480-1491.[1]

Secondary Causes of Constipation

- Medications (opioids, NSAIDs, tricyclic antidepressants, and calcium channel blockers)
- Neurologic disorders (eg, MS)
- Metabolic/GI disorders (diabetes mellitus)
- Endocrine disorders (hypothyroidism)
- Malignancy (eg, ovarian)
- Mechanical obstruction
- Pregnancy
- Collagen vascular and muscular disorders

MS = multiple sclerosis; NSAID = nonsteroidal anti-inflammatory drug.

American College of Gastroenterology CC Task Force. *Am J Gastroenterol.* 2005;100:S1-S4.

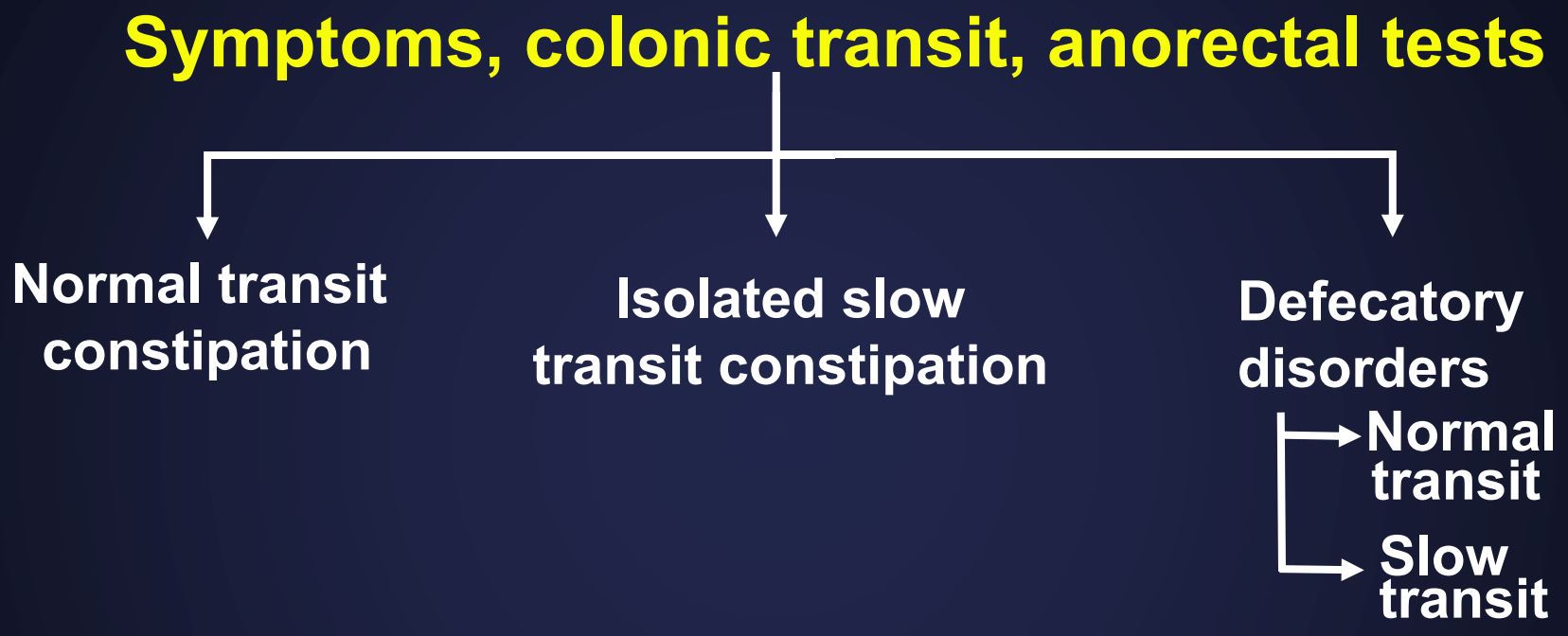
Medications Associated with CC

Prescription	OTC
Opiates	Antacids, especially Ca+
Anticholinergic drugs	Calcium supplements
Tricyclic antidepressants	Iron supplements
Calcium channel blockers	Antidiarrheal drugs
Sympathomimetic agents	NSAIDs
Antiparkinsonian agents	
Antipsychotic drugs	
Diuretics	
Antihistamines	

OTC = over-the-counter.

American College of Gastroenterology CC Task Force. *Am J Gastroenterol.* 2005;100:S1-S4.

Classification of CC



Longstreth et al. *Gastroenterology*. 2006;130:1480-1491.
Bharucha et al. *Gastroenterology*. 2006;130:1510-1518.
Adapted from Locke et al. *Gastroenterology*. 2000;119:1766-1778.

Distinguishing Subtypes in CC

Symptoms	Functional Constipation	Constipation-Predominant IBS	Defecatory Disorders
Constipation	Yes	Yes	Yes
Abdominal discomfort	Yes or No	Yes	Yes or No
Discomfort + bowel symptoms	No	Yes	No
Rectal examination	Normal	Normal	May be abnormal
Anorectal tests	Normal	Normal	Abnormal

Definition: IBS

Recurrent abdominal pain or discomfort for at least 6 months associated with ≥2 of the following:

- **Improvement with defecation**
- **Onset associated with a change in frequency of stool**
- **Onset associated with a change in form (appearance) of stool**

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

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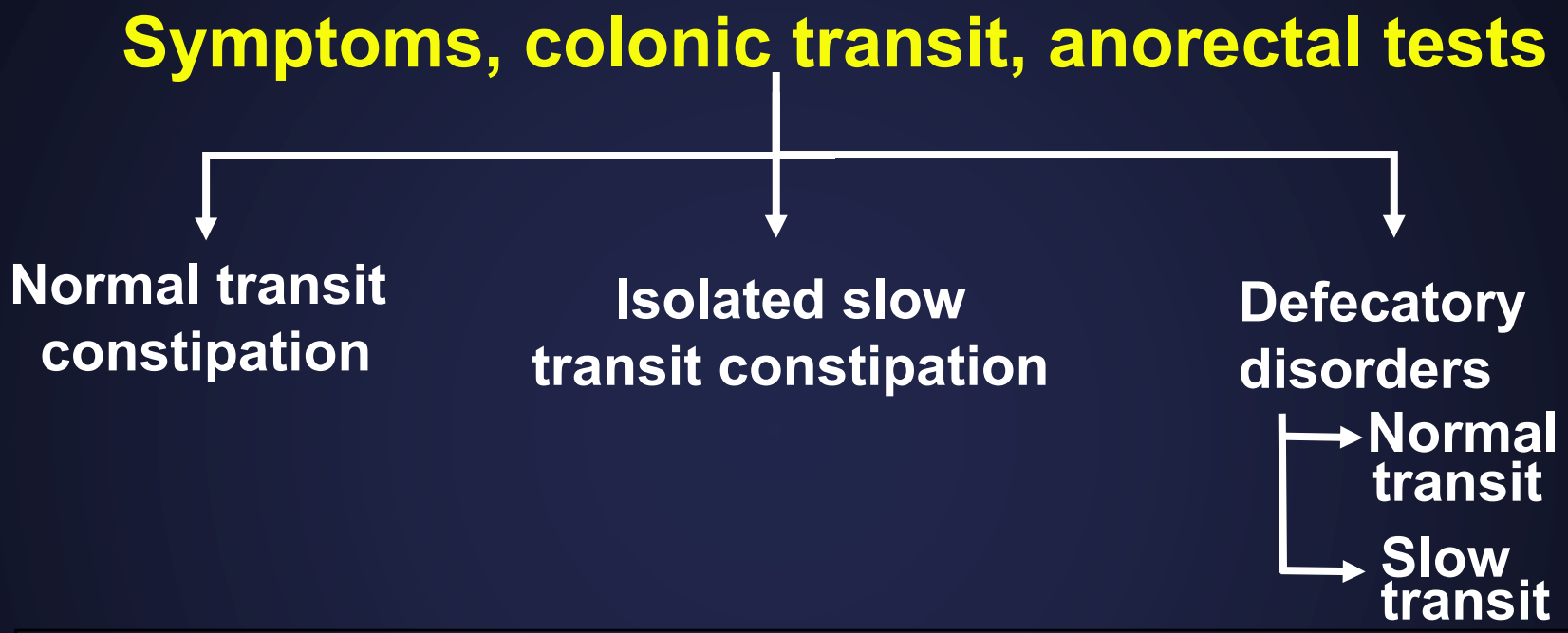

