Constipation & Defecation Disorders

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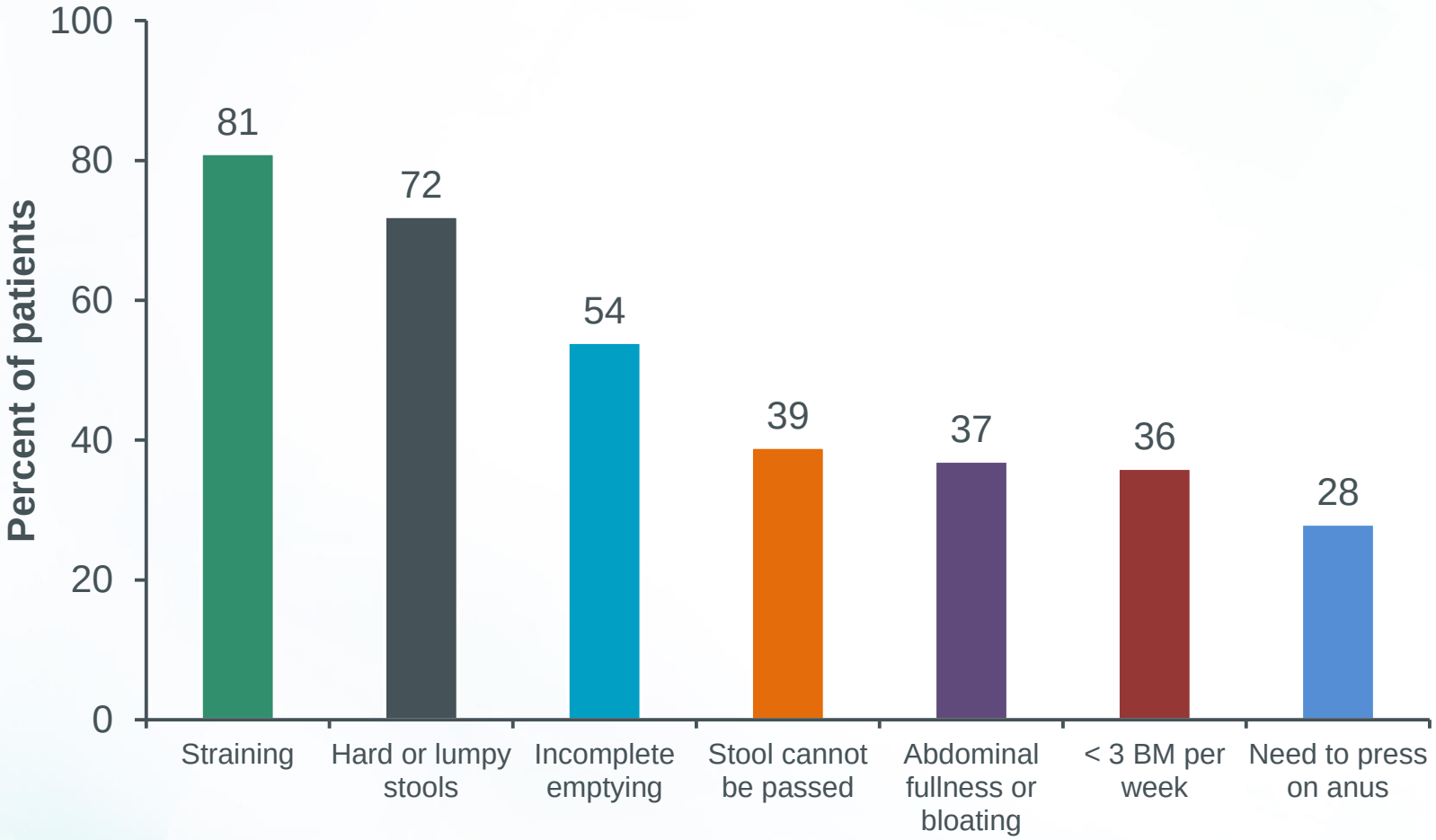
UPDATES
in the management of
FGIDs

DEFINITION

- What physicians mean:
  - Less frequent bowel movements
  - Abnormal stool form
  - Smaller bowel movements
  - (Dyschezia)
- What patients mean:
  - “I haven’t had a bowel movement today.”
  - “My stools are hard and lumpy.”
  - “It’s hard to have a bowel movement.”

CONSTIPATION SYMPTOM COMPLEX



Pare P, et al. *Am J Gastroenterol*. 2001;96:3130.

WHAT'S NORMAL?

