
Management of Elderly Patients with Chronic Constipation

William D. Chey, MD

Professor of Internal Medicine

Division of Gastroenterology

University of Michigan

Ann Arbor, Michigan

Sponsored by Veritas Institute for Medical Education, Inc.

Supported by an educational grant from
Takeda Pharmaceuticals International, Inc., U.S. Region

Learning Objectives

- Recognize the impact of chronic idiopathic constipation in the elderly
- Differentiate newer agents for the treatment of chronic constipation in terms of safety, efficacy and the patient populations for which they are approved
- Apply treatment strategies utilizing newer agents after the failure of laxatives or as first line agents for the management of chronic constipation when appropriate
- Utilize appropriate outcome measures to determine treatment response and impact on quality of life in order to guide treatment decisions

Note: Due to space constraints, study limitations are not addressed for the studies presented. Participants are directed to the cited references for information on individual study limitations.

Demographic Question 1

Please indicate your profession

1. Gastroenterologists
2. Gerontologists
3. Primary Care Physician
4. Physician Assistant
5. Nurse Practitioner
6. Nurse
7. Other

Demographic Question 2

Which best describes your work environment?

1. Academic
2. Staff-model health maintenance organization
3. Single-specialty practice
4. Multispecialty practice
5. Community hospital
6. Fellowship/training
7. Other

Demographic Question 3

How many years have you been in practice?

1. 1-5
2. 6-10
3. 11-15
4. 16-20
5. 21+
6. N/A

Demographic Question 4

How many patients with chronic constipation do you see each week?

1. 1-5
2. 6-10
3. 11-15
4. 16-20
5. 21+
6. N/A

Pretest Question 1

Studies have suggested that the prevalence of chronic constipation in the elderly community may be greater than...

1. 40%
2. 50%
3. 60%
4. 70%

Pretest Question 2

Chronic Constipation has been demonstrated to have a significant impact on quality of life (QoL). In which of the following QoL measurement tools was chronic constipation shown to have the *greatest* impact as compared to other GI symptoms, such as abdominal bloating, abdominal pain, or chronic diarrhea?

1. Activity impairment score
2. Overall work impairment score
3. SF-12 mental component summary score
4. SF-12 physical component summary score
5. A and B
6. All of the above

Pretest Question 3

According to the American Gastroenterological Association, the initial treatment for chronic constipation should be fiber supplementation and/or osmotic or stimulant laxatives. However, studies have shown that these approaches are not effective or suitable in all patients. More than 40% of patients have reported dissatisfaction with laxatives, mainly for reasons of efficacy, in which of the following patient populations?

1. Chronic idiopathic constipation (CIC)
2. Opioid induced constipation (OIC)
3. Irritable bowel syndrome with constipation (IBS-C)
4. A and B
5. All of the above

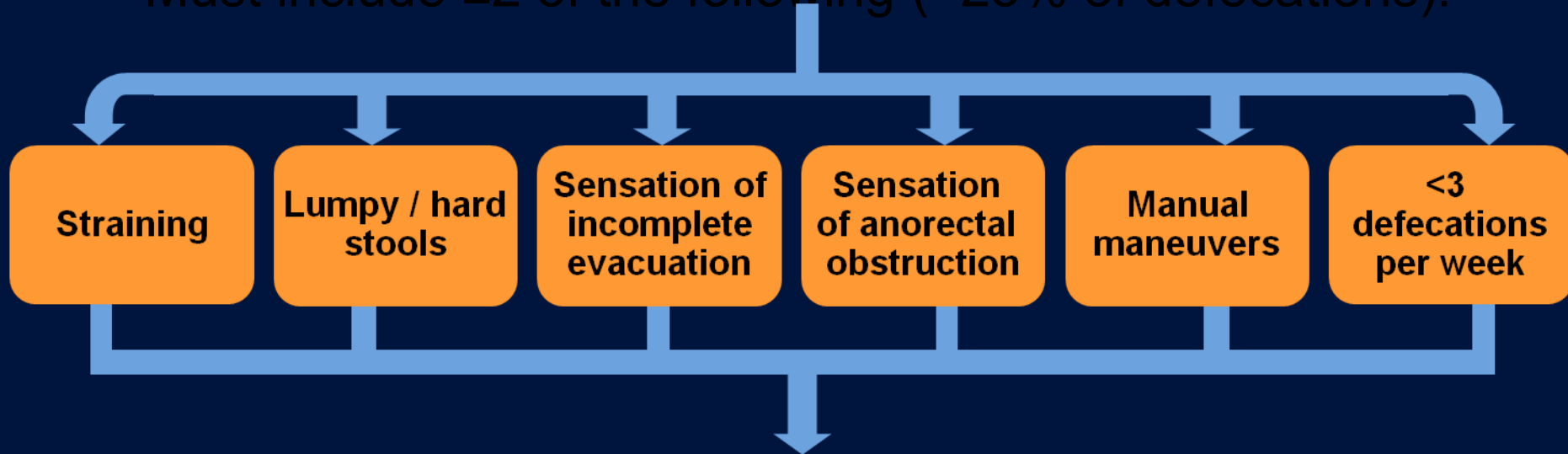
Pretest Question 4

According to the American Gastroenterological Association's Medical Position Statement on Constipation, "A newer agent should be considered when symptoms do not respond to laxatives." Which of the following is/are approved for the treatment of opioid induced constipation in patients unresponsive to laxatives.

1. Lubiprostone
2. Naloxegol
3. Plecanitide
4. Linaclootide
5. A and B
6. All of the above

What is Chronic Constipation: Rome III Criteria*

Must include ≥ 2 of the following ($>25\%$ of defecations):



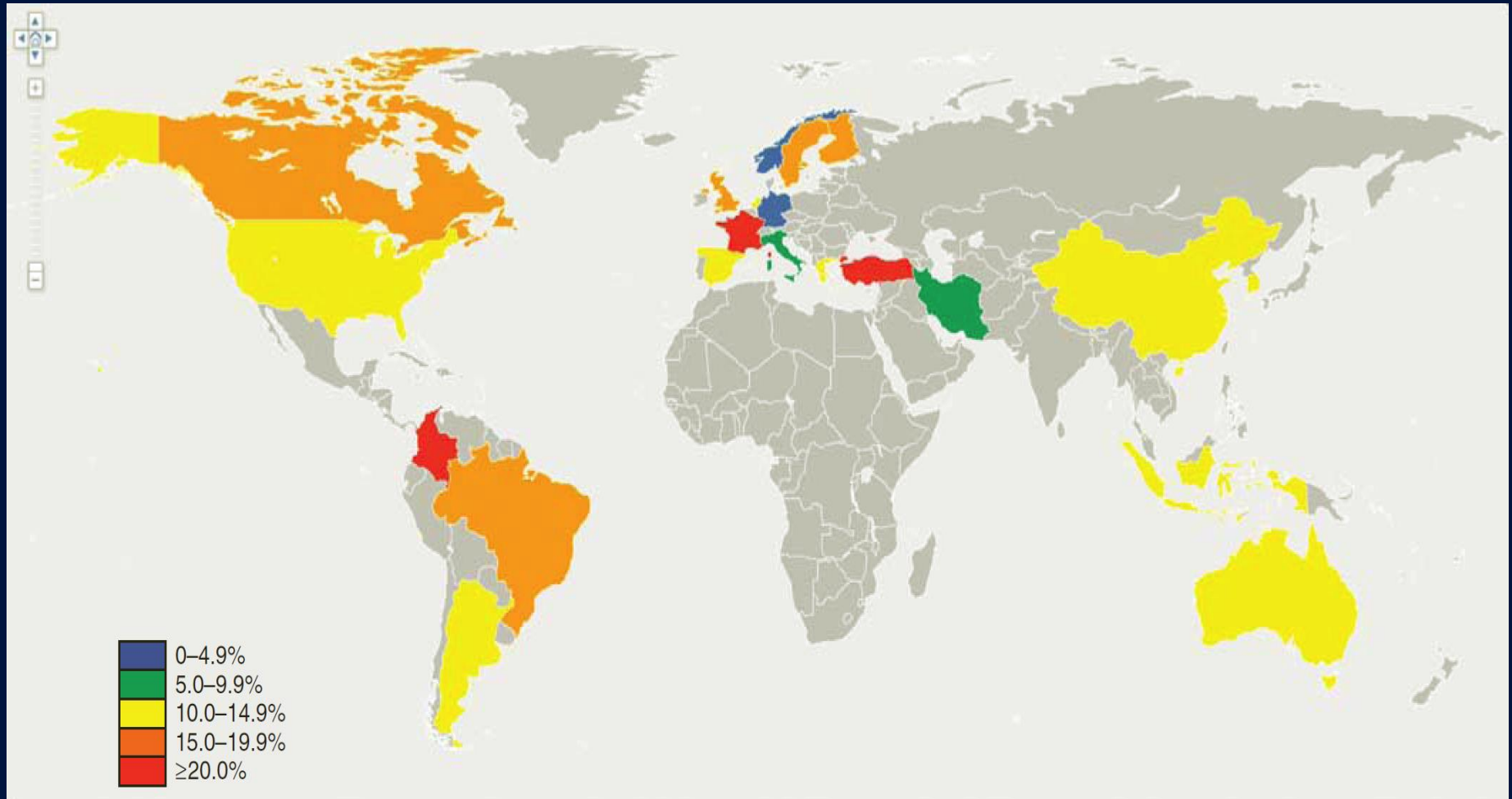
Loose stools rarely present without laxative use
insufficient criteria for IBS

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

The Key Questions

- *How common is it?*
- *What is the burden of illness?*
- *What causes constipation?*
- *What tests can be used to assess chronic constipation?*
- *What are the treatments?*

Prevalence of Chronic Idiopathic Constipation According to Country



Pooled prevalence of CIC

According to Age

Age band	Number of subjects	Pooled prevalence of CIC (95% confidence interval)	Odds ratio for CIC (95% confidence interval)
< 29 years	7,153	12.0 (10.0 - 14.0)	1
30 - 44 years	7,092	15.0 (12.0 - 19.0)	1.20 (1.09 - 1.33)
45 - 59 years	5,314	16.0 (11.0 - 21.0)	1.31 (1.09 - 1.58)
≥60 years	3,443	17.0 (13.0 - 22.0)	1.41 (1.17 - 1.70)
CIC, chronic idiopathic constipation.			

Chronic Constipation in an Aging Population

- U.S. individuals ≥ 65 years of age in 2010 was 40.2 million - projected to rise to 88.5 million in 2050 ¹
- Constipation prevalence in an elderly community setting was 40.1% in individuals with a mean age of 76 years ²
- Studies report that chronic constipation affects the majority of long-term patients in hospitals and residents in nursing homes ^{3,4}

1. Vincent et al. 2010. Available at <https://www.census.gov/prod/2010pubs/p25-1138.pdf>

2. Talley, et al. Am J Gastroenterol. 1996;91(1):19–25

3. Tariq. J Am Med Dir Assoc 2007; 8:209–18

4. Bosshard et al. Drugs Aging. 2004;21(14):911–930

The Key Questions

- *How common is it?*
- *What is the burden of illness?*
- *What causes constipation?*
- *What tests can be used to assess chronic constipation?*
- *What are the treatments?*

Leading GI Symptoms Prompting an Outpatient Visit

Rank	Symptom	Estimated visits
1	Abdominal pain	15,863,956
2	Diarrhea	4,236,051
3	Constipation	3,175,842
4	Vomiting	2,861,790
5	Nausea	2,814,364
6	Heartburn and indigestion	1,982,517
7	Rectal bleeding	1,702,331

Impact of Select GI Diseases and Symptoms on QOL, Activity and Work Productivity

	SF-12 mental component summary score Mean (SD) ^a	SF-12 physical component summary score Mean (SD) ^a	Activity impairment score Mean (SD) ^b	Overall work impairment score Mean (SD) ^b
Gastrointestinal symptoms				
Abdominal bloating	43 (12)	46 (12)	35 (31)	26 (29)
Abdominal pain	42 (12)	45 (12)	38 (32)	28 (30)
Chronic constipation	41 (13)	39 (13)	51 (32)	37 (33)
Chronic diarrhea	42 (12)	43 (12)	42 (32)	31 (30)
Heartburn	46 (12)	46 (11)	30 (30)	21 (27)
Other references				
Population norm	50 (10)	50 (10)	24 (29)	16 (25)
^a A lower score is associated with worse quality of life; ^b A higher percentage is associated with greater impairment				

The Key Questions

- *How common is it?*
- *What is the burden of illness?*
- *What causes constipation?*
- *What tests can be used to assess chronic constipation?*
- *What are the treatments?*

Factors Associated with Constipation Among US Men and Women from NHANES, 2005-06 & 2007-08

	Women ^a POR (95% CI), N=3,841	Men ^a POR (95% CI), N=3,561
African-American race/ethnicity	1.39 (1.00, 1.93)	1.40 (0.82, 2.41)
Living above poverty income	0.93 (0.72, 1.20)	0.71 (0.48, 1.04)
Higher education	0.82 (0.71, 0.94)	0.92 (0.69, 1.21)
Comorbidity	1.00 (0.87, 1.15)	0.97 (0.79, 1.19)
Body mass index (obese)	0.65 (0.49, 0.88)	0.91 (0.55, 1.52)
Poor/fair self-rated health	1.24 (0.86, 1.78)	1.31 (0.83, 2.05)
Vigorous physical activity	0.96 (0.68, 1.36)	0.74 (0.45, 1.20)
Low fiber intake (lowest quartile)	1.07 (0.84, 1.36)	1.40 (0.88, 2.20)
Low dietary liquid intake (lowest quartile)	1.29 (1.02, 1.64)	2.42 (1.51, 3.88)

CI, confidence interval; NHANES, National Health and Nutrition Examination Surveys; POR, prevalence odds ratio

^aAll multivariable models controlled for age (in decades) and included appropriate sampling weight. Bolded items represent significant POR (95% CI), $P < 0.05$.