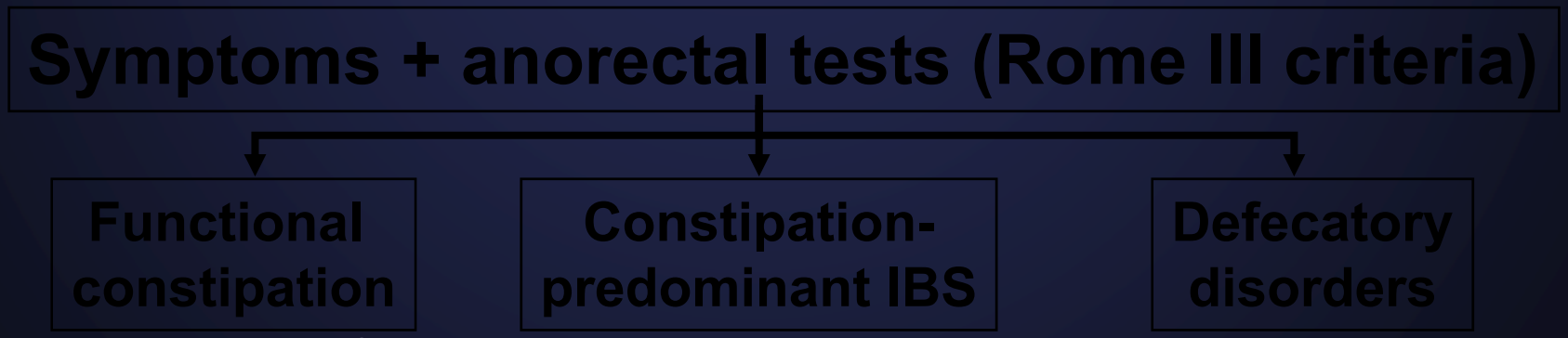

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Bharucha et al. *Gastroenterology*. 2006;130:1510-1518.
Adapted from Locke et al. *Gastroenterology*. 2000;119:1766-1778.

Normal Transit Constipation

- Used synonymously with IBS
- Normal colonic transit and anorectal functions
- Pathophysiology of symptoms unclear
  - Some symptoms (e.g., abdominal discomfort and bloating) may be attributable to disordered sensation
- Patients frequently respond to dietary measures (eg, fiber) and OTC laxatives

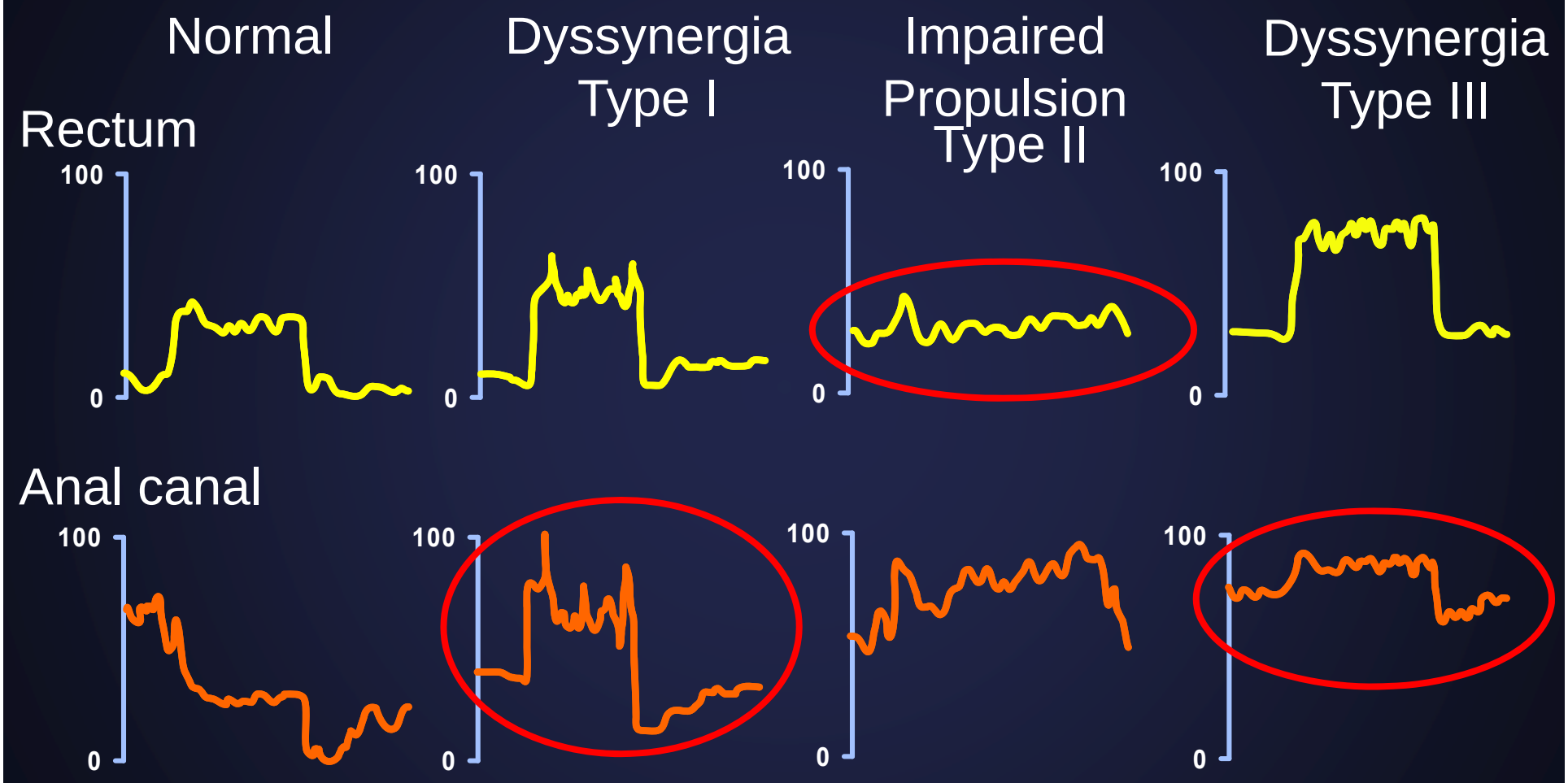
Lembo A, Camilleri M. *N Engl J Med* 2003; 349:1360-8.
Rao SSC, *Gastroenterol Clin N Am* 36 (2007) 687–711
Cash BD et al. J FJ Fam Pract 2007; 56 (Suppl 6): S13-S20

Defecatory Disorders Characteristics

- Symptoms of functional constipation
  - Patients may have symptoms (excessive straining, anorectal blockage, and anal digitation) that suggest pelvic floor dysfunction
- Rectal examination may reveal pelvic floor dysfunction
- Diagnosis based on anorectal manometry, rectal balloon expulsion test, ± defecography
  - Requires 2 of 3 features
    - Impaired rectal evacuation
    - Inappropriate pelvic floor contractions
    - Inadequate rectal propulsive forces

Bharucha et al. *Gastroenterology*. 2006;130:1510-1518.