- Stool frequency
  - In most surveys 3 BM/week to 2 BM/day
  - Depends in part on diet[1]
    - Healthy young men had 25.2 ± 1.4 BM/month
    - Dropped to 19.0 ± 2.3 BM/month on low fiber diet
    - Increased to 40.3 ± 4.9 BM/month on high fiber diet
- Stool consistency ("hardness")
  - Small range when measured objectively[2]
  - Did not differ significantly between normal subjects and constipated patients

[1]Tucker et al. *Gastroenterology* 1981;81:879-83
[2]Aichbichler et al. *Dig Dis Sci* 1998;43:2353-2362

STOOL CHARACTERISTICS[1]

- Normal individuals (N=20)
  - Frequency
    - 7.1+ 0.3 BM/week
    - ~1 BM/day
  - Weight
    - 589.4 + 60.2 g/week
    - 84.5 + 8.1 g/BM
  - % solids
    - 29.0 + 0.8%
  - Physical hardness
    - 26.6 + 3.9 g

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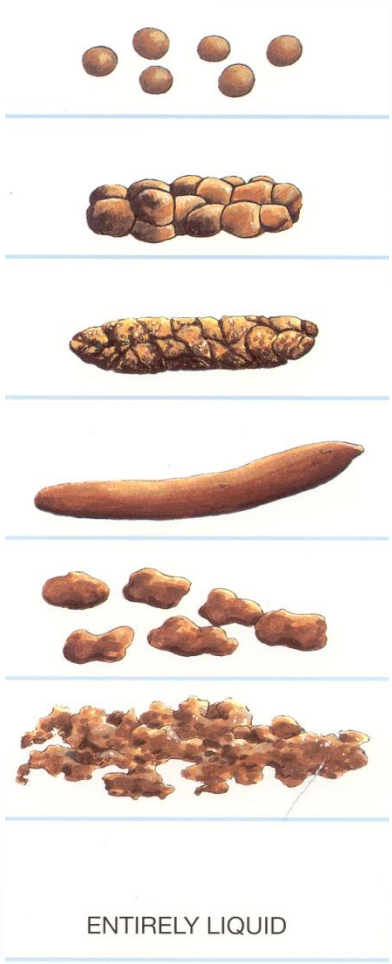
- Constipated individuals (N=20)
  - Frequency
    - 1.7+ 0.2 BM/week*
    - ~0.24 BM/day
  - Weight
    - 153.4 + 27.0 g/week*
    - 90.3 + 12.3 g/BM
  - % solids
    - 31.7 + 0.8%
  - Physical hardness
    - 39.3 + 7.0 g

*P<0.001 vs. normals

[1]Aichbichler et al. *Dig Dis Sci* 1998;43:2353-2362

BRISTOL STOOL FORM[1]

- Seven categories defined
- Form depends upon colon transit time
  - Lumpier stools correlate with longer colon transit
- Often used in studies
- Subjective
- Categorical variable
  - Should not average results



Type 1

Type 2

Type 3

Type 4

Type 5

Type 6

Type 7

[1]Davies et al. *Gut* 1986;27:164-169

DEFINITIONAL PROBLEMS WITH STUDIES

- Constipation not always defined precisely
  - Criteria not employed or specified
  - Many coexisting symptoms
- Symptom of constipation not always fully evaluated
  - May be secondary to some disease process
  - Confusion between symptom and condition of idiopathic or functional constipation
- Confusion between “irritable bowel syndrome with constipation” and “functional constipation”

ROME III CRITERIA FOR FUNCTIONAL CONSTIPATION[1]

- At least 3 months in the preceding 6 months of two or more of:
  - Straining in >1/4 defecations
  - Lumpy or hard stools in >1/4 defecations
  - Sensation of incomplete evacuation in >1/4 defecations
  - Sensation of anorectal obstruction/blockade in >1/4 defecations
  - Manual maneuvers to facilitate >1/4 defecations (e.g., digital evacuation, support of the pelvic floor); and/or
  - <3 defecations/week
- Loose stools not present. Insufficient criteria for IBS.