Issues in the Elderly that might contribute to Constipation

- *Physiological Changes?*
- *Dietary Changes*
 - *Reduced fiber intake, increased fat & protein*
 - *Reduced fluid intake*
 - *Smaller meals*
- *Reduced Physical Activity/Mobility*
- *Cognitive impairment/Neurological Diseases*
- *Depression*

Constipation Associated with Irritable Bowel Syndrome

- Consultation rates with healthcare providers for patients meeting the diagnostic criteria for IBS rise progressively with increasing patient age
- Although the prevalence of IBS does not increase in the elderly population, clinicians may actually see more elderly patients with IBS (and constipation associated with IBS) than they do younger patients

Constipation Associated with Chronic Pain and Opioid Use in the Elderly

- Chronic pain – 45% to 85% of elderly patients report moderate-to-severe chronic pain ¹
- The American Geriatric Society (AGS) recommendation: opioids preferred over NSAIDs for management of moderate-to-severe chronic pain among older adults ²
- Opioid prescriptions significantly increased in patients aged ≥65 years between 1995 to 2010, compared to younger aged patients (OR = 8.85) ³
- Opioid treatment for moderate-to-severe chronic pain is associated with bowel dysfunction leading to constipation in **the majority** of patients ⁴

1. Gianni, et al. Drugs Aging. 2009;26: S63–S73;

2. AGS. J Am Geriatr Soc. 2009;57:1331–1346;

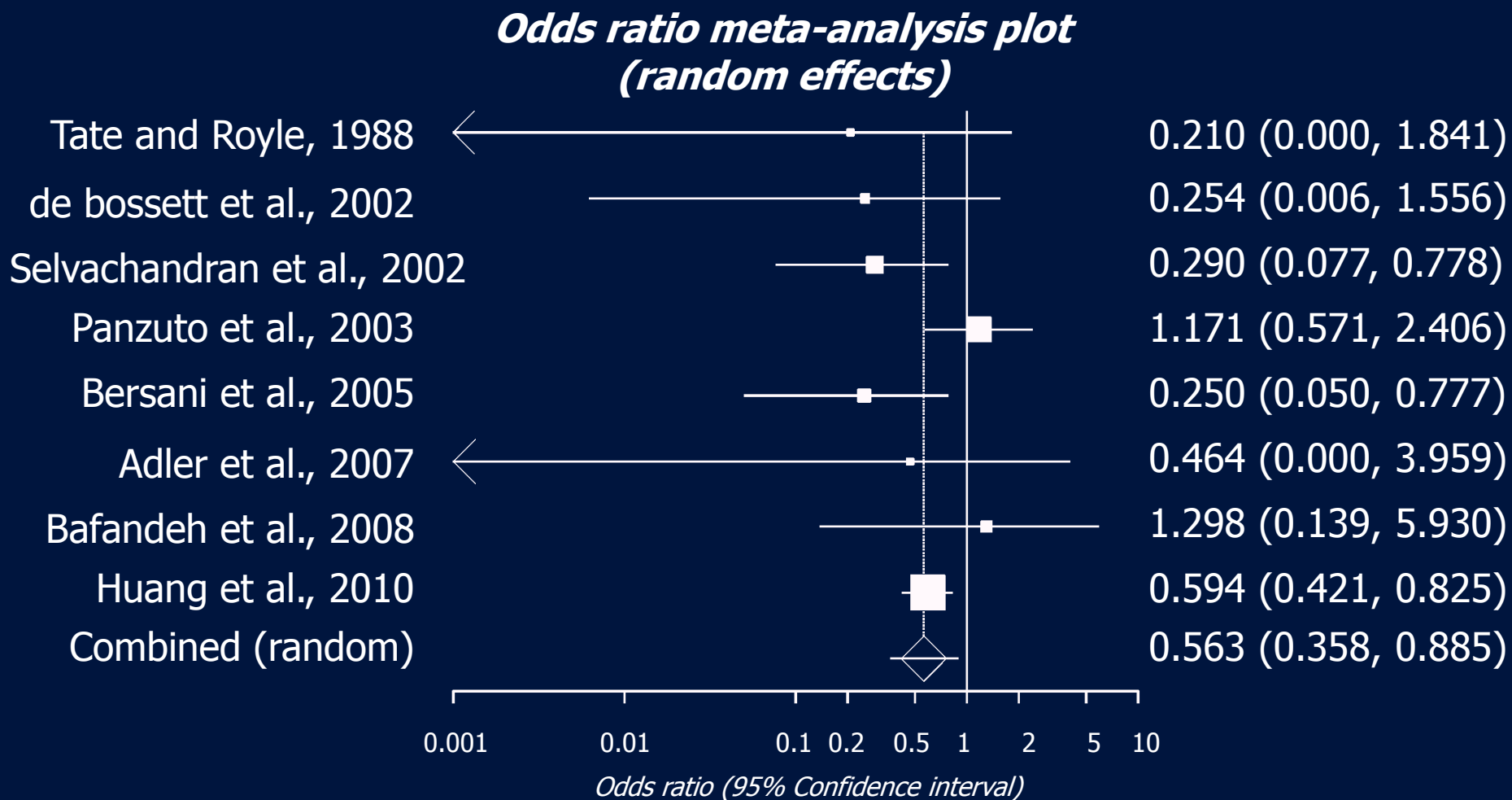
3. Olfson et al. J Clin Psychiatry. 2013 Sep;74(9):932-9

4. Manchikanti et al. Pain Physician. 2012 Jul;15(3 Suppl):S67-116.

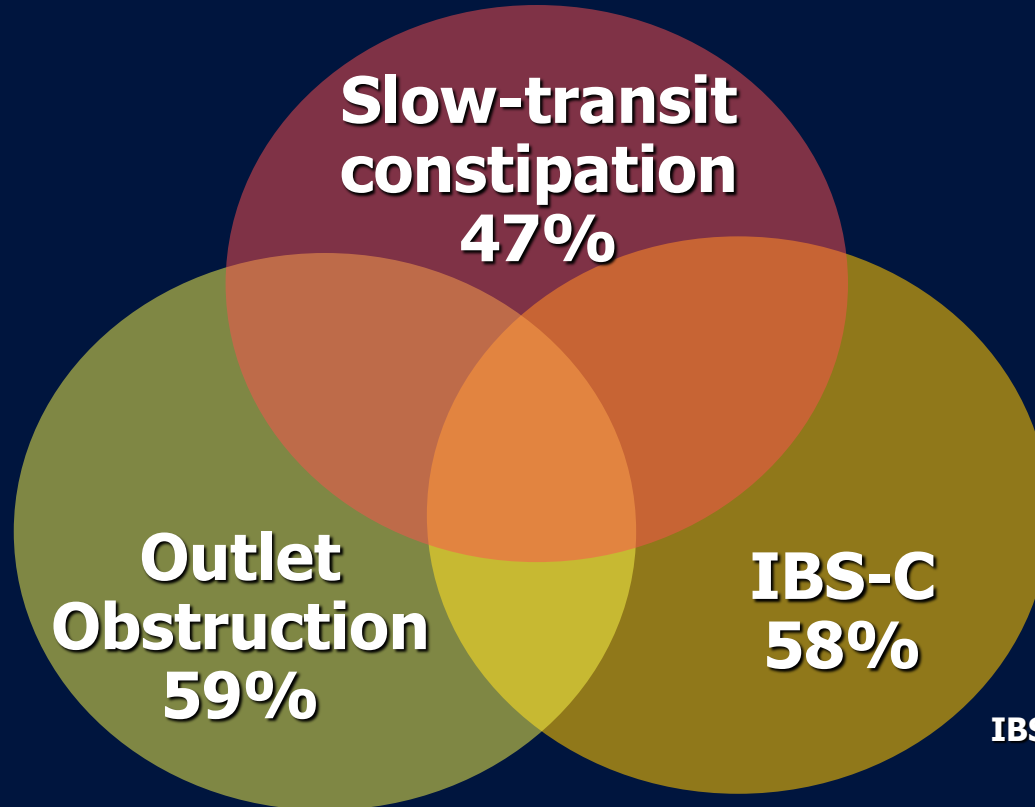
Medications Are a Common Cause of Constipation in the Elderly

- *Asa/NSAIDs*
- *Opioids*
- *Anticholinergics*
- *Antidepressants*
- *Antihistamines*
- *Antihypertensives*
- *Anti-parkinsonian drugs*
- *Diuretics*
- *Calcium & Iron supplements*

Risk of Colorectal Cancer in Patients with or without Constipation (Cross-Sectional Surveys)



Subtypes of Constipation



IBS-C: IBS with constipation

- **Slow transit and IBS-C overlap in half of each group**
- **Recent SR found prevalence of STC to be 38-80%**

Causes of Outlet Obstruction Constipation

Dyssynergic Defecation

Anal fissure

Anal stricture

Intussusception

Pelvic floor descent (impaired or excessive)

Proctitis

Rectal prolapse

Rectocele/Enterocoele

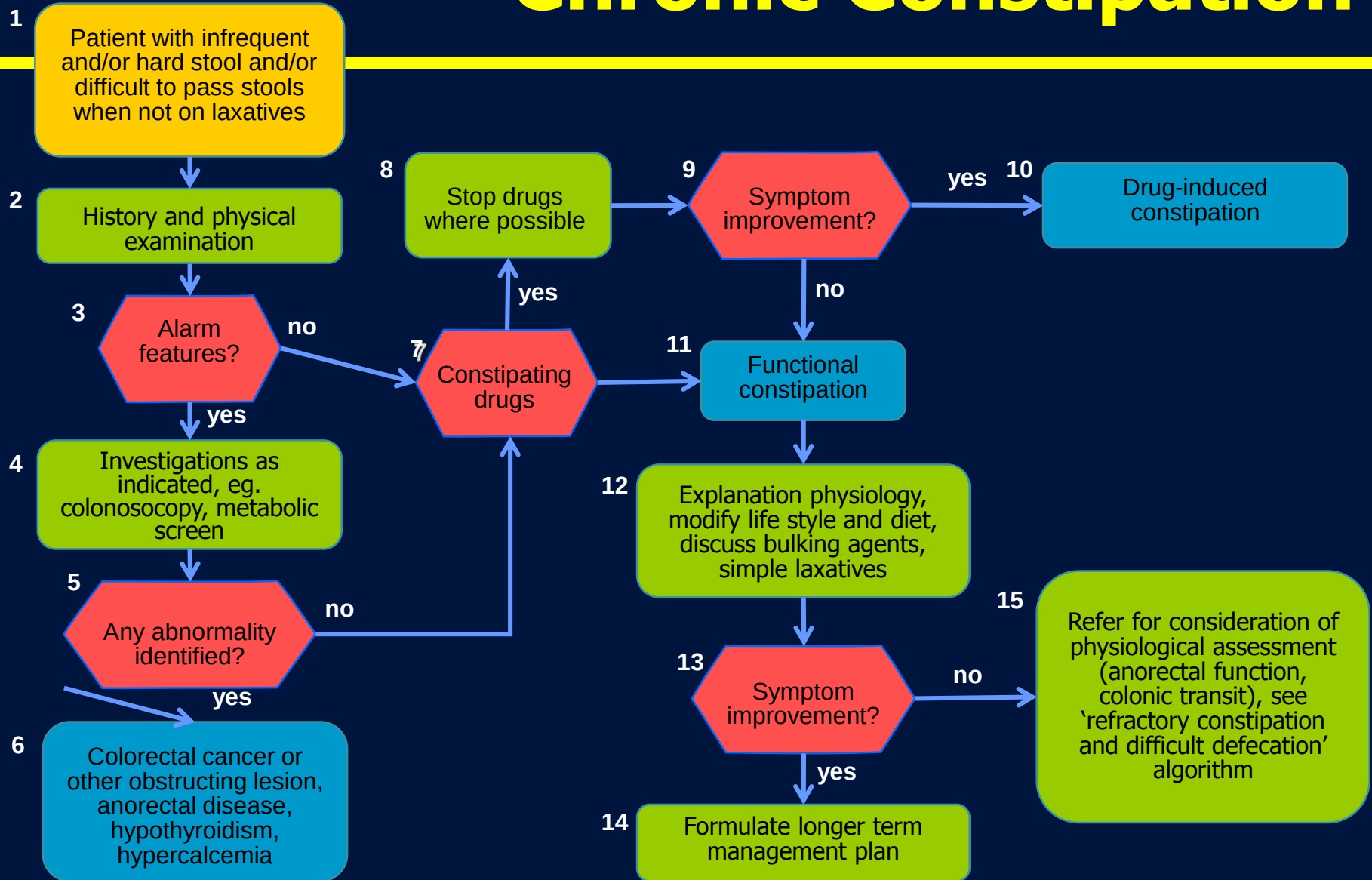
Thrombosed hemorrhoids

Urogynecologic dysfunction

The Key Questions

- *How common is it?*
- *What is the burden of illness?*
- *What causes constipation?*
- *What tests can be used to assess chronic constipation?*
- *What are the treatments?*