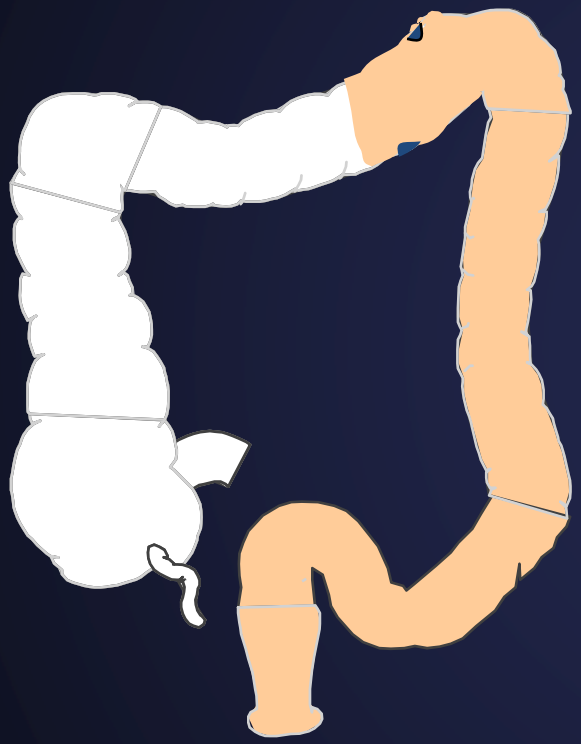
Defecatory Disorders Pathophysiology



- Even *asymptomatic* people may have dyssynergia
- Diagnosis based on clinical features AND anorectal testing

Defecatory Disorders

Pathophysiology (cont'd)



Delayed colonic transit

↑

Rectocolonic inhibitory reflexes

↑

Pelvic floor dysfunction

↓

Impaired defecation

Law et al. *Am J Physiol Gastrointest Liver Physiol*. 2002;283:G384-389.
Rao et al. *AM J Gastroenterol*. 1998; 93:1042-1050.

Slow Transit Constipation Characteristics

- Initial description[1]
  - Women with intractable constipation, requiring laxatives
  - Normal barium enema + slow colonic transit
  - Gynecologic and somatic symptoms
  - ± Anal digitation during defecation
- Now[2]
  - Limited to patients with slow transit but without pelvic floor dysfunction
- Generally managed with laxatives
  - Surgery (subtotal colectomy) required in some patients

Preston and Lennard-Jones. *Gut*. 1986;27:41-48.[1]
Bharucha and Phillips. *Gastroenterol Clin North Am*. 2001;30:77-95.[2]

Slow Transit Constipation Pathophysiology

- Often "idiopathic"
- May be associated with loss of colonic nerves and impaired colonic motor function (eg, reduced gastrocolic response)
- May be associated with:
  - Pelvic surgery (eg, hysterectomy)
  - Intestinal pseudo-obstruction

Bharucha and Phillips. *Gastroenterol Clin North Am*. 2001;30:77-95.

Patient Satisfaction with Traditional Treatments

- According to a recent study, a majority of patients are not satisfied with the effectiveness of traditional treatment for constipation.
- As research has broadened the availability of drugs to treat this condition, patient satisfaction may increase.

Johanson JF, Kralstein J, *Aliment Pharmacol Ther* 2007;25: 599-608

Summary

- Normal bowel habits require normal colonic motor activity and anorectal functions
- CC may be classified into subtypes, based on clinical features AND tests (colonic transit and anorectal functions)
  - Normal transit, isolated slow transit constipation, or pelvic floor dysfunction
- Classification facilitates management
    - Pelvic floor dysfunction—biofeedback therapy
    - The rest—fiber supplements, laxatives, and lubiprostone
    - Refractory slow transit—subtotal colectomy

Evaluation, Diagnosis, and Treatment of Constipation

Satish Rao, MD, PhD
Professor of Medicine
Director of Neurogastroenterology and Gastrointestinal Motility
University of Iowa Carver College of Medicine
Iowa City, IA

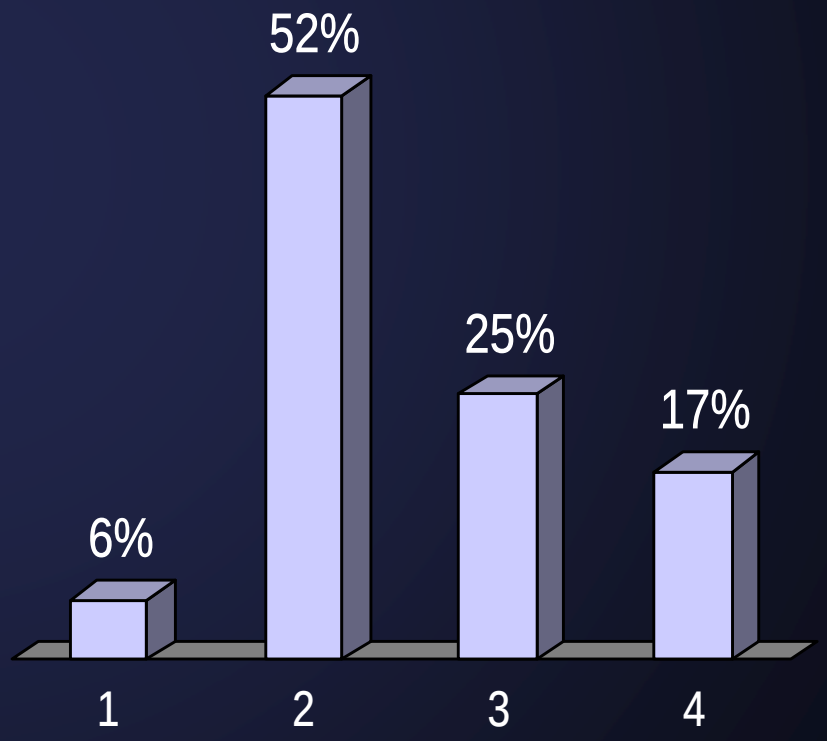
Constipation

- A symptom-based diagnosis
- May result from:
  - Structural issues
  - Mechanical issues
  - Metabolic conditions
  - Functional disorders that affect the colon or anorectum either directly or indirectly

Rao. *Gastroenterol Clin North Am*. 2007;36:687-711.

Which of the following tests would you recommend for this patient?

- Plain x-ray of the abdomen
- Colon transit studies
- Anorectal manometry
- Balloon expulsion



The Educational Initiative on Constipation: Focus on IBS-C and CC

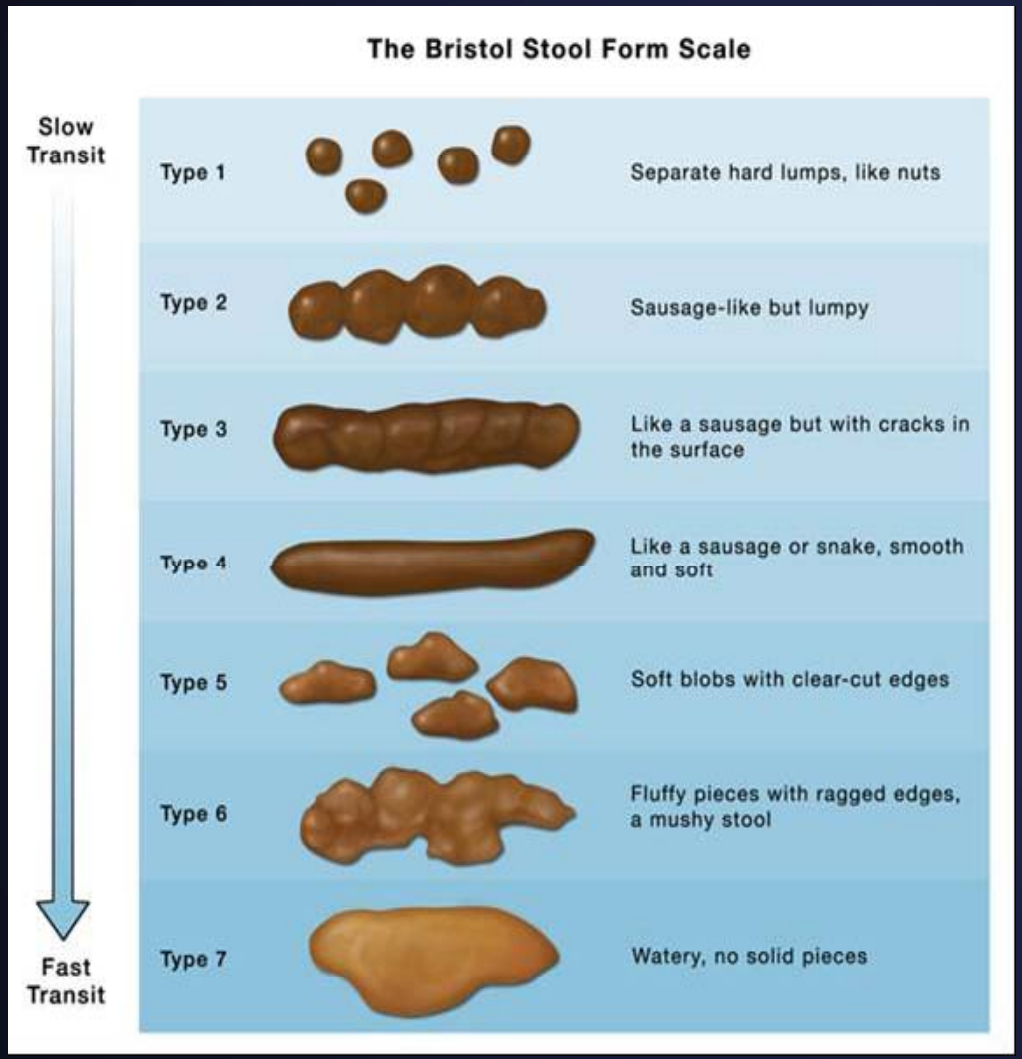
VIDEO CASE CHALLENGE

Tools for Evaluation

- History
- Physical Examination
  - Digital Rectal Examination
- Stool Diary-Bristol Stool Scale
- Diagnostic Tests
  - Physiological
  - Morphological
  - Structural