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

CONSTIPATION AS A SYMPTOM

- Constipation may be due to other diseases/conditions
  - Mechanical obstruction
  - Metabolic diseases
  - Painful anorectal conditions
  - Collagen-vascular disease
  - Neurological diseases
  - Pregnancy
  - Medications
- Constipation may be idiopathic
  - Slow transit constipation
  - Functional outlet obstruction

NORMAL FUNCTIONS OF THE COLON

- Absorption
  - Fluid & electrolytes
  - Bacterial fermentation products
- Transit of material to rectum
- Timely emptying of feces
  - Reservoir function
  - Defecation

HYPOTHETICAL MECHANISMS OF CONSTIPATION

- Excessive absorption rate
  - Never demonstrated
- Slow transit
  - “Colonic inertia”
- Impaired defecation
  - Capacious reservoir (megarectum)
  - Functional outlet obstruction

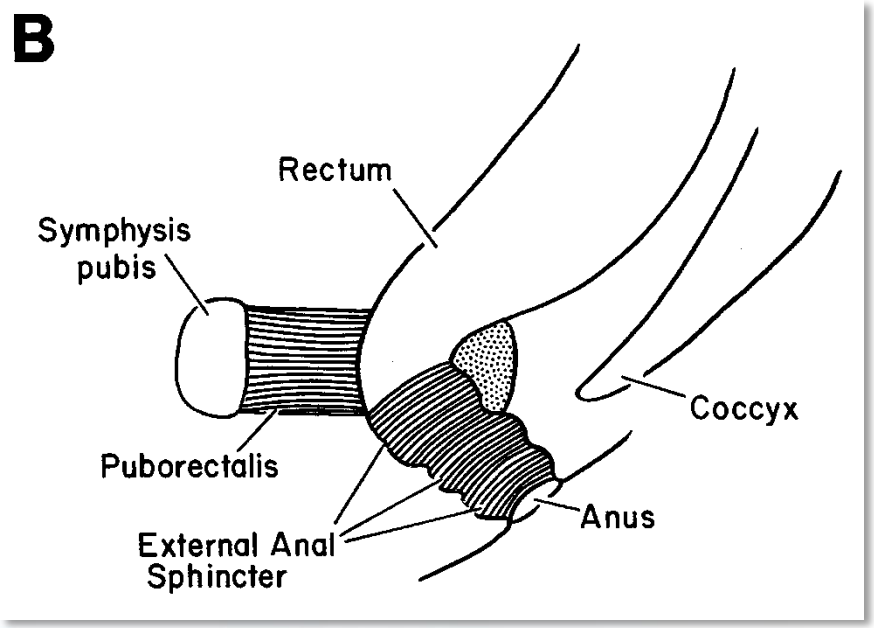
SLOW TRANSIT CONSTIPATION

- Predominant mechanism of severe infrequency in patients with idiopathic constipation
- Presumably a problem with colonic neuromuscular function or coordination
- Less common than once thought
- May be aggravated by functional outlet obstruction
- May be part of a generalized disorder
  - Chronic intestinal pseudo-obstruction
  - Hollow visceral myopathy
  - Enteric nervous system disorders

FUNCTIONAL OUTLET OBSTRUCTION

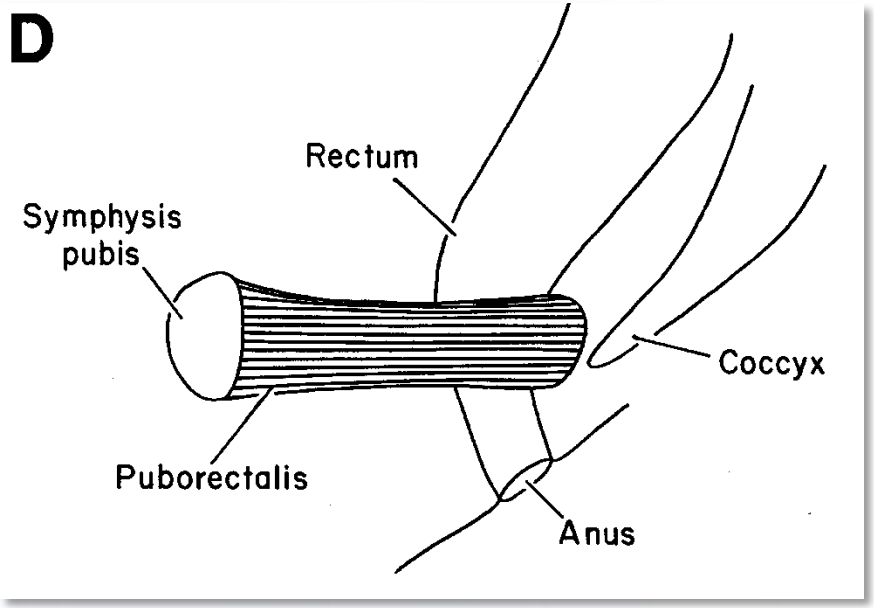
- May be sole cause of constipation or co-exist with slow transit constipation
- Many possible etiologies
  - Intrarectal intussusception
  - Anterior rectal wall ulcer syndrome
  - Perineal descent
  - Hirschsprung's disease
  - Paradoxical puborectalis & external anal sphincter contraction during defecation ("dyssynergia," "spastic pelvic floor," "anismus")