Chronic Constipation



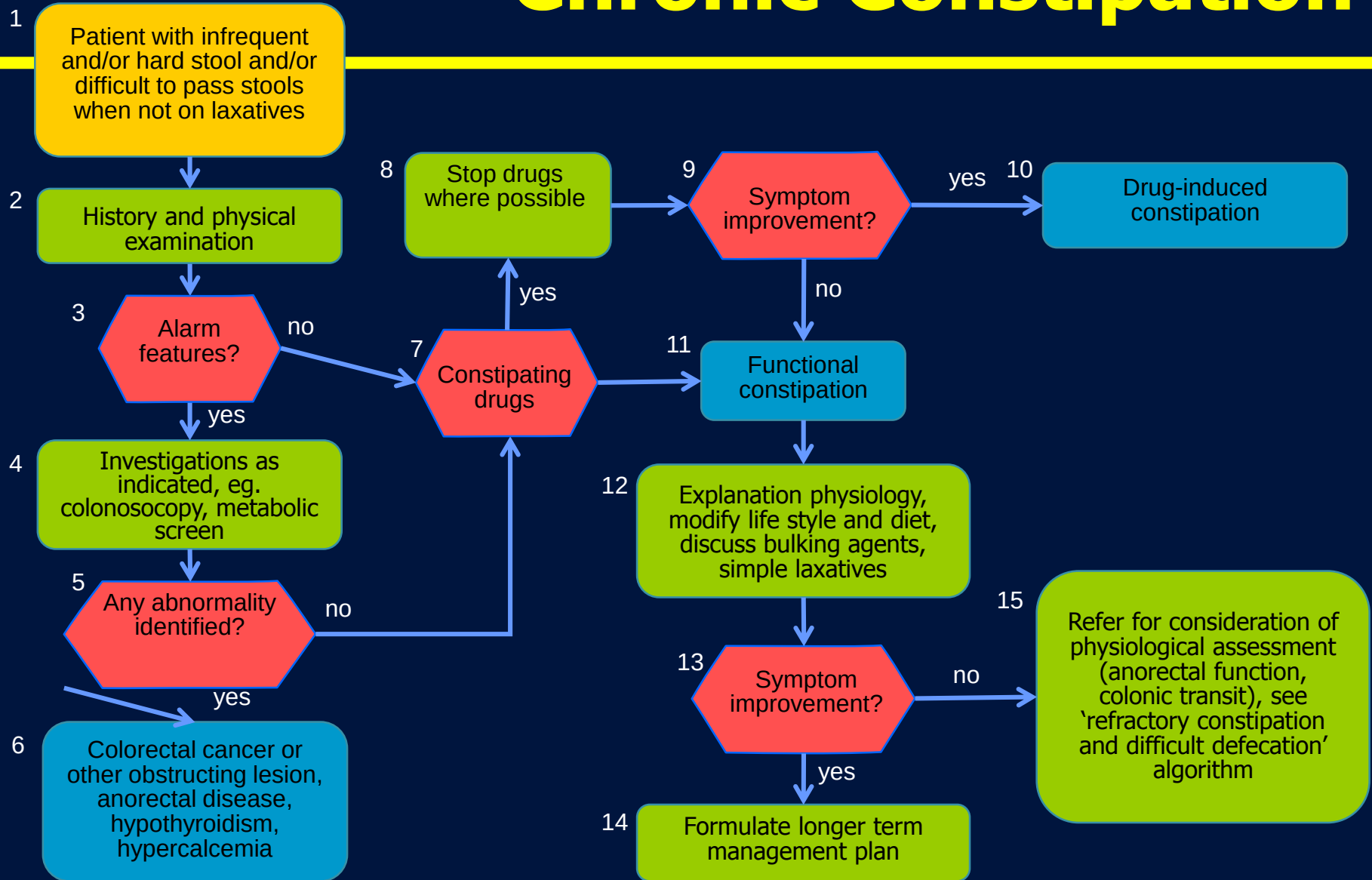
Alarm Features for Chronic Constipation

- Age >50 years; >45 years if African-American
- New onset constipation in elderly
- Severe symptoms not investigated
- Rectal bleeding
- Fever
- Weight loss
- Family history of organic GI disease
- Palpable abdominal / rectal mass



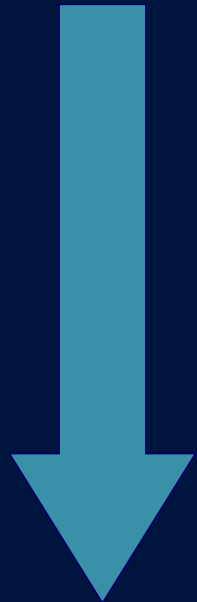
Investigate and
treat
appropriately;
colonoscopy may
be indicated

Chronic Constipation



Bristol Stool Form Scale

Slow gut transit



Rapid gut transit

Type 1



Separate hard lumps

Type 2



Sausage-like but lumpy

Type 3



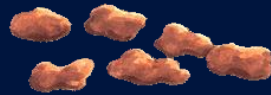
Sausage-like but with cracks in the surface