Rao SSC. *Gastroenterol Clin N Am* 36 (2007) 687-711

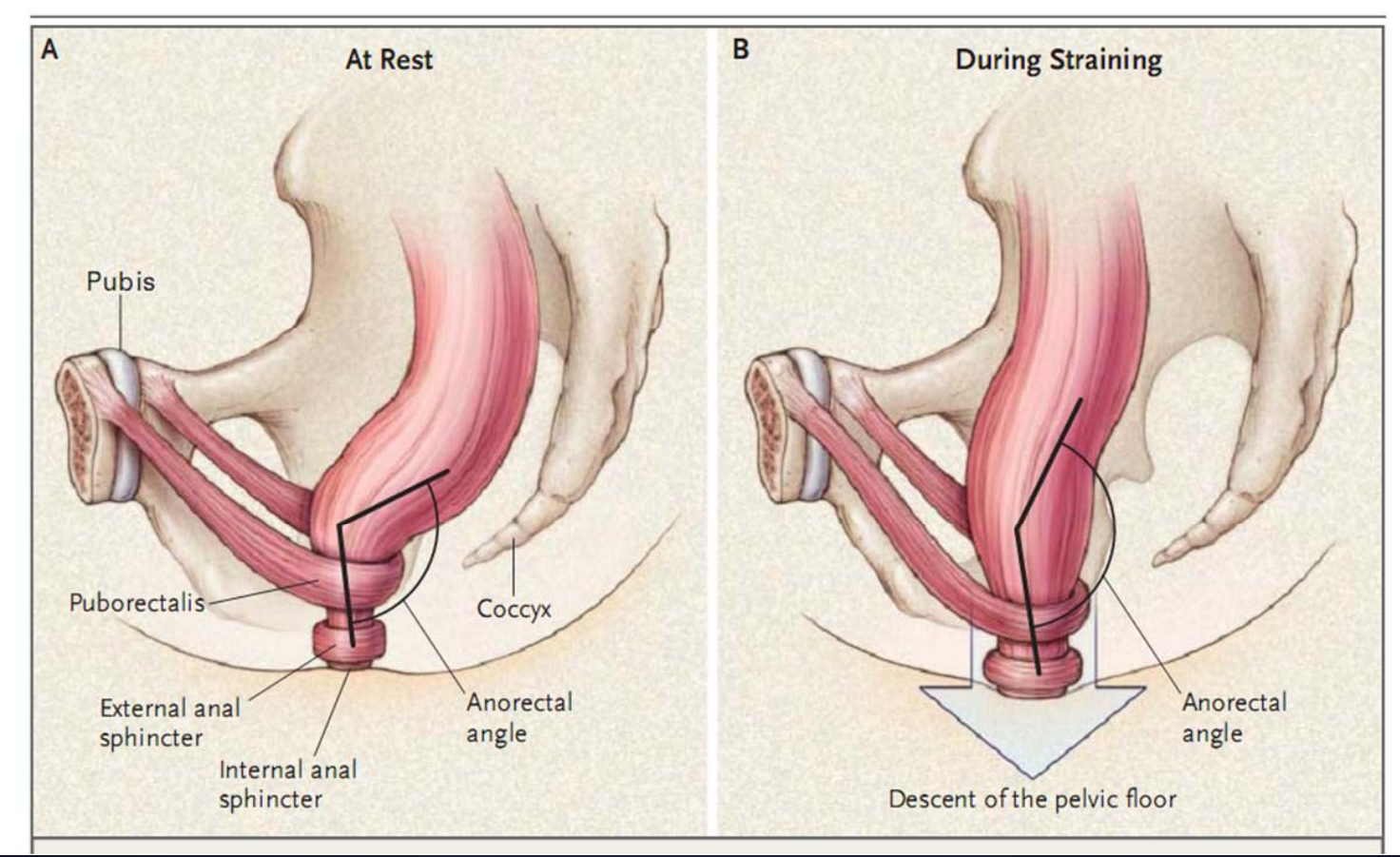
Bristol Stool Form Scale



Saad R, Chey W, Rao SS et al DDW 2008

Correlation of stool frequency & stool form with colonic and whole gut transit times as assessed by SmartPill®		
	Stool Frequency	Stool Consistency
	Constipated N = 62	Constipated N = 65
Colonic Transit Time	r = -0.14 p = 0.29	r = -0.35 p = 0.004
Whole Gut Transit Time	r = -0.16 p = 0.22	r = - 0.27 p = 0.03

DRE and Defecatory Function



Reprinted with permission from Lembo and Camilleri. *N Engl J Med.* 2003;349:1360-1368.

Red Flags

Further workup indicated in the presence of:

- Hematochezia
- Family history of colon cancer
- Family history of inflammatory bowel disease
- Anemia
- Severe, persistent constipation that is unresponsive to treatment

- New-onset constipation in an elderly patient
- Positive fecal occult blood test
- "Unexplained" weight loss ≥10 pounds

Reprinted with permission from Brandt et al. *Am J Gastroenterol.* 2005;100(suppl 1):S5-S21.

Can Symptoms Predict Dyssynergia?

100 Patients With Difficult Defecation

Symptom Prevalence	Normal Pattern (n = 30)	Type I (n = 32)	Type (n = 24)	Type III (n = 14)
Excessive straining	92	96	89	83
Abdominal fullness	80	96	89	67
Incomplete evacuation	72	96	89	100
Abdominal discomfort	88	81	74	75
Digital maneuvers to defecate	28	56	47	50

Rao SSC et al. *Neurogastroenterol Motil.* 2004;16:589-596.

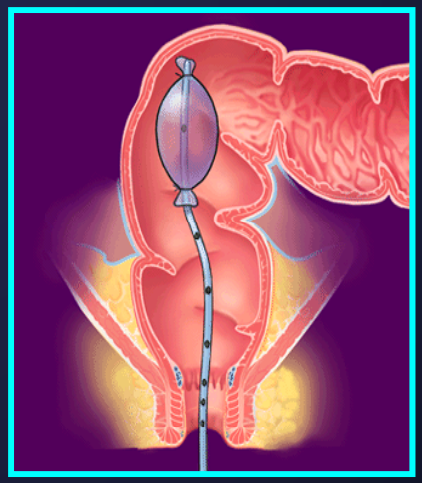
Diagnostic Tests

- **In patients with alarm symptoms**
  - Flexible sigmoidoscopy
  - Colonoscopy
  - Rectal biopsy
  - Barium enema
  - Abdominal ultrasound
  - Routine laboratory investigations
  - Fecal occult blood test
- **Little consistent evidence to support routine use of laboratory testing in the absence of alarm symptoms/signs**

Brandt et al. *Am J Gastroenterol.* 2005;100(suppl 1):S5-S21.

Diagnostic Tests

- **Colonic Transit Study**
  - Radio-opaque markers
    - Sitzmark
  - Scintigraphy
  - Wireless pH and Pressure Capsule (SmartPill)
- **Anorectal manometry**
- **Balloon Expulsion Test**
- **Defecography**
- **Colonic manometry**



Lembo and Camilleri. *N Engl J Med*. 2003;349:1360-1368.
Rao. *Gastroenterol Clin North Am.* 2007;36:687-711.
Lacy and Brunton. *MedGenMed*. 2005;7:19.