NORMAL PELVIC FLOOR FUNCTION



- Contraction of puborectalis muscle (pelvic floor) produces a 90° angle between the axis of the rectum and anal canal; provides continence for solids
- Contraction of external anal sphincter produces firm closure of anal canal and promotes continence for liquid stool and gas

NORMAL PELVIC FLOOR FUNCTION



- Relaxation of the puborectalis muscle and external anal sphincter allows straightening of the rectoanal angle and permits defecation

SPASTIC PELVIC FLOOR SYNDROMES

- Psychiatric overtones
  - Physical and sexual abuse
  - Somatization syndrome
  - Malingering
  - Obsessive-compulsive disorder
  - Psychosis
  - Anxiety

IRRITABLE BOWEL SYNDROME WITH CONSTIPATION

- Overlap of normal transit constipation patients and IBS patients
  - Similar psychological profiles as other IBS patients
  - Similar problems with pain as other IBS patients
- Less clear how to classify these patients
- Not always distinguished in “constipation” trials

EVALUATION OF CONSTIPATION

- History
- Physical examination
  - Digital rectal examination
- Laboratory testing
  - Systemic diseases: thyroid, diabetes, hypercalcemia
- Imaging
  - Sigmoidoscopy
  - Barium enema
  - Colonic transit time (Sitz markers)
  - Defecography

OTHER TESTS

- Balloon expulsion
  - Used to evaluate outlet problems
- Anorectal manometry
  - Used to evaluate dyssynergia
- Electromyography
  - Used to evaluate dyssynergia

TREATMENT

- Treat underlying disorders
- Review medications and revise as needed
- Assess diet/fiber intake
- Laxatives
- Systemically-active agents (most not approved for treatment of constipation by FDA)
- Investigational agents with systemic actions
- Chloride-channel activator
- Biofeedback training (pelvic floor dysfunction)
- Surgery

DIET & FIBER

- Older individuals may decrease their overall food intake
  - This may reduce postprandial stimulation of colon motor activity (gastrocolic reflex)
- Fiber intake may be low
  - Difficulty in buying or preparing fruits & vegetables
  - Problems chewing
  - Rapid satiety
- Ideal fiber intake not defined in older population
  - Should aim for 20—30 g fiber per day
  - Excess fiber may accentuate bloating

LAXATIVES

- Drugs that alter stool composition or gastrointestinal motility to increase stool frequency or ease defecation
  - Bulking agents
    - Natural and synthetic fiber
  - Osmotic agents
    - Poorly absorbed ions, disaccharides/sugar alcohols
    - Polyethylene glycol

LAXATIVES

- Topically-active (“stimulant”) agents
  - Detergents (docusates, bile acids)
  - Diphenylmethane derivatives (e.g., bisacodyl)
  - Ricinoleic acid (castor oil)
  - Anthraquinones (e.g., senna, cascara)
- Lubricant
  - Mineral oil

LAXATIVES

- Laxatives are best applied as part of a preventive program
- Goal should be production of 2—3 BMs weekly and control of secondary symptoms (bloating, discomfort)
- Osmotic laxatives currently favored, but may accentuate bloating
- Intermittent use of topically-active laxatives probably is safe

PROBLEMS WITH LAXATIVE THERAPY FOR CHRONIC CONSTIPATION

- Lack of effect on coexisting symptoms (e.g., bloating, incomplete evacuation, abdominal pain)
- Loss of effect with time
- Side effects
  - Bloating
  - Diarrhea
  - Electrolyte abnormalities
  - Melanosis
  - Fecal incontinence
- ?Toxicity
  - “Cathartic colon”

SYSTEMICALLY-ACTIVE AGENTS FOR CHRONIC CONSTIPATION

- Cholinergic agonists
  - Bethanechol*
  - Neostigmine*
- Prostaglandin agonist
  - Misoprostol*
- Colchicine*
- Opiate antagonists
  - Naloxone*
  - Naltrexone*
  - Methylnaltrexone*
  - Alvimopan*