Type 4



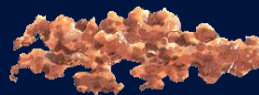
Smooth and soft

Type 5



Soft blobs with clear-cut edges

Type 6



Fluffy pieces with ragged edges, a mushy stool

Type 7



Watery, no solid pieces

Normal Anorectal Physiology

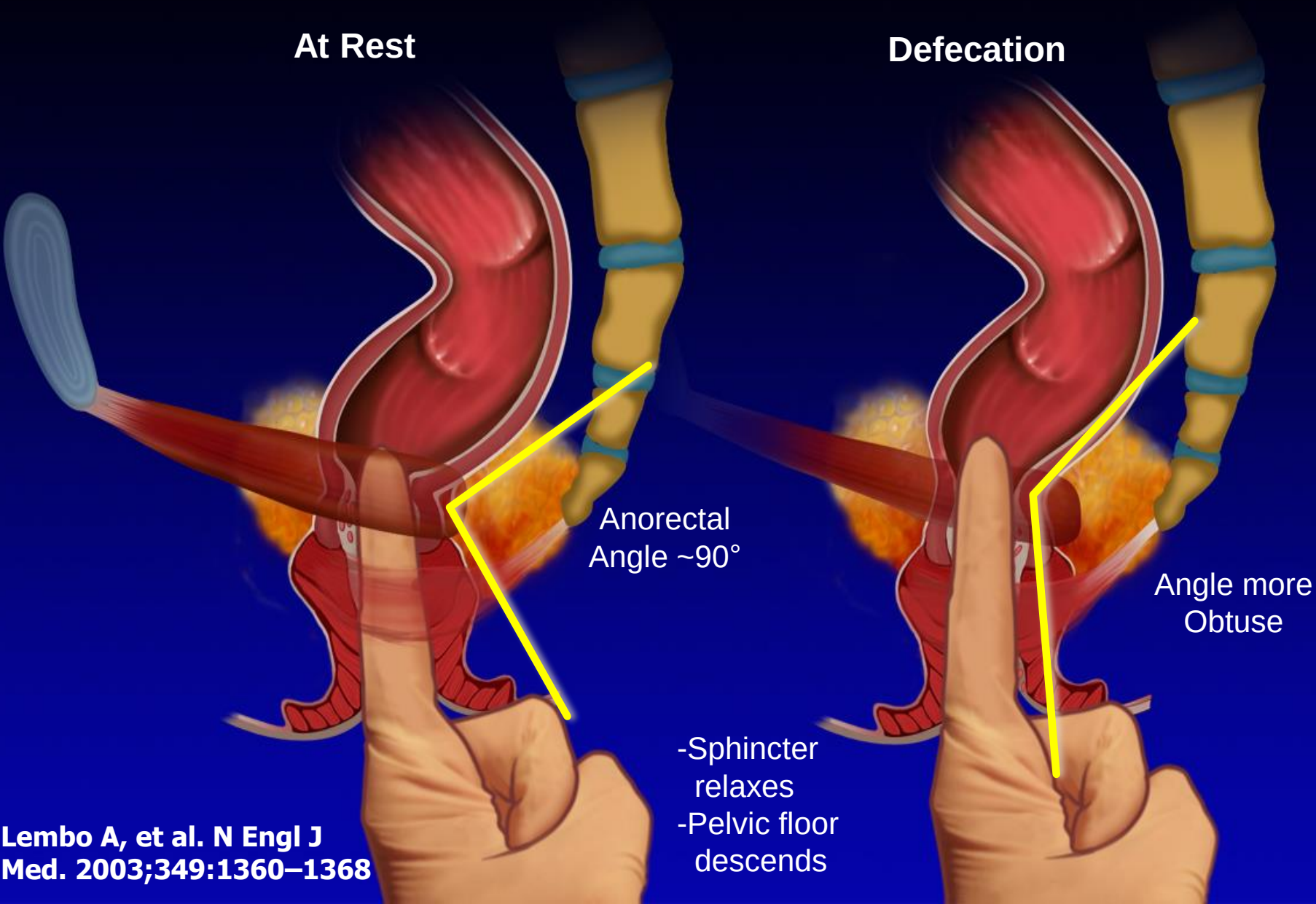
At Rest

Defecation

Anorectal
Angle $\sim 90^\circ$

Angle more
Obtuse

-Sphincter
relaxes
-Pelvic floor
descends



Other tests for Chronic Constipation

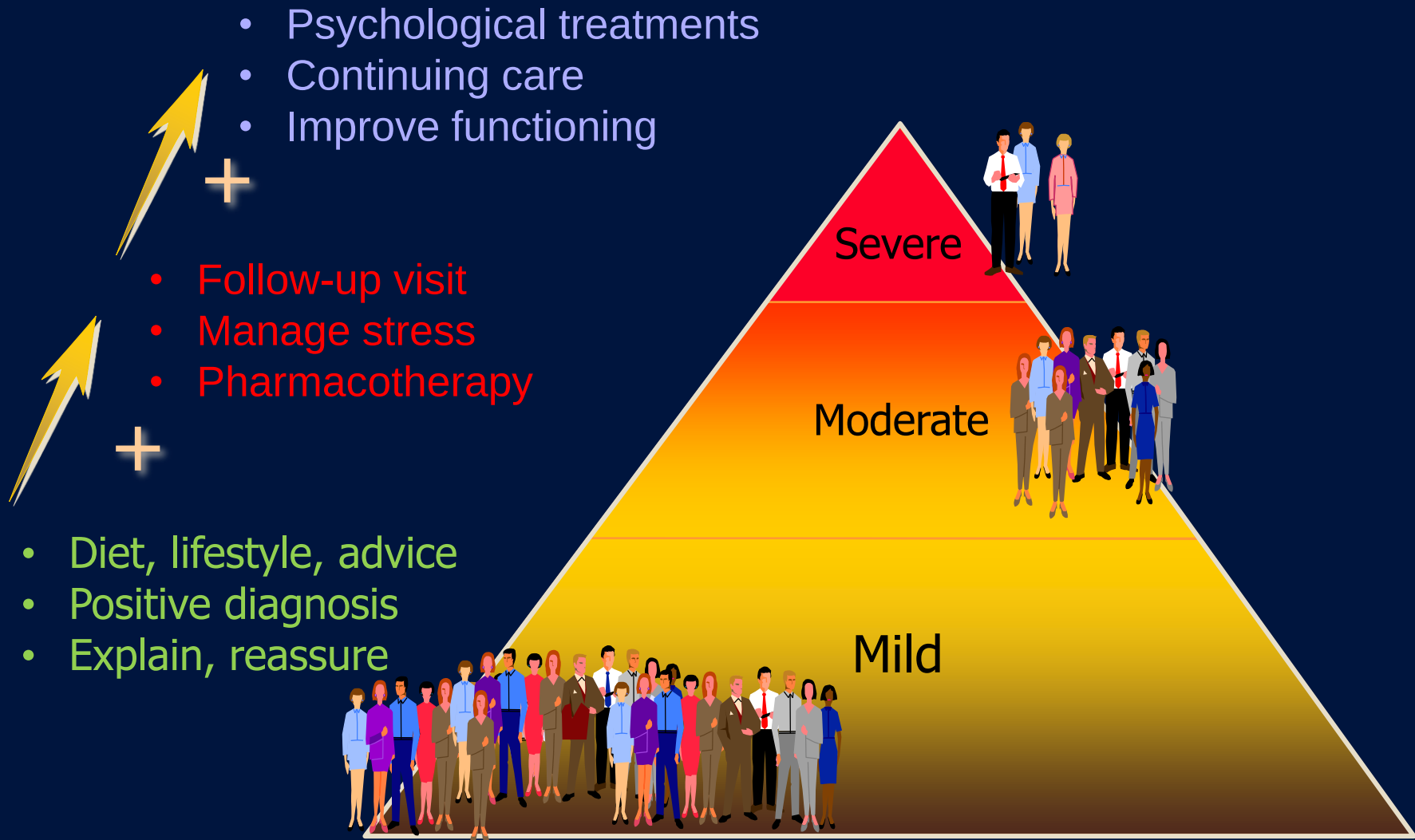
For patients with alarm features; lack of response to treatment consider:

- **Balloon expulsion**: Suspected outlet problems / dyssynergia
- **Anorectal manometry**: Suspected dyssynergia; Hirschsprung's disease
- **Defecography**: Suspected outlet problems / pelvic floor dysfunction
- **Colonic transit** (Sitz markers or Wireless pH-motility capsule testing): Identify slow colon transit

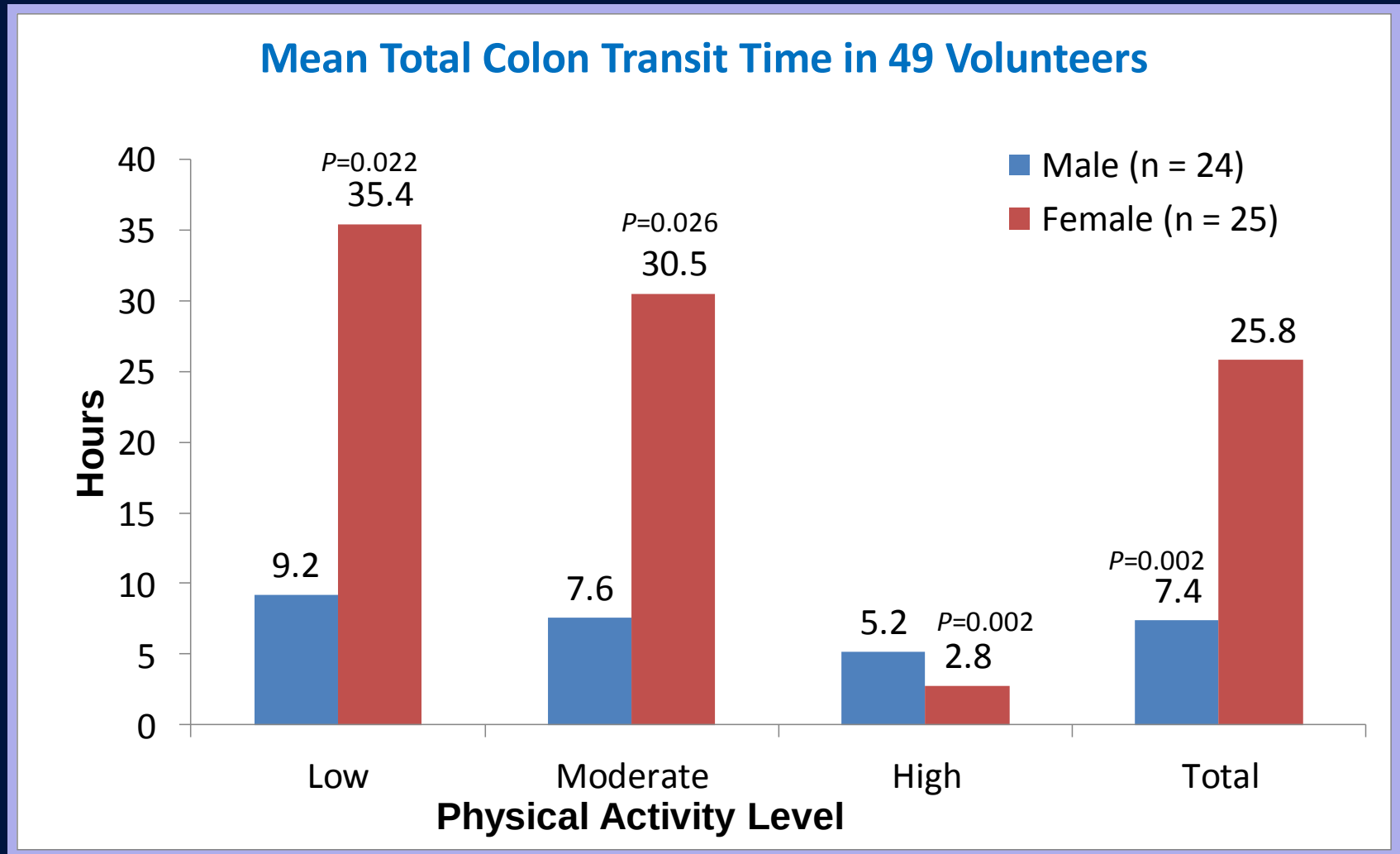
The Key Questions

- *How common is it?*
- *What is the burden of illness?*
- *What causes constipation?*
- *What tests can be used to assess chronic constipation?*
- *What are the treatments?*

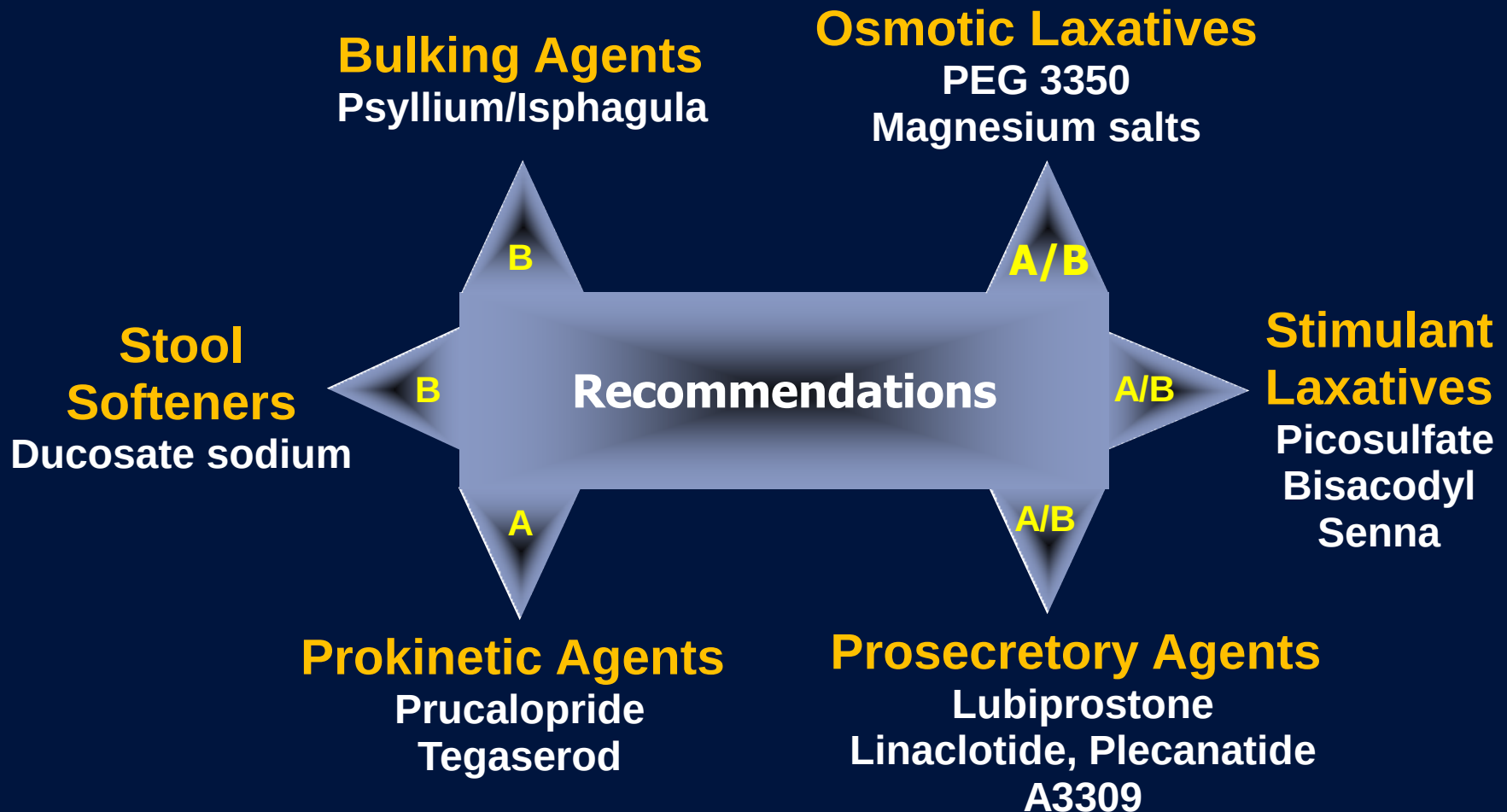
Graded Treatment of Chronic Constipation