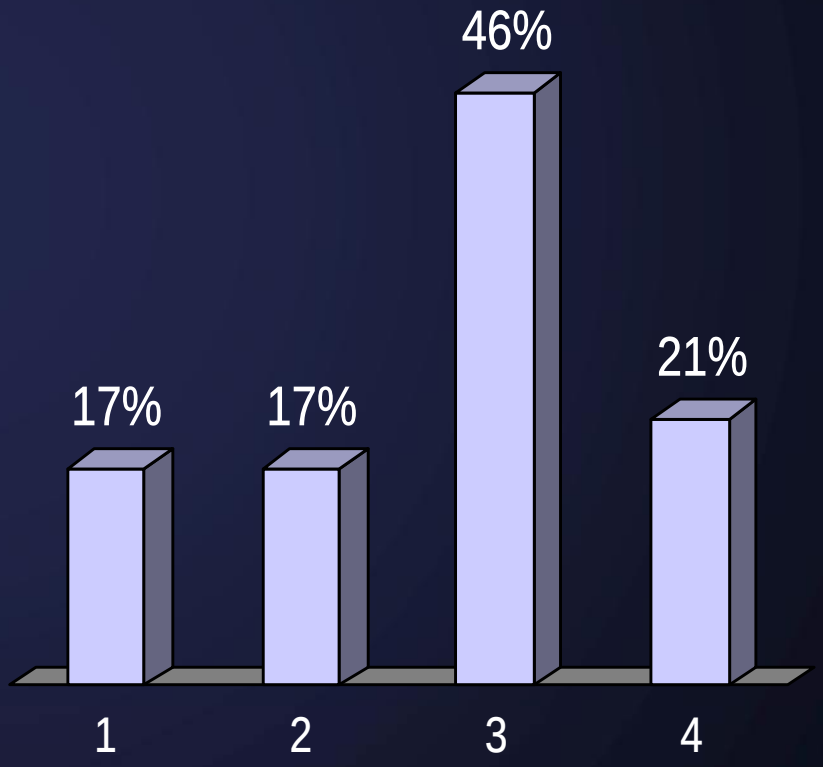
Diagnostic Tests for Constipation: Summary

- No single test is useful because constipation is multifactorial
- Study methodology lacks high quality—mostly 4–5/8
- ARM, Colonic Transit Study, and balloon expulsion are useful and complimentary (Grade B2)
- Defecography: Perhaps not helpful in initial work-up (Grade B2)
- Colonic manometry (Grade B3)

Rao SS, et al. *Am J Gastroenterol*. 2004;99:2405–2416.
Rao SCC. *Gastroenterol Clin N Am* 36 (2007) **699**.

In this patient what is your presumptive diagnosis?

- Slow transit constipation
- Dyssynergic defecation
- Mixed STC and dyssynergic defecation
- IBS-C



The Educational Initiative on Constipation: Focus on IBS-C and CC

VIDEO CASE CHALLENGE

Therapeutic Options

- Diet/exercise
- Biofeedback
- Laxatives
  - Bulk
  - Stimulants
  - Osmotic
  - Stool softeners
- Novel agents
  - Lubiprostone (chloride channel activator)
  - Methylnaltrexone
- Psychiatric drugs
  - SSRI
- Miscellaneous
  - Colchicine
  - Misoprostol
- Under investigation:
  - renzapride
  - mosapride
  - linaclotide
  - prucalopride
- Surgery

BF = biofeedback.

Lembo and Camilleri. *N Engl J Med*. 2003;349:1360-1368.
Rao. *Gastroenterol Clin North Am.* 2007;36:697-711.

Diet/Exercise/Lifestyle

- Fiber intake: 20 to 35 g each day
  - High-fiber foods include beans, whole grains and bran cereals, fresh fruits, and vegetables
- Adequate hydration
- Exercise (eg, walking or swimming)
- Allow time for toileting
- Limited data supporting efficacy

Horn. *US Pharmacist*. Available at: http://www.uspharmacist.com/index.asp?page=ce/105173/default.htm. Accessed September 19, 2008.

Laxatives

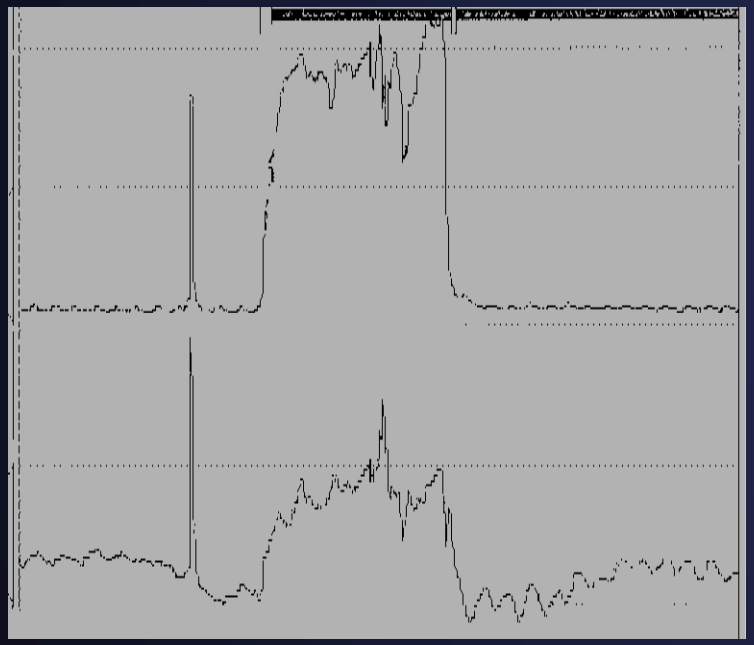
- Osmotic (Grade A)
  - Lactulose
  - Polyethylene glycol (PEG)
  - Magnesium hydroxide (milk of magnesia)
- Bulk (Grade B)
  - Psyllium
  - Methylcellulose
  - Polycarbophil
- Stimulants (Grade B)
  - Bisacodyl
  - Senna
  - Castor oil
- Stool softeners (Grade B)
  - Docusate sodium
  - Docusate calcium

PEG = polyethylene glycol.

Brandt et al. *Am J Gastroenterol*. 2006;100(suppl 1):S5-S21.