*Not FDA-approved for treatment of chronic constipation

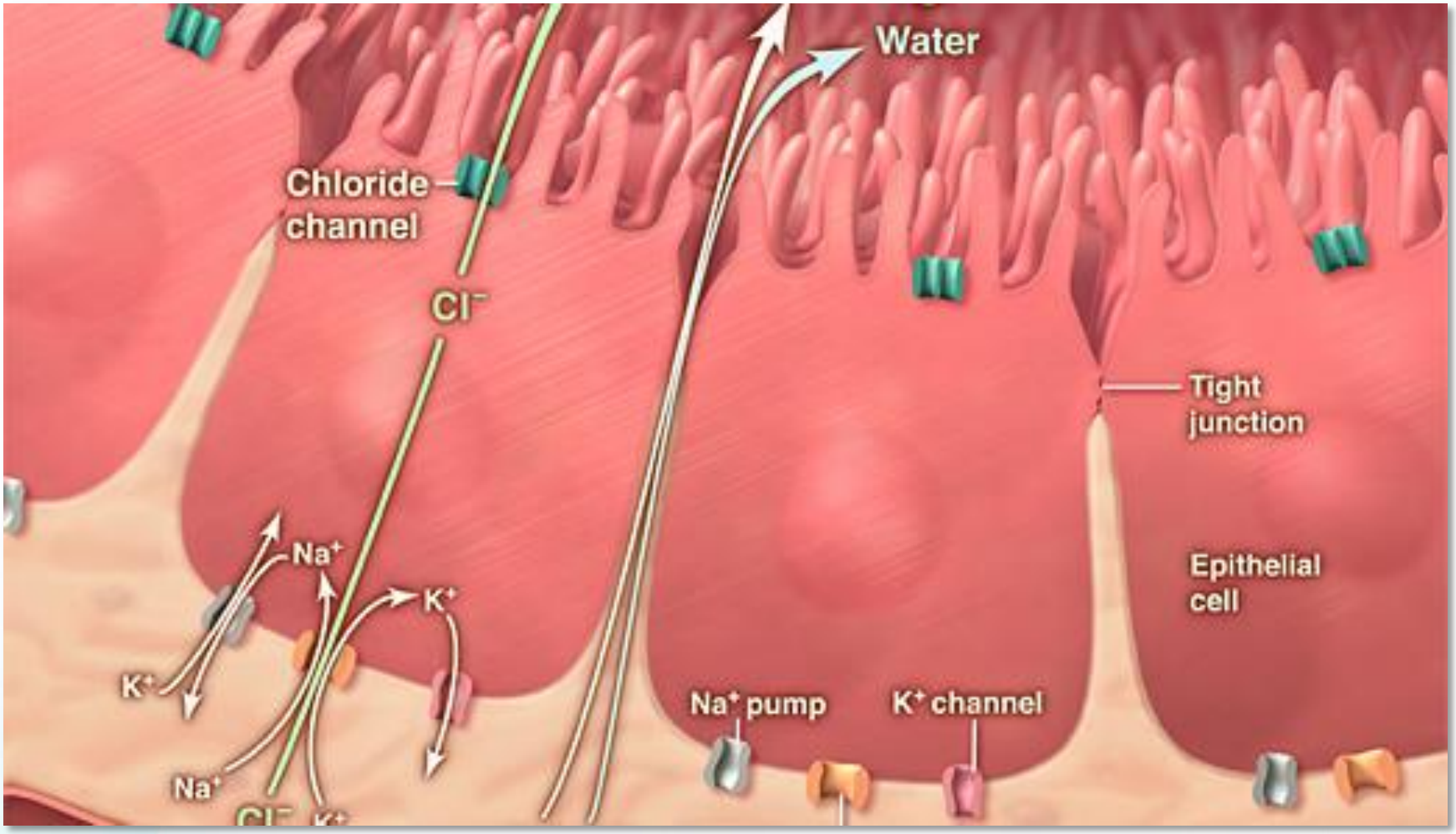
INVESTIGATIONAL SYSTEMIC AGENTS FOR CHRONIC CONSTIPATION

- 5-HT_4 agonists
  - Prucalopride
  - Renzapride
- Neurotrophic peptide
  - NT-3

POTENTIAL PROBLEMS WITH SYSTEMICALLY-ACTIVE DRUGS

- Unwanted effects elsewhere in the gut
- Systemic toxicity/side-effects
- Tachyphylaxis
- Lack of receptor sites/effector mechanisms in advanced disease