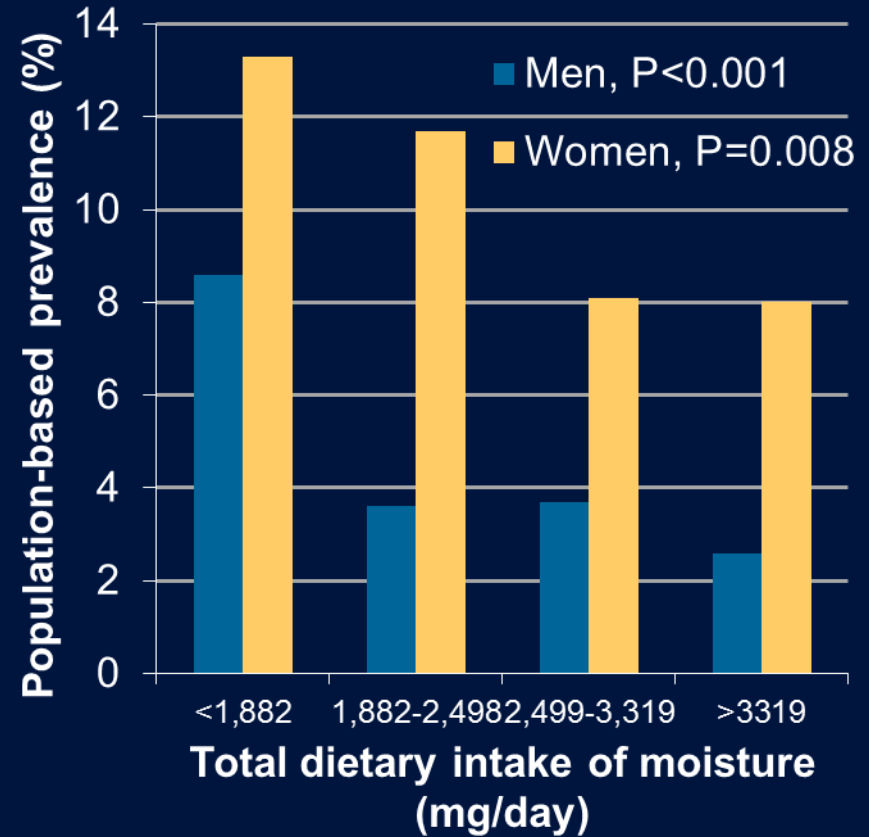
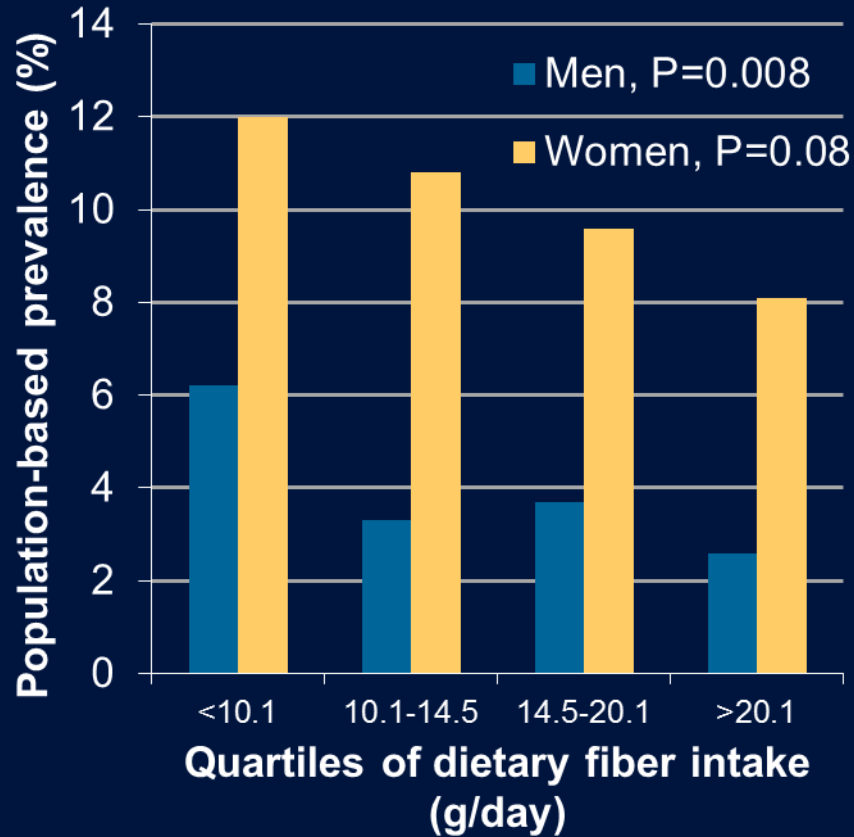
Colon Transit Time According to Physical Activity Level



Pharmacological Treatments for Chronic Constipation:



Prevalence of Constipation According to Intake of Dietary Fiber & Total Dietary Moisture

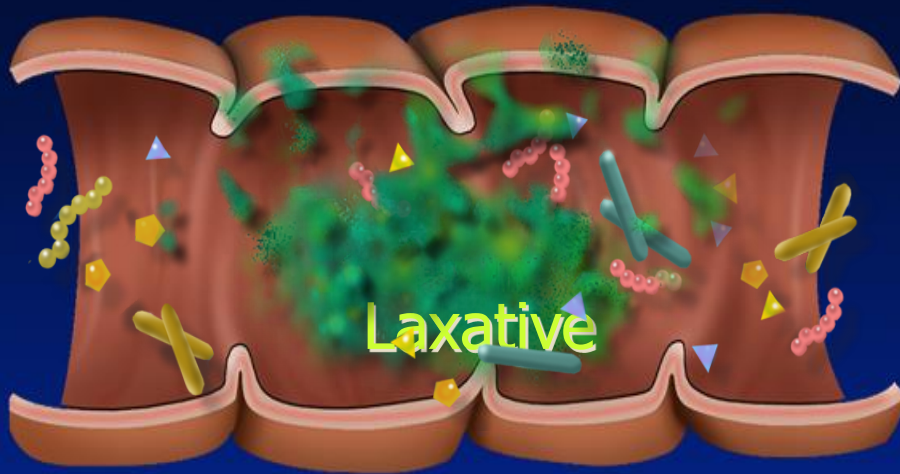


Fiber and Stool Softeners

- Fiber and stool softeners (Ducosate) are most useful in patients with mild, infrequent constipation
 - Best evidence for psyllium up to 25 gr/d
- Their role in patients with significantly delayed colon transit or dyssynergia is limited
 - Fiber may worsen symptoms in patients with significantly delayed colon transit or DD



Osmotic Laxatives: Sugars and Sugar Alcohols



- These laxatives are metabolized by bacteria in the colon to short-chain fatty acids which create an osmotic load and decrease the pH

Lactulose (Cephulac, Chronulac) 10-40 grams (15-60 mls) per day

Sorbitol 30-150 mls (70% solution) per day

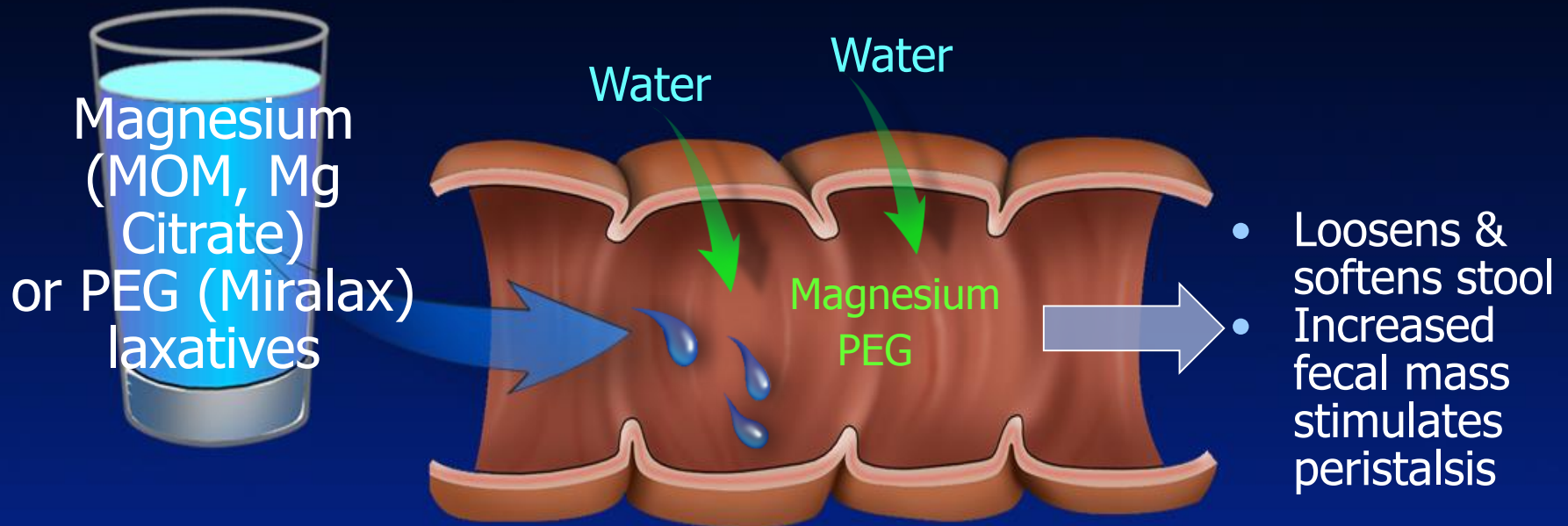
Main side effects: dose dependent cramping, bloating, diarrhea

Bass P, Dennis S. J Clin Gastroenterol. 1981; 3 (Suppl 1):23

Ramkumar D, Rao SS. Am J Gastroenterol. 2005; 100:936

Kot TV, Pettit-Young NA. Ann Pharmacother. 1992 Oct;26(10):1277-82.

Osmotic Laxatives: Saline Laxatives



Milk of Magnesia 20-30 cc per day

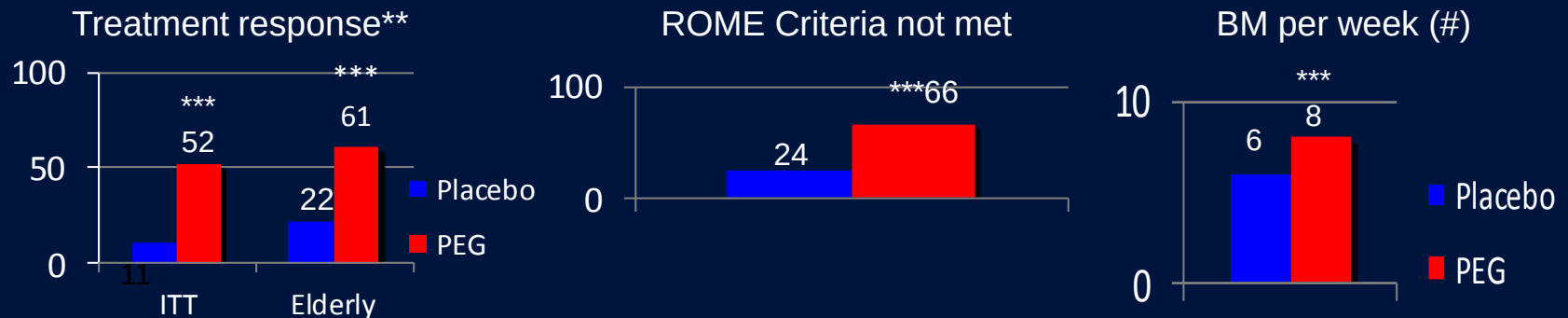
Magnesium Citrate 240 ml once daily as a purgative

Polyethylene Glycol 17-51 grams per day

Main side effects: bloating, gas, borborygmi diarrhea. Pts with significant heart/kidney disease should use magnesium laxatives with caution

PEG* for Chronic Constipation

- US multicenter, double-blind, randomized placebo-controlled trial of PEG vs. placebo for 6 months



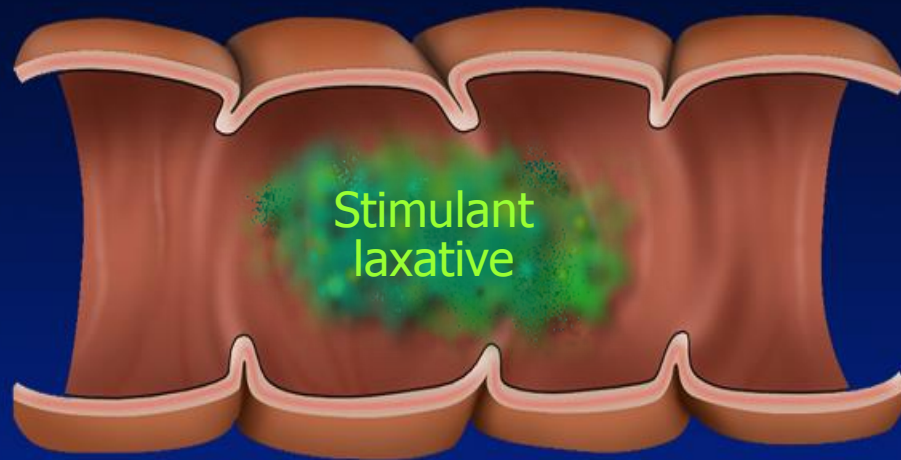
*PEG = polyethylene glycol 3350 ***p<001 vs placebo

**treatment response = ≥ 3 BMs/week and no more than 1 of the remaining 3 Rome symptoms in the absence of rescue medications = $\geq 50\%$ of the time

- Adverse events not different between PEG and placebo

Stimulant Laxatives: Classification and Mechanism of Action

- Anthraquinones (sennosides, cascara, aloe)
- Bisacodyl, Picosulfate
- Castor oil



- ↓ Absorption
- ↑ Motility
- ↑ Prostaglandins

Senna (Ex-Lax, Sennekot, various laxative teas) 15-30 mg per day

Bisacodyl (Carters, Correctol, Dulcolax, Magic Bullet) 5-20 mg per day

Main side effects: cramping, bloating, borborygmi, diarrhea

Randomized, Placebo-controlled Trial of Bisacodyl for Chronic Constipation

- **RCT, 27 centers in UK**
 - 368 adults with CC (Rome III), 75% female
 - Bisacodyl 10mg/d x 4 wks (n=247) vs. placebo (n=121)

	Bisacodyl	Placebo	P value
CSBM/wk (1.1)	5.2 ± 0.3	1.9 ± 0.3	< 0.001
SBM/wk (4)	12-8	unchanged	< 0.001
Global assessment*	79.5%	49.6%	< 0.001
QOL			< 0.001

Bisacodyl superior to placebo for straining, sense of anorectal blockage and stool form (p < 0.001)

AEs 72% vs. 37%, SAEs 6.5% vs. 1.7%

* "good or "satisfactory"