Biofeedback-Attempted Defecation

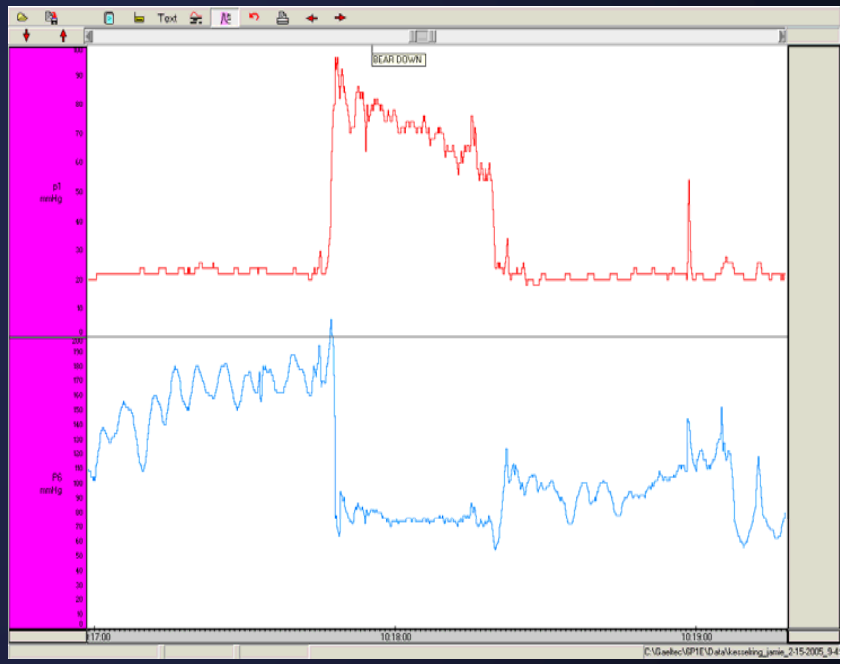
Pre-Biofeedback



RECTUM

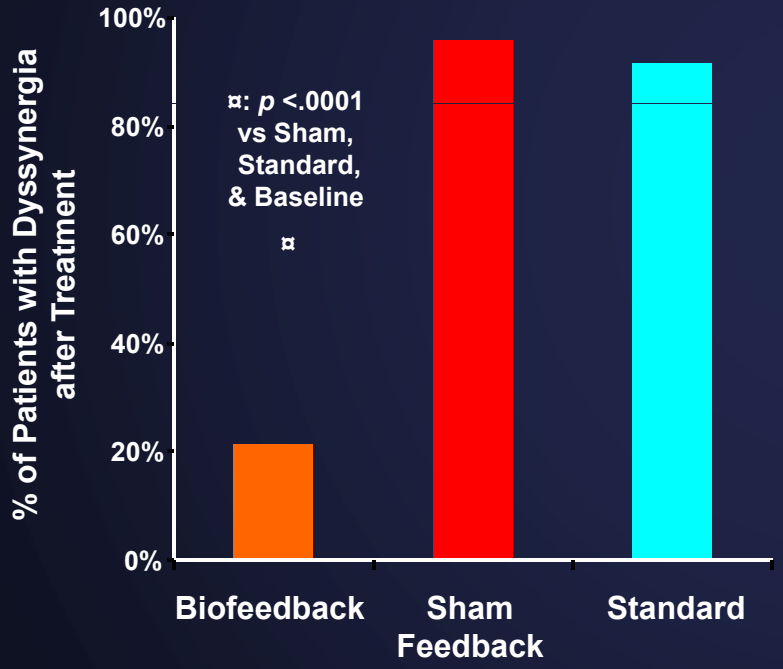
ANUS

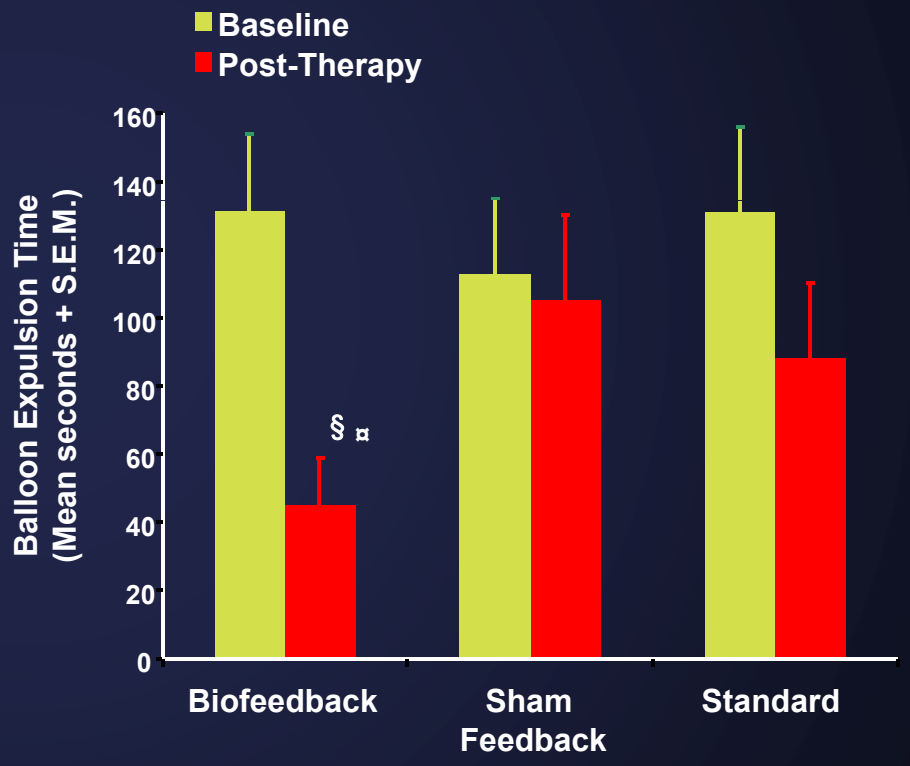
Post-Biofeedback



Courtesy: Satish Rao

Effects of Biofeedback on Dyssynergia & BET-ITT Analysis





§: p = 0.0024 vs Sham & p = 0.0290 vs Standard
¤: p < 0.0001 vs Baseline

Rao et al Clin Gastro Hepatol 2007

The Educational Initiative on Constipation: Focus on IBS-C and CC

VIDEO CASE CHALLENGE

Maximizing Therapeutic Strategies in Patients with CC

Jonathan Kaunitz, MD

Professor of Medicine

Division of Digestive Diseases/Gastroenterology

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Los Angeles, CA

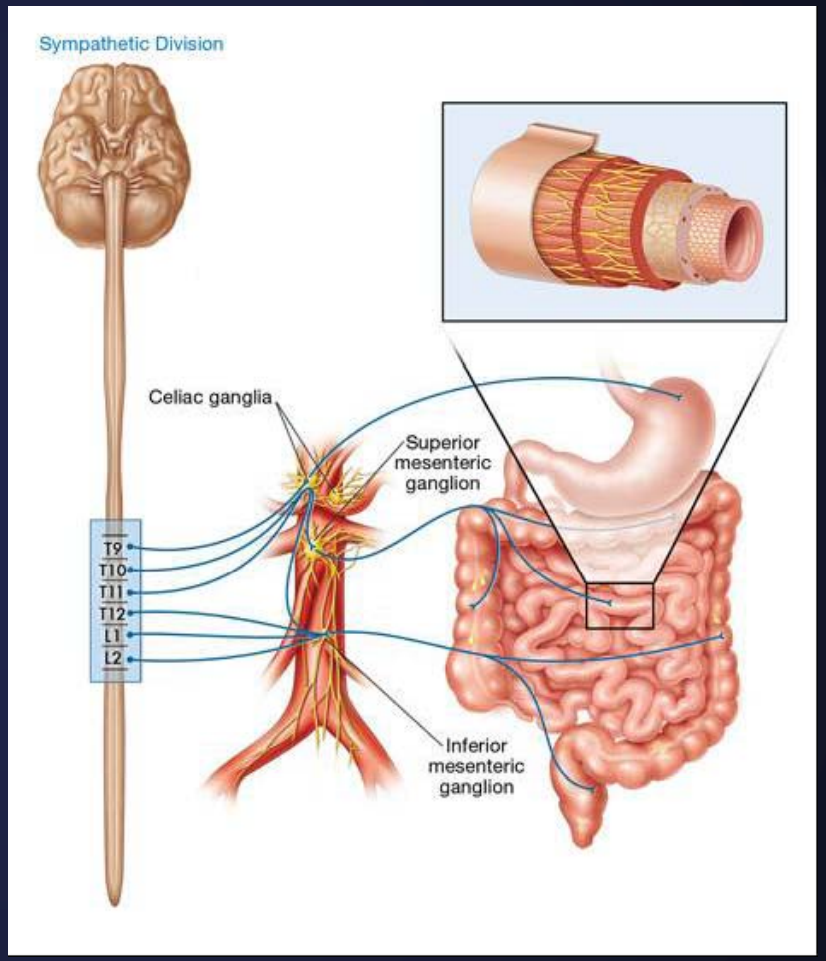
Dysmotility

The ENS mediates neuronal control of colonic motility

ENS is affected by multiple pathways:

- **Sympathetic**
- **Parasympathetic**
- **Extrinsic afferent**

Sympathetic innervation of proximal colon arises from inferior mesenteric ganglion and projects through the lumbar colonic nerves to the ascending and transverse colon



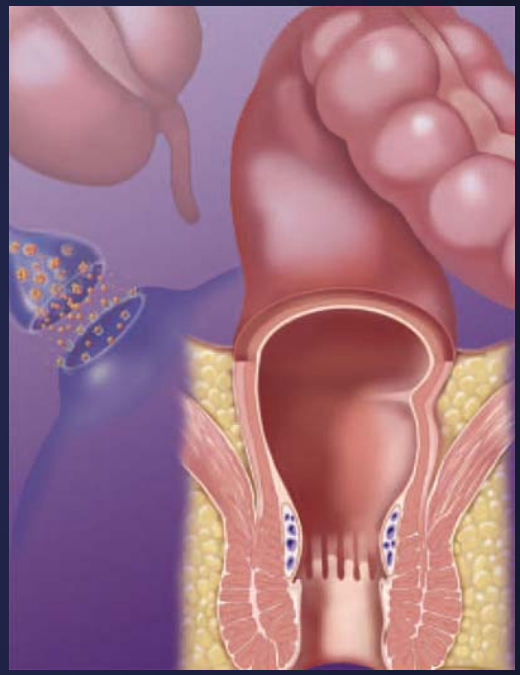
ENS = enteric nervous system.