LOCALLY-ACTING THERAPY: Modulation of Chloride Channels



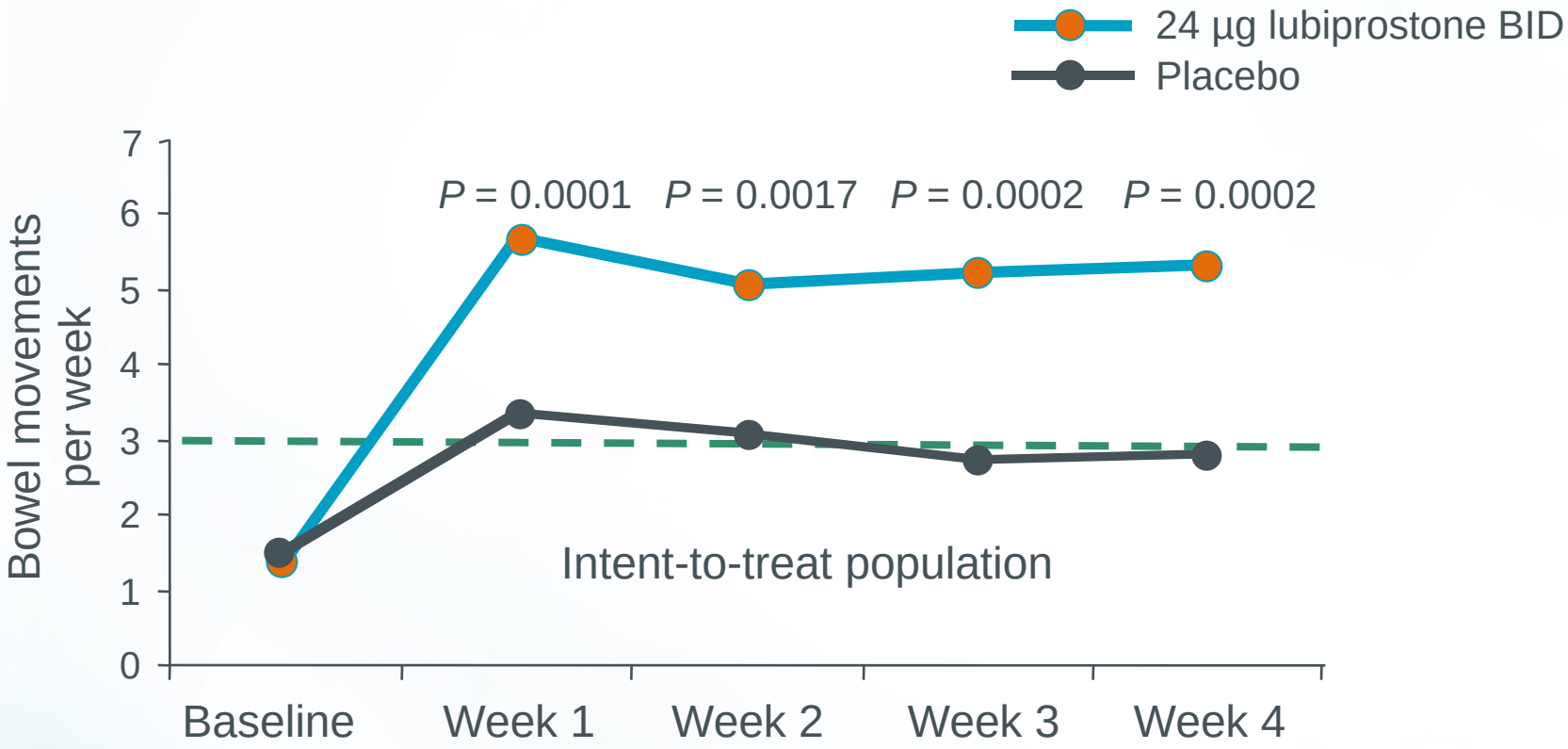
CHLORIDE CHANNELS OF THE GUT

- Chloride C-2 channel (ClC2)
  - Mainly concerned with regulation of tight junction permeability
  - Moderate capacity channel
  - Directly activated by lubiprostone from luminal side
- Cystic fibrosis transmembrane regulator(CFTR)
  - High capacity chloride channel
  - Mainly concerned with electrolyte transport (Cl secretion)
  - Activated by cAMP and cGMP
  - Linaclotide opens channel by increasing intracellular cGMP levels

LUBIPROSTONE

- Bicyclic fatty acid
- Prostaglandin derivative but does not interact with prostaglandin receptor
- Topical effect on C-2 chloride channels
- Mostly metabolized within gut; no detectable absorption of intact molecule (metabolite can be absorbed)
- Stimulates small bowel fluid and electrolyte secretion
- Motility stimulated
- FDA approved for chronic constipation and IBS-C in women

EFFECTIVENESS OF LUBIPROSTONE IN CHRONIC CONSTIPATION



N = 242

Johanson JF. *Gastroenterology*. 2003;124:A-48. Abstract 372.