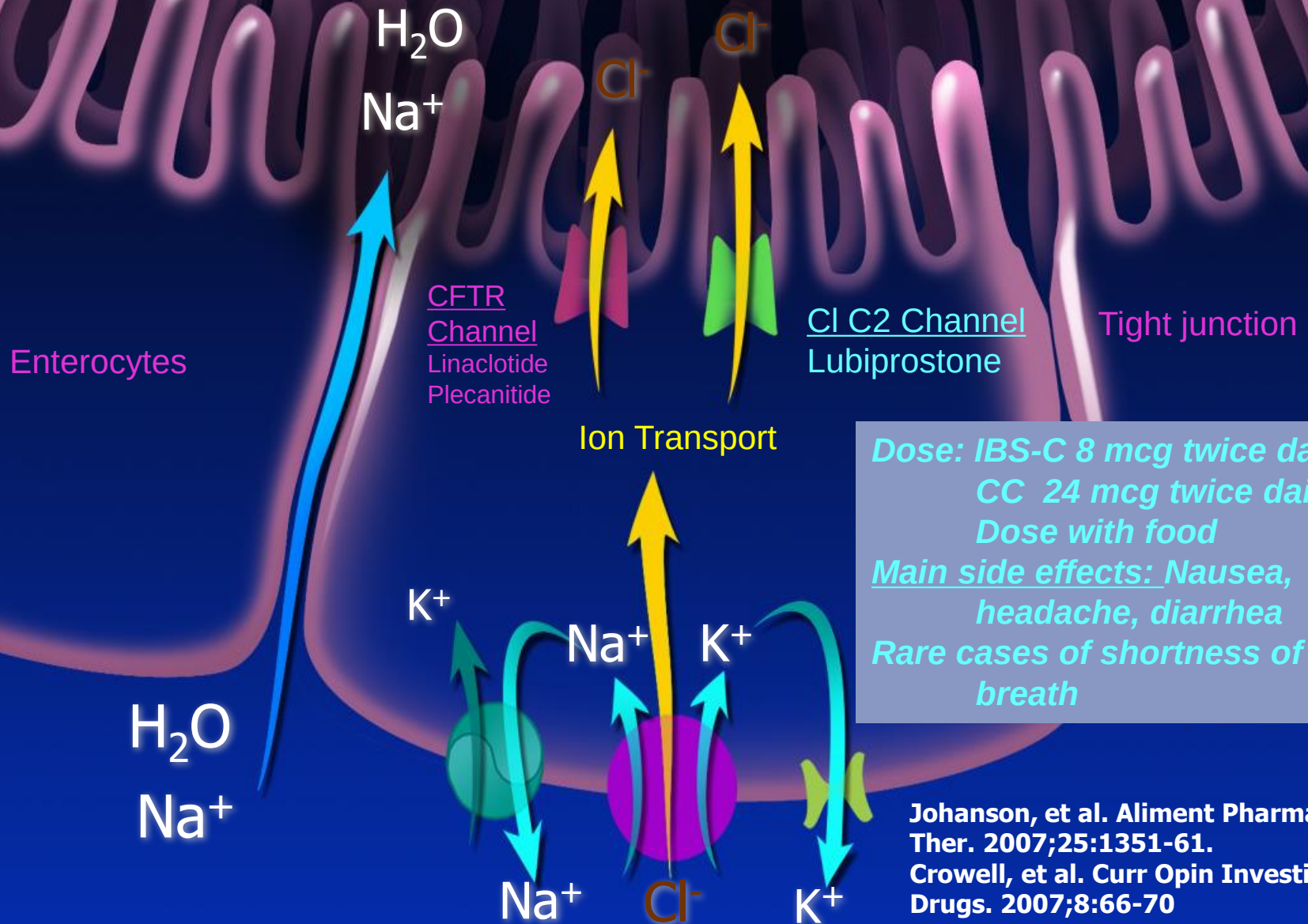
Unmet Needs

- Stool softeners, stimulant laxatives, osmotic agents, and lubricants are not effective or suitable in all patients
- Up to 47% of patients with CIC using laxatives were not completely satisfied with their treatment, mainly for reasons of efficacy
- In patients with opioid induced constipation who required laxative therapy, only 46% reported achieving the desired treatment results more than 50% of the time
- A 2009 survey among patients with IBS found that 34% of patients were not satisfied with IBS medications & remedies available at the time

Recently Approved Pharmacologic Agents For The Management of Constipation

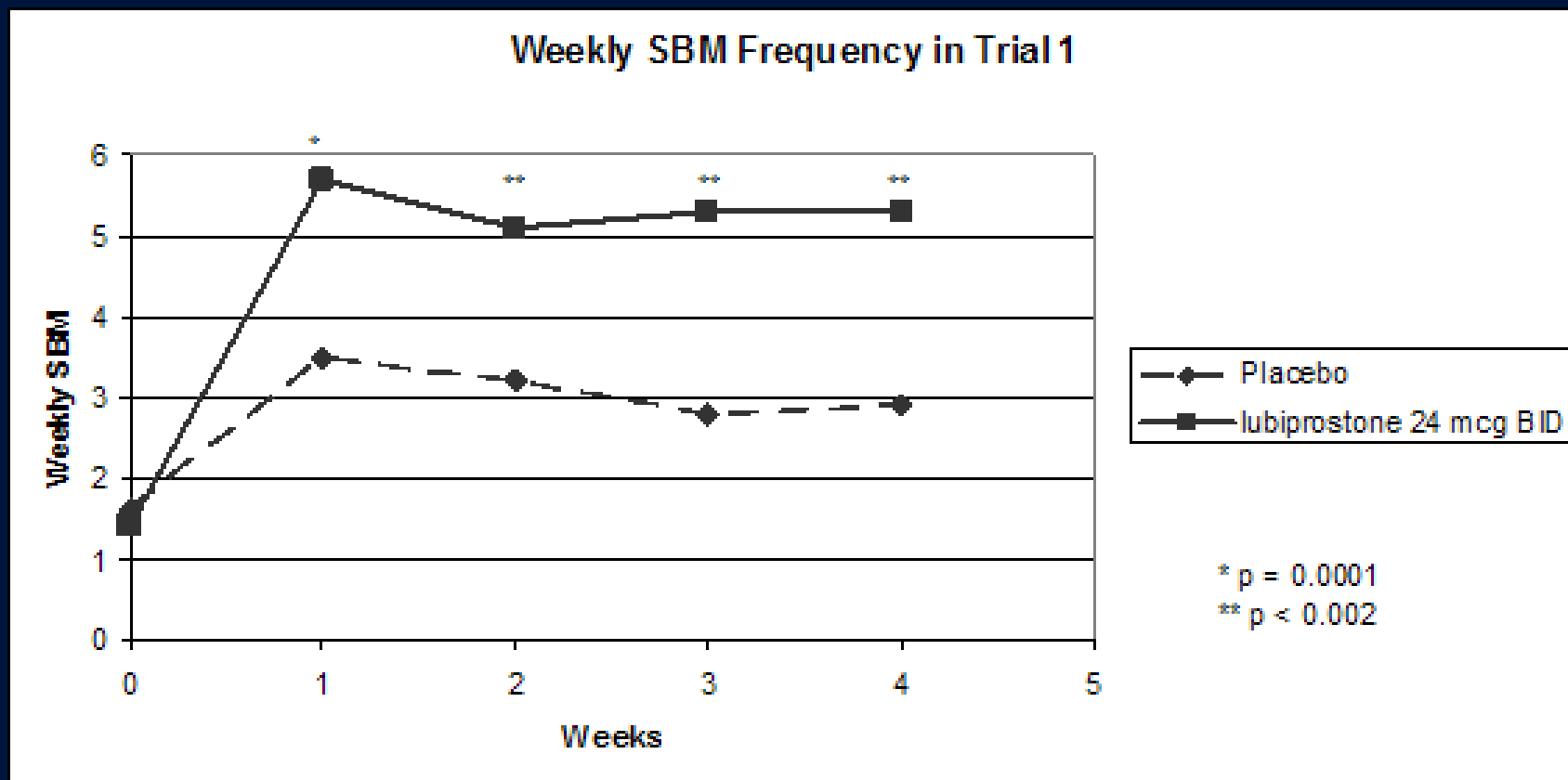
- “A newer agent should be considered when symptoms do not respond to laxatives.”
(American Gastroenterological Association)
 - Lubiprostone and linaclotide are newer agents approved in the United States for chronic idiopathic constipation and IBS-C
 - Lubiprostone is also approved for the treatment of opioid-induced constipation in adults with chronic, non-cancer pain