Reprinted with permission from Kellow et al. *Gastroenterology.* 2006;130:1412-1420.

Cook and Brookes. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease.* 8th ed. Philadelphia, PA: Saunders Elsevier; 2005.

Neuromuscular Transmission

- Major excitatory transmitters
  - Acetylcholine
  - Substance P
- Serotonin signaling also impacts sensitivity and motility
  - Serotonin-selective reuptake transporter



Reprinted with permission from Rao. *Gastroenterol Clin North Am.* 2007;36:687-711.
Cook and Brookes. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease*; 8th ed. Philadelphia, PA: Saunders Elsevier; 2005.
Image reprinted with permission from USPharmacist.com. Available at: www.uspharmacist.com/ce/105173/colonmuscles.jpg. Accessed September 23, 2008.

Drugs Used to Treat Constipation: MOA

Osmotic laxatives

- Rely on the body's tendency to dilute a high concentration solute
- Water is drawn into (or held in) the lumen without the accompanying electrolytes

5-HT_4 receptor agonists

Act systemically to affect motility primarily by stimulating 5-HT_4 receptors in the ENS

Lubiprostone

- Activates CIC-2 channels to transport chloride ions into the intestinal lumen; sodium ions and water follow paracellularly
- Net movement of fluid into the lumen, without changes in serum electrolyte concentrations
- Increased intestinal secretion increases stool volume

Chloride Channel Activator: Lubiprostone

- **Lubiprostone**
  - **Fatty acid derivative of prostaglandin E1**
  - **Activates CIC-2 channels, which augments chloride movement into intestinal lumen, which facilitates fluid entry into the gut**

CIC = chloride channel.
US Food and Drug Administration. Available at: http://www.fda.gov/cder/drug/InfoSheets/patient/lubiprostonePIS.htm. Accessed September 23, 2008.

Lubiprostone in CC

- *N* = 129; 24, 48, and 72 µg/d versus placebo, 3 weeks
- Efficacy and safety study
  - SBM frequency
  - Rescue medication use
  - Symptom assessments
  - AEs
- SBM frequencies were higher for lubiprostone groups (5.1–6.1) versus placebo (3.8; *P* = .046)
- Higher doses (48, 72 µg/d) more effective at first week; all doses effective at 2 weeks
- Most common AEs: nausea, headache, and diarrhea

AE = adverse events; SBM = spontaneous bowel movement.
Johanson and Ueno. *Aliment Pharmacol Ther*. 2007;25:1351-1361.

Lubiprostone in CC

- Multicenter randomized controlled trial: 242 patients with CC
  - 120 lubiprostone versus 122 placebo
  - 24 µg/bid x 4 weeks
- Primary end point: number of SBMs at 1 week
- Lubiprostone increased number of SBMs vs placebo (5.69 vs 3.46; *P* = .0001)
- Also Improved:
  - Straining and consistency
  - Constipation severity
  - Abdominal bloating/discomfort
- AE: mild-to-moderate nausea (31.7%)

Johanson et al. *Am J Gastroenterol.* 2008;103:170-177.

Lubiprostone in IBS-C

- 195 patients with IBS-C
  - 8, 16, and 32 µg x 3 months
- Abdominal pain/discomfort
  - Month 2: significantly greater improvements in mean abdominal discomfort/pain scores ($P \leq .039$)
  - Also improvements in :
    - SBMs
    - Straining and consistency
    - Constipation severity
    - Abdominal bloating/discomfort
    - Safety
    - Global treatment effect
- Optimal dose: 16 µg/d
- AEs: diarrhea and nausea

Johanson et al. *Aliment Pharmacol Ther*. 2008;27:685-696.

5-HT_4 Agonist

- Tegaserod (5-HT_4 partial agonist): withdrawn from market
  - MOA: induces colonic propagating contractions and accelerates colonic transit
  - Higher risk of cardiovascular effects
    - Myocardial infarction and Stroke and Unstable angina

IND = investigational new drug.
US Food and Drug Administration. Available at: http://www.fda.gov/cder/drug/advisory/tegaserod.htm. Accessed September 23, 2008.

Emerging Therapies: Prucalopride

- **Prucalopride: selective, high-affinity 5-HT$_4$ receptor agonist**
  - **Prokinetic effects**
  - **Improves colonic transit**
  - **Cardiovascular effects have not yet been fully characterized**

Camilleri et al. *N Engl J Med*. 2008;358:2344-2354.
Moss. *N Engl J Med*. 2008;358:2402-2403.

Emerging Therapies: Prucalopride

12-week study (*n* = 620)

Dosage: 2 mg or 4 mg

Primary efficacy end point:

- **Proportion of patients having ≥3 spontaneous, complete bowel movements weekly**
  - **47.3% 2 mg**
  - **46.6% 4 mg**
  - **25.8% placebo**

Prucalopride superior efficacy compared to placebo (*P* <.001)

Reprinted with permission from Camilleri et al. *N Engl J Med*. 2008;358:2344-2354.

Emerging Therapies: Alvimopan

- Semisynthetic peripherally restricted mu-receptor opioid antagonist
  - Studied in treatment of opiate-induced constipation and postoperative ileus
  - Similar agents: methylnaltrexone, naloxone, and nalbuphine
- 23 studies on 2871 opioid antagonist-treated patients
- Insufficient evidence of safety and efficacy

McNicol et al. *Cochrane Database Syst.Rev.* 2008;2:CD00633l.

Emerging Therapies: Renzapride

- Mixed 5-HT_4 receptor agonist/5-HT_3 receptor antagonist
- Pilot study: 17 patients with IBS-C
  - Accelerated segmental colonic transit (2 mg twice a day)
  - Reduced abdominal discomfort
  - Increased number of pain-free days
  - Improved stool consistency

Tack et al. *Aliment Pharmacol Ther*. 2007;23:1655-1665.

Emerging Therapies: Renzapride

RCT, phase IIb trial in patients with IBS-C to study the effect on abdominal pain/discomfort

- 1, 2, or 4 mg/d x 12 weeks
- Patient self-assessment of pain/discomfort
- No statistically significant difference between placebo and treatment drug in pain/discomfort
- However . . . statistically significant improvement noted with 4-mg dose:
  - Bowel movement frequency
  - Stool consistency
- Drug well tolerated

George et al. *Aliment Pharmacol Ther.* 2008;27:830-837.

Emerging Therapies: Linaclotide

- Guanylate cyclase agonist
  - Stimulates intestinal fluid secretion/transit
  - Decreases visceral hypersensitivity
- 36 patients with IBS-C
  - 12 patients received 100 µg/d
  - 12 patients received 1000 µg/d
  - 12 patients received placebo
- 5-day course of treatment versus placebo
  - 100 µg/d
  - 1000 µg/d
- 1000 µg/d significantly improved colonic transit (24 hr; $P < .004$)
  - Overall improvement in stool frequency, consistency, ease of passage, and time to first bowel movement ($P < .001$)

Andresen et al. *Gastroenterology.* 2007;133:761-768.