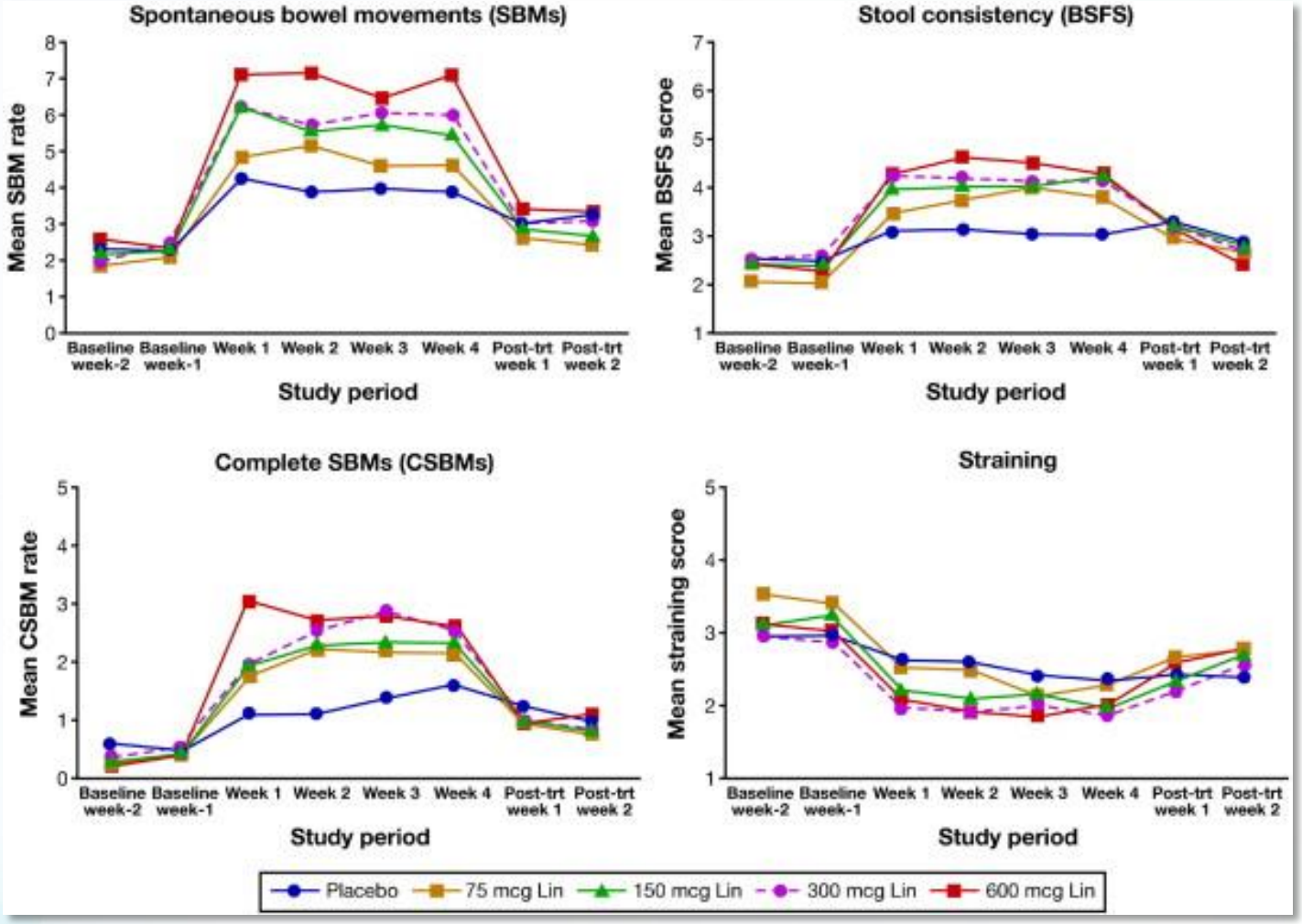
SIDE EFFECTS OF LUBIPROSTONE

- Nausea in ~30% of patients given 24 μg BID
  - Mitigated by giving drug with food or reducing dose
  - Drug discontinued in ~8% of patients for nausea
  - Less common in older patients (~12—19%)
- Headache, diarrhea, abdominal pain other side-effects
- Avoid if mechanical bowel obstruction, pregnancy

LINACLOTIDE

- Peptide analogue of guanylyn, a luminally-secreted peptide that modulates chloride secretion in the gut
- Activates guanylate cyclase C which opens CFTR chloride channel and increases chloride secretion
  - May also release cGMP into subepithelial space that may modulate enteric sensory nerve function
- Enhances secretion and transit
- Mostly metabolized within gut; no detectable absorption of intact molecule or active metabolites
- FDA approved for treating chronic constipation and IBS-C

LINACLOTIDE IN CHRONIC CONSTIPATION



Lembo AJ et al. *Gastroenterology*. 2010 Mar;138(3):886-95.