Chloride Channels in Intestinal Transport

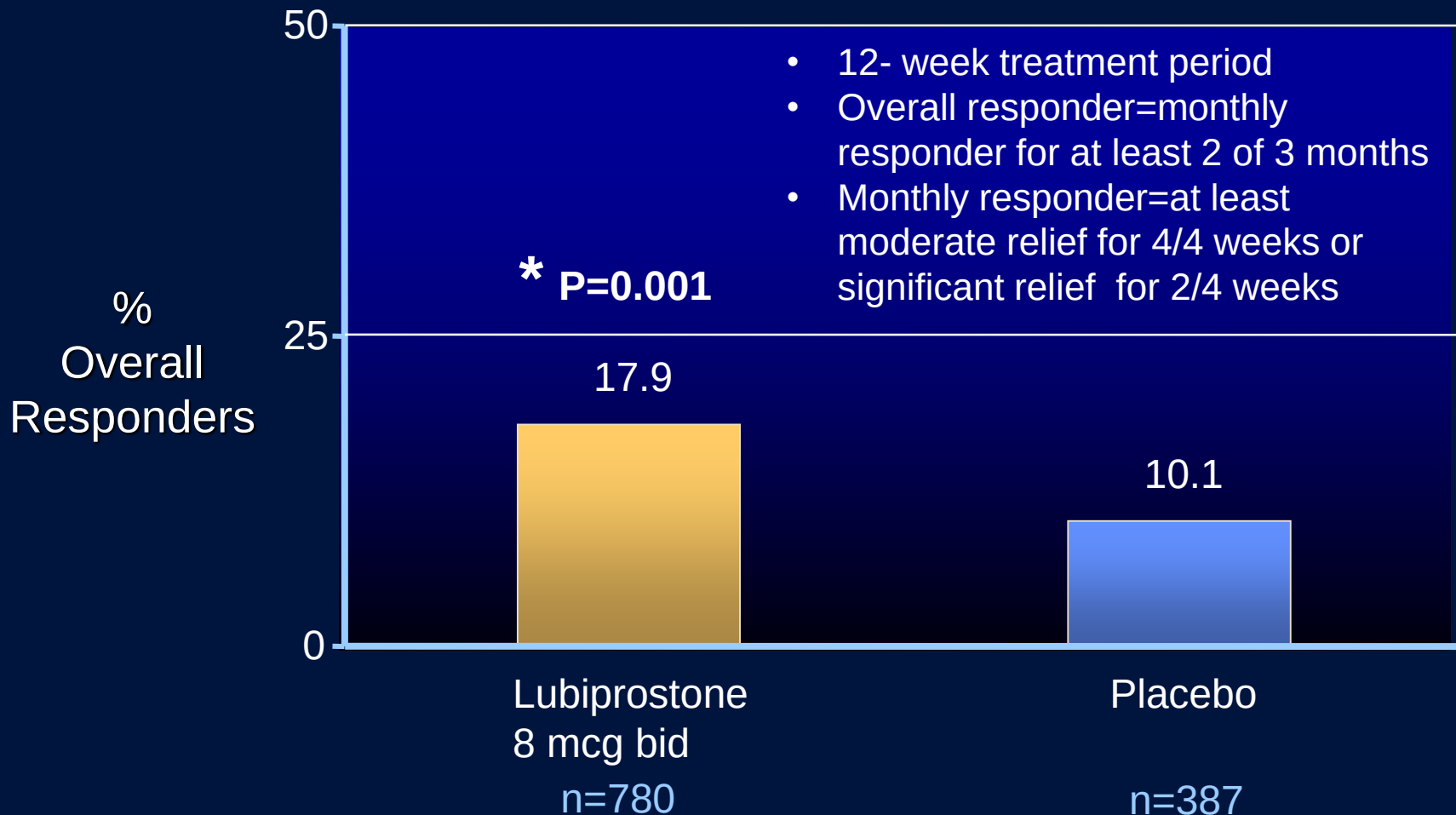


Lubiprostone for CC: Results from Phase III

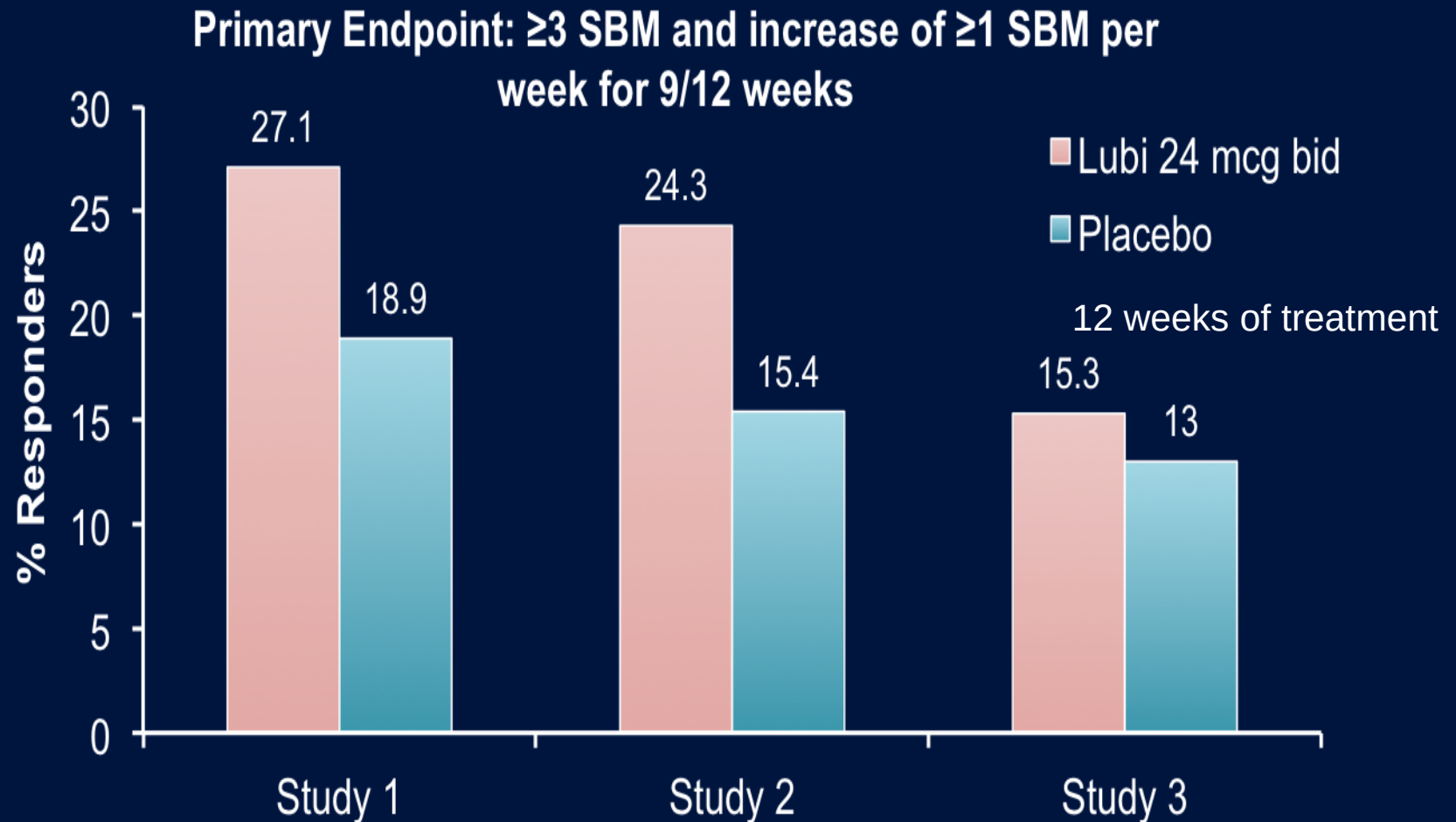
Lubiprostone 24 mcg bid vs. placebo x 4 weeks
242 adults with CC (Modified Rome II)



Lubiprostone for IBS-C: Data from 2 Phase III Trials



Lubiprostone for Opiate Induced Constipation



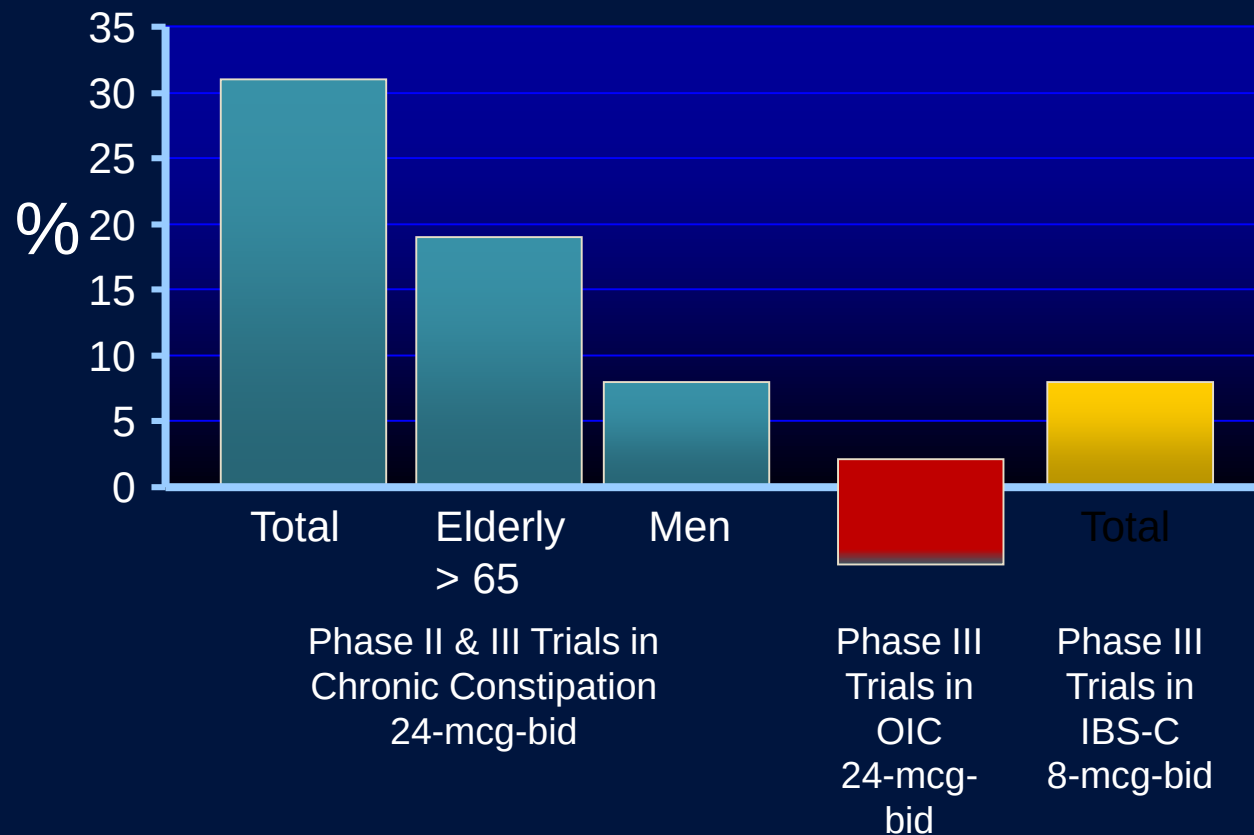
Medical Letter 2013

¹Cryer et al. DDW 2010;906; ²US FDA CDER. Amitiza NDA 021908 Label 4/19/13;

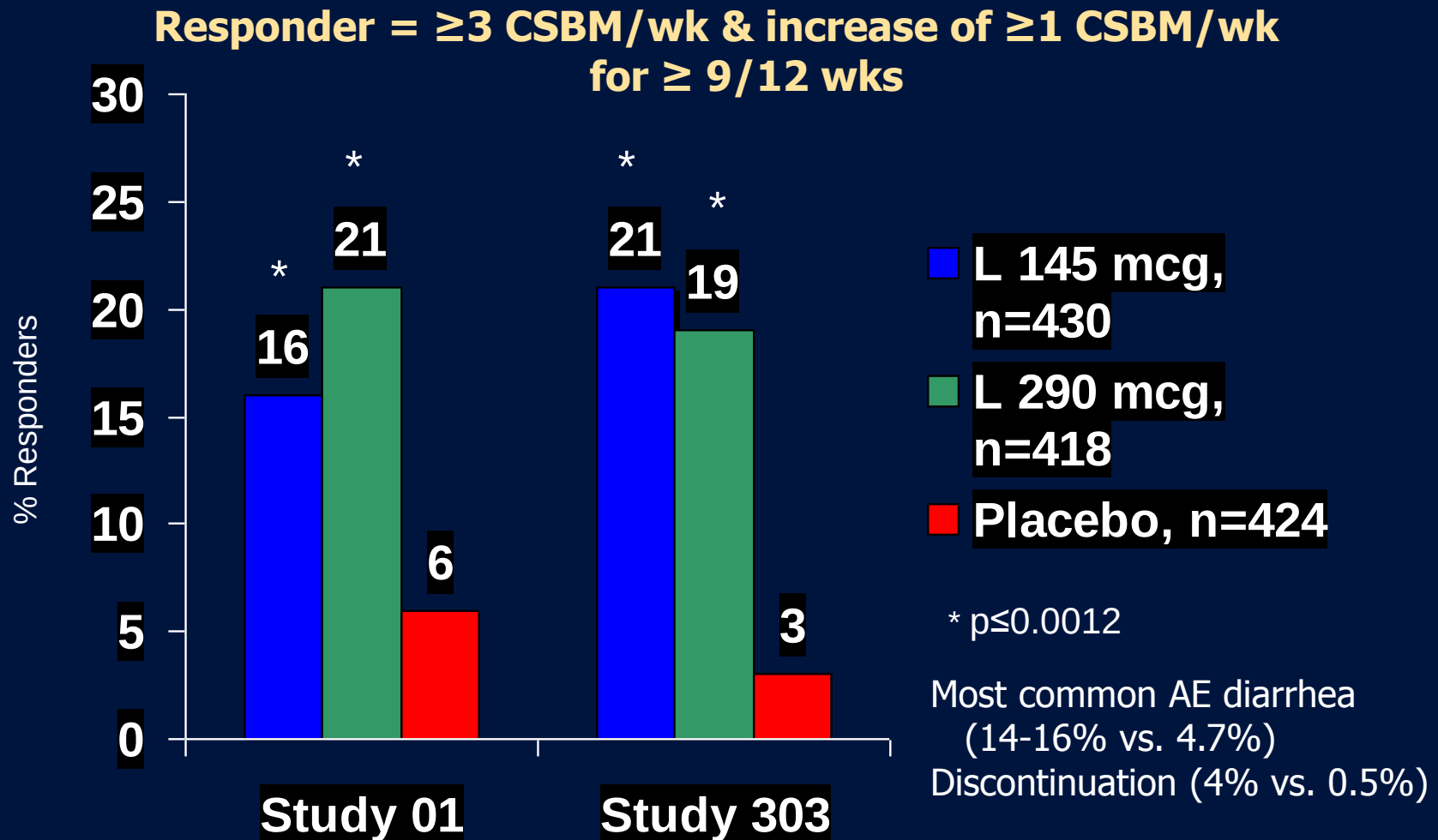
³Mazen Jamal et al. DDW 2012;848a

Incidence of Nausea with Lubiprostone in Clinical Trials

- Chronic idiopathic constipation: 24 mcg bid with food
- Irritable bowel syndrome with constipation: 8 mcg bid with food



Linaclootide for Chronic Constipation: Primary Results from 2 Phase III Clinical Trials



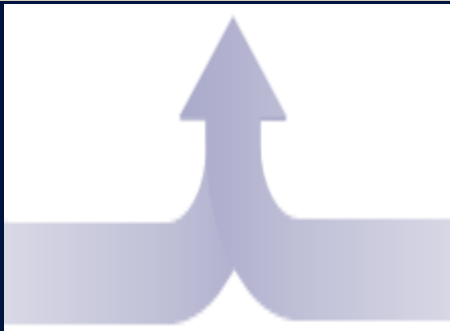
Linaclootide Phase 3 IBS-C Trial

6/12 Week Responder Primary Endpoint

Composite Responder (FDA Interim Endpoint)