Surgery

- Colectomy may be needed for refractory slow transit constipation without disordered defecation
- Ileostomy/Colostomy may be the only option for patients with refractory pelvic floor dysfunction
- Colectomy with ileorectal anastomosis does not improve symptoms in patients with dyssynergic defecation unless dyssynergia is corrected first
- Colectomy may not provide relief for patients with abdominal pain or psychosocial problems

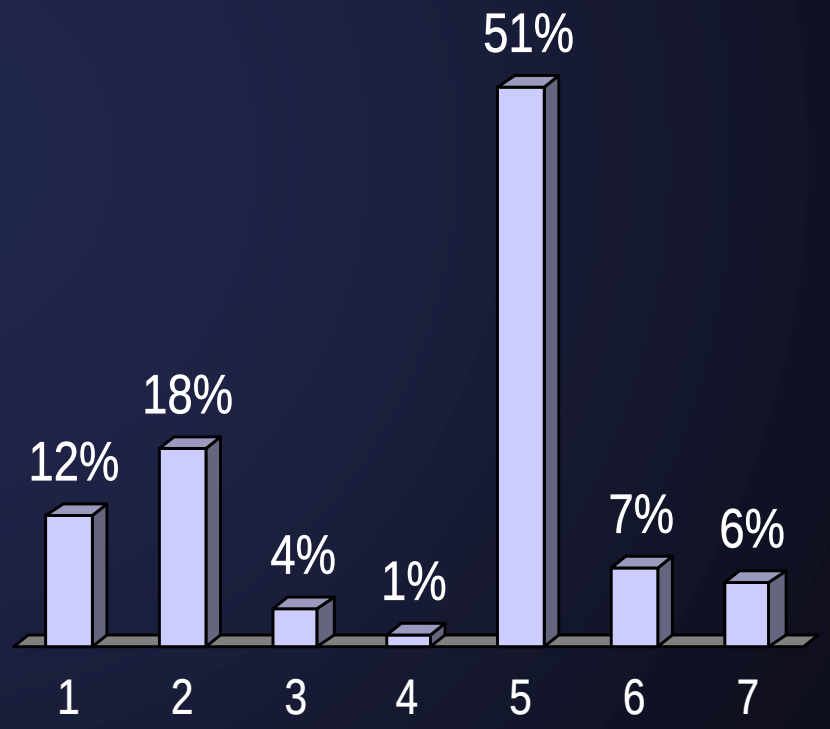
Rao. *Gastroenterol Clin North Am.* 2007;36:687-711.

Integrated Approach for Patients with Constipation

Henry Parkman, MD
Director, Gastrointestinal Motility Laboratory
Professor of Medicine
Temple University School of Medicine
Philadelphia, PA

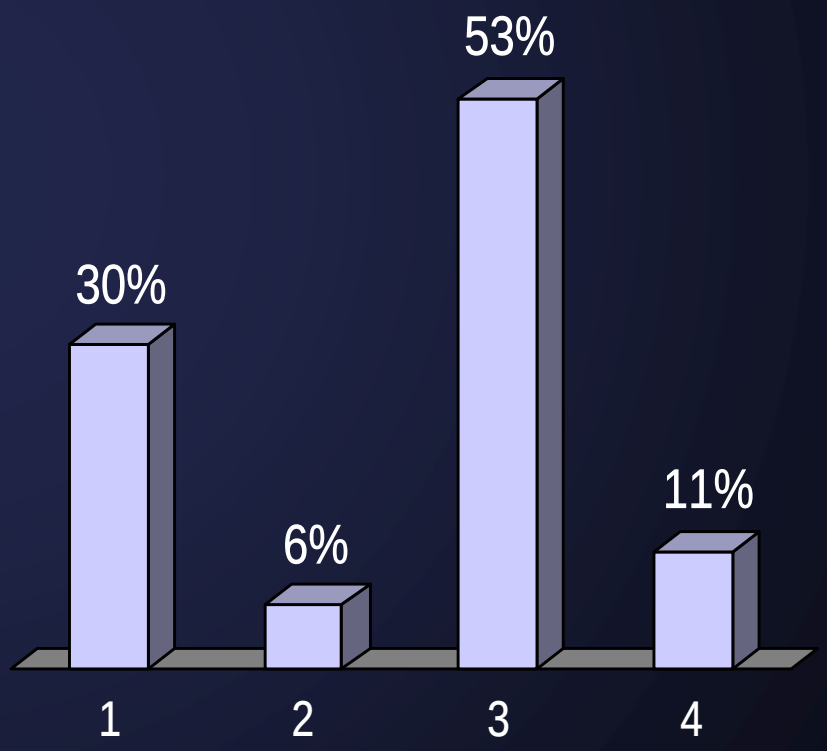
Which elements of this patient's workup and treatment could have been managed by her primary care provider?

- Diagnostic testing for colon transit
- Abdominal X rays
- Balloon expulsion test
- Defecography
- Nutritional counseling
- Timed toileting
- Biofeedback treatment



Which of the following tests can you obtain to evaluate your patients with refractory constipation?

- Colonic Transit Test
- anorectal manometry and/or Balloon Expulsion
- Both of the above
- Neither



An Integrated Approach: Understanding the Patient's Problem

- What are your concerns?
- What do you mean by constipation?
- What bothers you the most about your constipation?
- How long have you experienced these symptoms?
- Does constipation limit or affect your daily activities?

Locke et al. *Gastroenterology.* 2000;119:1761-1778.

Evaluation and Management: A Team Approach

- Comprehensive history, physical examination, and diagnostic workup may be time consuming
- Multiple providers may interact with the patient
  - Primary care provider
  - Family nurse practitioner/physician assistant
  - Psychiatrist/psychologist
  - Gastroenterologist
  - Radiologist
  - Surgeon
- Clear, empathetic communication with the patient is critical
- Clear, efficient communication between providers is key!

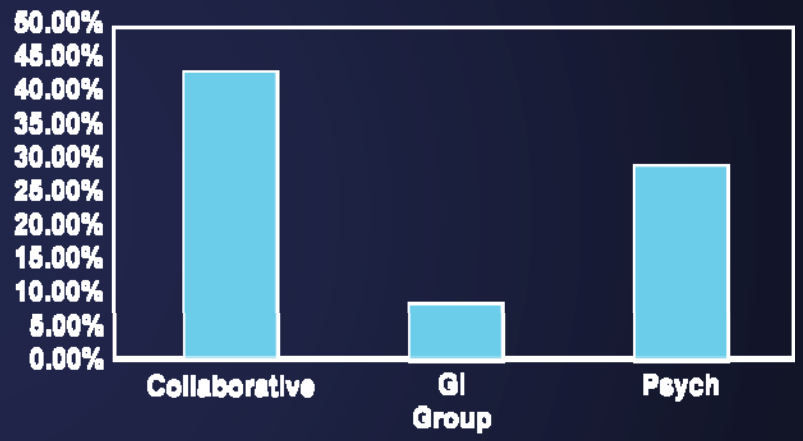
An Integrated Approach: Understanding the Patient's Problem

- Patient dissatisfaction may be a result of:
  - Poor understanding of condition
  - Explanation of test results may be seen as denying the legitimacy of their condition
  - Negative test results seen as absence of cause of symptoms/concerns
- Establishing a trusting relationship between the patient and healthcare provider is a key ingredient to successfully managing CC and IBS
- Patient education is an important function for primary care providers

Chang et al. *Gastroenterology*. 2006;130:1435-1446.

Multidisciplinary Approach to Management of IBS is Effective

- 41 patients with IBS randomized:
  - 16 patients completed collaborative program
  - 8 completed medical treatment program
  - 6 completed psychologic therapy program
- Global self-assessment improved in patients in the collaborative program (*P* <.0002)
- Abdominal pain, diarrhea, and constipation also improved significantly in the collaborative treatment group (*P* <.001)
- Collaborative treatment was statistically more effective than medical treatment alone (*P* <.05)



Gerson and Gerson. *Clin Gastroenterol Hepatol.* 2003;1:446-452.

Clinical Challenges

Communication Issues

- Patients reluctant to discuss defecation with physician
- Physician reluctance to discuss defecation with patient

Clinical Issues

- Pathophysiology is multifactorial
- CC and IBS-C symptoms overlap

Conclusions

- Constipation is a symptom-based diagnosis
- Abdominal pain is the differentiating symptom between IBS-C and CC
- Diagnostic tests can differentiate the types of constipation to ensure optimal management decisions
- Secondary causes of CC should be ruled out
- Patients with normal transit constipation frequently respond well to lifestyle changes and OTC laxatives
- Collaboration among healthcare providers has been shown to enhance patient outcomes

The Educational Initiative on Constipation: Focus on IBS-C and CC

VIDEO CASE CHALLENGE