SIDE EFFECTS OF LINACLOTIDE

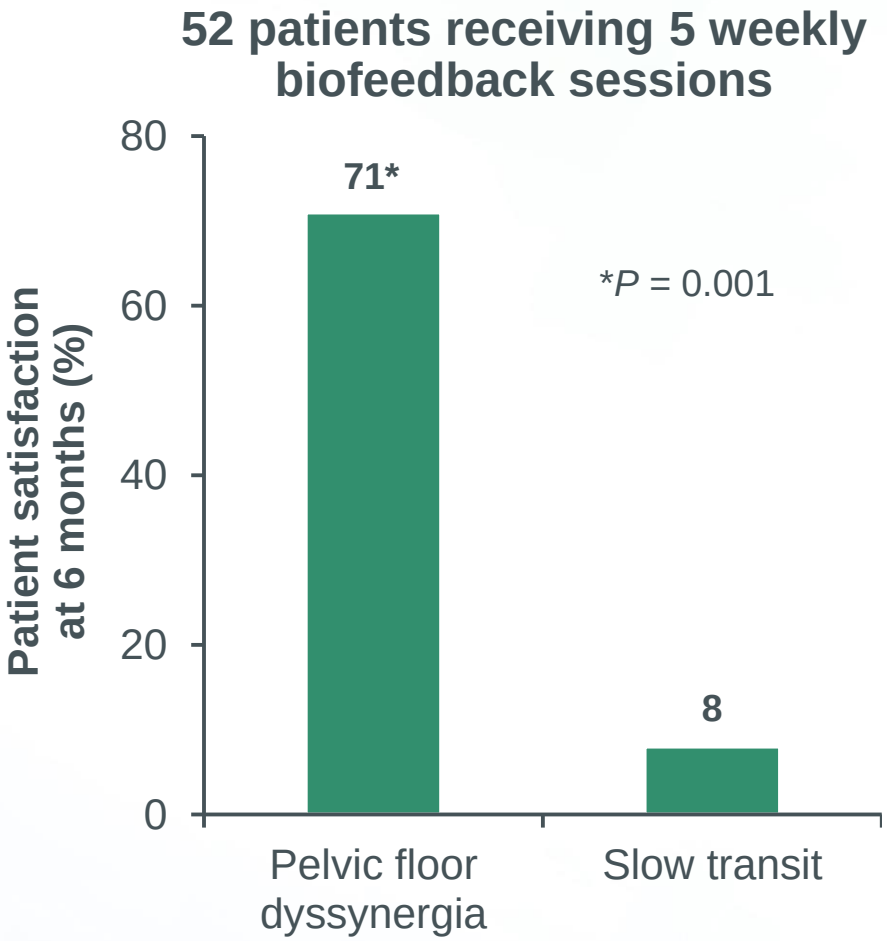
- Diarrhea is most common side effect
  - Can be managed by lowering dose or frequency of dosing
- Not approved for patients <18 years old
  - Never use in children <6 years old

BIOFEEDBACK TRAINING

- In patients with pelvic floor dysfunction (i.e., anismus, puborectalis muscle relaxation failure) biofeedback training has been shown to reduce symptoms
- Patients are taught to relax the puborectalis muscle when straining to ease evacuation
- Repeated sessions over 2—4 weeks usually needed
- Limited availability outside of major motility centers

BIOFEEDBACK THERAPY FOR PELVIC FLOOR DYSSYNERGIA

- Patient views anorectal pressures generated during relaxing and squeezing pelvic floor muscles, emphasizing coordination
- Rapport with therapist is crucial to success
- Effects appear to be long lasting



Lembo A, et al. *N Engl J Med*. 2003;349:1360.
Rao SSC, et al. *Am J Gastroenterol*. 2005;100:S150. Abstract 386.
Chiarioni G, et al. *Gastroenterology*. 2005;129:86.

SURGICAL MANAGEMENT OF CHRONIC CONSTIPATION

- Subtotal colectomy can improve stool frequency
- Candidates for colectomy need to be screened for outlet problems
- Patients with significant abdominal pain have more complications with postoperative small bowel obstruction
- Ileostomy is a less morbid option for higher-risk patients

PROSPECTS FOR THE FUTURE

- Better assessment of pathophysiology in individuals
- Therapy targeted at pathophysiology
  - New agents/techniques
- Preventive therapy

Thank you for your attention!

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