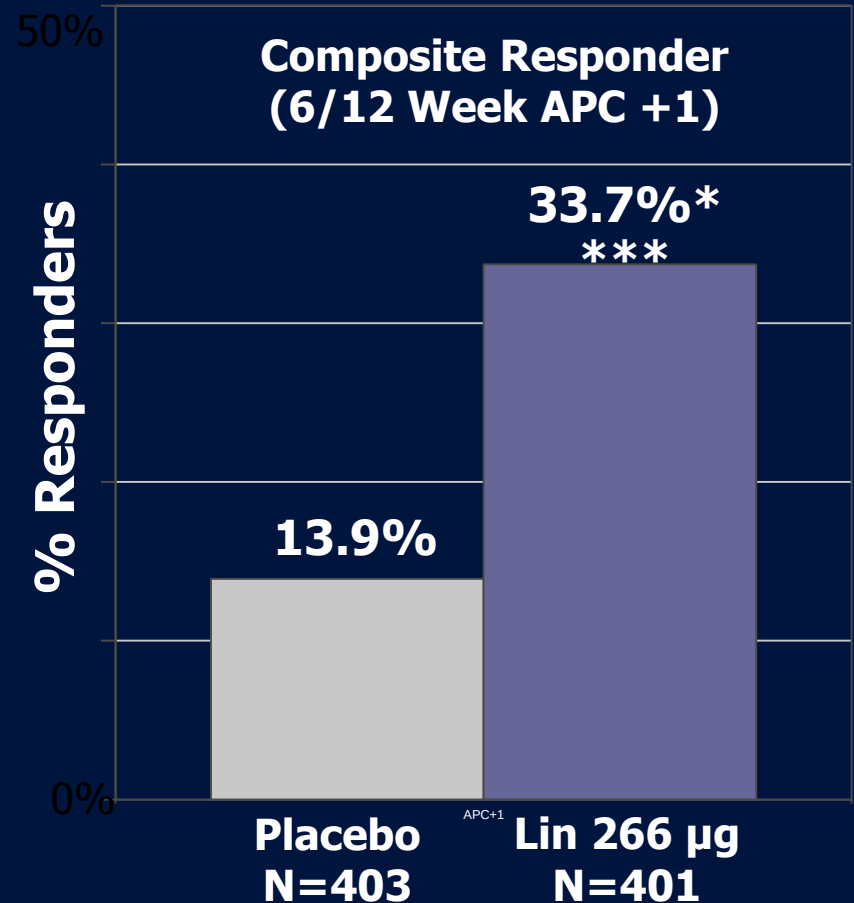
≥30% abdominal pain reduction
+ increase ≥1 CSBM from
baseline; **in the same week**

Abdominal
Pain
Responder



CSBM +1
Responder

Most common AE: Diarrhea 18%



****p< 0.0001, ITT Population (266 µg vs. placebo, CMH test)

Emerging Therapies for IBS-C and Chronic Constipation (CC)

- **Luminally Acting Drugs**
 - *Prosecretory Drugs:*
 - *Plecanatide (phase III)*
 - *RDX5791 (phase IIb)*
 - *Bile Acid Modulators*
 - *Elobixibat (phase III)*
- **Systemic Drugs**
 - *Prokinetics*
 - *5-HT₄ Agonists (various drugs)*

Concluding Remarks

- Constipation is a multi symptom condition
- The main causes of constipation are slow colon transit and/or disordered defecation
- Diet and lifestyle changes can help with mild or intermittent constipation symptoms
- Laxatives including osmotics, stimulants, and prosecretory agents improve many patients
- When patients fail to respond to laxatives, diagnostic testing should be pursued to determine the etiology of constipation symptoms
 - A multi-disciplinary approach is optimal for severely affected patients
 - Biofeedback and PT are the preferred treatments for dyssynergic defecation

Posttest Question 1

Studies have suggested that the prevalence of chronic constipation in the elderly community may be greater than...

1. 40%
2. 50%
3. 60%
4. 70%

Posttest Question 2

Chronic Constipation has been demonstrated to have a significant impact on quality of life (QoL). In which of the following QoL measurement tools was chronic constipation shown to have the *greatest* impact as compared to other GI symptoms, such as abdominal bloating, abdominal pain, or chronic diarrhea?

1. Activity impairment score
2. Overall work impairment score
3. SF-12 mental component summary score
4. SF-12 physical component summary score
5. A and B
6. All of the above

Posttest Question 3

According to the American Gastroenterological Association, the initial treatment for chronic constipation should be fiber supplementation and/or osmotic or stimulant laxatives. However, studies have shown that these approaches are not effective or suitable in all patients. More than 40% of patients have reported dissatisfaction with laxatives, mainly for reasons of efficacy, in which of the following patient populations?

1. Chronic idiopathic constipation (CIC)
2. Opioid induced constipation (OIC)
3. Irritable bowel syndrome with constipation (IBS-C)
4. A and B
5. All of the above

Posttest Question 4

According to the American Gastroenterological Association's Medical Position Statement on Constipation, "A newer agent should be considered when symptoms do not respond to laxatives." Which of the following is/are approved for the treatment of opioid induced constipation in patients unresponsive to laxatives.

1. Lubiprostone
2. Naloxegol
3. Plecanitide
4. Linaclotide
5. A and B
6. All of the above

References

- American College of Gastroenterology Chronic Constipation Task Force. An evidence-based approach to the management of chronic constipation in North America. *Am J Gastroenterol*. 2005;100 Suppl 1:S1-4.
- American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc*. 2009;57:1331–1346
- American Gastroenterological Association, Bharucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association medical position statement on constipation. *Gastroenterology*. 2013 Jan;144(1):211-7.
- Bass P, Dennis S. The laxative effects of lactulose in normal and constipated subjects. *J Clin Gastroenterol*. 1981;3 (Supl 1):23-28.
- Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1) *Pain Med*. 2009;10:35–42.
- Bosshard W, Dreher R, Schnegg JF, Büla CJ. The treatment of chronic constipation in elderly people: an update. *Drugs Aging*. 2004;21(14):911–930.
- Cash BD, Chang E, Talley NJ, Wald A. Fresh perspectives in chronic constipation and other functional bowel disorders. *Rev Gastroenterol Disord*. 2007 Summer;7(3):116-33.
- Chey WD, Maneerattaporn M, Saad R. Pharmacologic and complementary and alternative medicine therapies for irritable bowel syndrome. *Gut Liver*. 2011 Sep;5(3):253-66.

References

- Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012 Nov;107(11):1702-12.
- Crowell MD, Harris LA, DiBaise JK, Olden KW. Activation of type-2 chloride channels: a novel therapeutic target for the treatment of chronic constipation. *Curr Opin Investig Drugs*. 2007 Jan;8(1):66-70.
- Dipalma JA, Cleveland MV, McGowan J, Herrera JL. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. *Am J Gastroenterol*. 2007 Jul;102(7):1436-41.
- Drossman DA. Rome Foundation Diagnostic Algorithms. Preface. *Am J Gastroenterol*. 2010 Apr;105(4):741-2. http://www.romecriteria.org/education/algorithm/pdfs/Chronic_constipation.pdf
- Drossman DA, Chey WD, Panas R, et al. Lubiprostone significantly improves symptom relief rates in adults with irritable bowel syndrome and constipation (IBS-C): data from two, twelve-week, randomized, placebo-controlled, double blind trials. *Gastroenterology*. 2007;132:639f.
- Eswaran S, Guentner A, Chey WD. Emerging Pharmacologic Therapies for Constipation-predominant Irritable Bowel Syndrome and Chronic Constipation. *J Neurogastroenterol Motil*. 2014 Apr 30;20(2):141-151.
- Gallegos-Orozco JF, Foxx-Orenstein AE, Sterler SM, Stoa JM. Chronic constipation in the elderly. *Am J Gastroenterol*. 2012 Jan;107(1):18-25; quiz 26.
- Gianni W, Ceci M, Bustacchini S, et al. Opioids for the treatment of chronic non-cancer pain in older people. *Drugs Aging*. 2009;26 Suppl 1: S63–S73.

References

- Gonzalez-Martinez MA, Ortiz-Olvera NX, Mendez-Navarro J. Novel pharmacological therapies for management of chronic constipation. *J Clin Gastroenterol*. 2014 Jan;48(1):21-8.
- International Foundation for Functional Gastrointestinal Disorders. IBS patients: their illness experience and unmet needs, 2009. Available at: <http://www.aboutibs.org/pdfs/IBSpatients.pdf>. Accessed February 17, 2013.
- Johanson JF, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol*. 2008 Jan;103(1):170-7.
- Johanson J, Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther*. 2007;25:599–608.
- Johanson JF, Ueno R. Lubiprostone, a locally acting chloride channel activator, in adult patients with chronic constipation: a double-blind, placebo-controlled, dose-ranging study to evaluate efficacy and safety. *Aliment Pharmacol Ther*. 2007 Jun 1;25(11):1351-61.
- Jones R, Lydeard S. Irritable bowel syndrome in the general population. *BMJ*. 1992 January 11; 304(6819): 87–90.
- Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. *Clin Gastroenterol Hepatol*. 2011 Jul;9(7):577-83.
- Kellow JE. Introduction: A Practical Evidence-Based Approach to the Diagnosis of the Functional Gastrointestinal Disorders. *Am J Gastroenterol* 105: 743-746
http://www.romecriteria.org/education/algorithm/pdfs/Chronic_constipation.pdf

References

- Khokhar N, Niazi AK. A long-term profile of patients with irritable bowel syndrome. J Coll Physicians Surg Pak. 2013 Jun;23(6):388-91.
- Kot TV, Pettit-Young NA. Lactulose in the management of constipation: a current review. Ann Pharmacother. 1992 Oct;26(10):1277-82.
- Lacy BE, Brunton SA. Partnering with gastroenterologists to evaluate patients with chronic constipation. MedGenMed. 2005 Apr 28;7(2):19.
- Lembo A, Camilleri M. Chronic constipation. N Engl J Med. 2003 Oct 2;349(14):1360-8.
- Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011 Aug 11;365(6):527-36.
- Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997 Sep;32(9):920-4.
- Locke GR 3rd, Pemberton JH, Phillips SF. AGA technical review on constipation. American Gastroenterological Association. Gastroenterology. 2000 Dec;119(6):1766-78.
- Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006 Apr;130(5):1480-91.
- Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012 Jul;10(7):712-721.

References

- Manchikanti L, Abdi S, Atluri S, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part 2--guidance. *Pain Physician*. 2012 Jul;15(3 Suppl):S67-116.
- Markland AD, Palsson O, Goode PS, Burgio KL, Busby-Whitehead J, Whitehead WE. Association of low dietary intake of fiber and liquids with constipation: evidence from the National Health and Nutrition Examination Survey. *Am J Gastroenterol*. 2013 May;108(5):796-803.
- Mertz H, Naliboff B, Mayer E. Physiology of refractory chronic constipation. *Am J Gastroenterol*. 1999 Mar;94(3):609-15.
- Olfson M, Wang S, Iza M, et al. National trends in the office-based prescription of schedule II opioids. *J Clin Psychiatry*. 2013 Sep;74(9):932-9.
- Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract*. 2007;61:1181–1187.
- Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *Am J Surg*. 2001 Nov;182(5A Suppl):11S-18S.
- Paré P, Bridges R, Champion MC, et al. Recommendations on chronic constipation (including constipation associated with irritable bowel syndrome) treatment. *Can J Gastroenterol*. 2007 Apr;21 Suppl B:3B-22B.
- Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012 Nov;143(5):1179-87.e1-3.

References

- Power AM, Talley NJ, Ford AC. Association between constipation and colorectal cancer: systematic review and meta-analysis of observational studies. *Am J Gastroenterol*. 2013 Jun;108(6):894-903; quiz 904.
- Ramkumar D, Rao SS. Efficacy and safety of traditional medical therapies for chronic constipation: systematic review. *Am J Gastroenterol*. 2005;100:936-971.
- Rao SS, Ozturk R, Laine L. Clinical utility of diagnostic tests for constipation in adults: a systematic review. *Am J Gastroenterol*. 2005 Jul;100(7):1605-15.
- Saad R, Chey WD. Lubiprostone in the treatment of chronic idiopathic constipation and irritable bowel syndrome and constipation. *Exp Review Gastroenterol Hepatol*. 2008 Aug;2(4):497-508.
- Song BK, Cho KO, Jo Y, Oh JW, Kim YS. Colon transit time according to physical activity level in adults. *J Neurogastroenterol Motil*. 2012 Jan;18(1):64-9.
- Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: systematic review and meta-analysis. *Am J Gastroenterol*. 2011 Sep;106(9):1582-91; quiz 1581, 1592.
- Talley NJ, Fleming KC, Evans JM, et al. Constipation in an elderly community: a study of prevalence and potential risk factors. *Am J Gastroenterol*. 1996;91(1):19-25.
- Tariq SH. Constipation in long-term care. *J Am Med Dir Assoc* 2007; 8:209-18
- Vincent GK, Velkoff VA. The Next Four Decades. The Older Population in the United States: 2010 to 2050. Washington: US Census Bureau; 2010. Available at <https://www.census.gov/prod/2010pubs/p25-1138.pdf> Accessed February 17, 2014.