Management of Difficult Constipation

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Financial Interest Disclosure:
Elyanne M. Ratcliffe

No relevant financial relationships with any commercial interests

(over the past 24 months)

Financial Interest Disclosure: Louis Liu

Relevant relationships with commercial entities over the last 48 months

Commercial Interest	Relationship
Takeda Canada Inc.	Speaker bureau, advisory board
AbbVie	Speaker bureau, advisory board
Allergan Canada	Speaker bureau, advisory board, consultant
Lupin Pharma Canada	Advisory board

CanMEDS Roles Covered

✔	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
✔	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
	Leader (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
	Health Advocate (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
✔	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Learning Objectives

By the end of this session, the attendees will be able to:

1. Identify the different etiologies of constipation between children and adults
2. Apply the evidence for current therapies to manage constipation in children and adults

FARNCOMBE
Farncombe Family Digestive Health Research Institute

Center for Child &
Youth Digestive Health

Difficult Constipation - Pediatrics

Elyanne M. Ratcliffe, MD, FRCPC
Associate Professor and Head, Division of Gastroenterology and Nutrition
Department of Pediatrics, McMaster University

Image courtesy of Dr. Bob Issenman

Difficult Constipation - Pediatrics

Pediatric Case

- 5 year old girl
- Daily liquid “stool accidents” (3-4x/day)
- Hard stool; refuses to use toilet; hides in room to pass bowel movement in underwear
- Investigations:
  - Normal TSH, negative celiac screen
  - Lower GI contrast study: severe fecal loading; no evidence of transition point to suggest Hirschsprung’s disease

Functional Constipation
Rome IV Diagnostic Criteria

H3a. Diagnostic Criteria for Functional Constipation

Must include 2 or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of irritable bowel syndrome:

(1) 2 or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
(2) At least 1 episode of fecal incontinence per week
(3) History of retentive posturing or excessive volitional stool retention
(4) History of painful or hard bowel movements
(5) Presence of a large fecal mass in the rectum
(6) History of large diameter stools that can obstruct the toilet

After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Hyams Gastro 2016

Approach to Functional Constipation

- Education
- Diary
- Toilet training
- Oral medication
- Manage fecal impaction

Management – What is the Evidence?

Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN

M.M. Tabbers, C. DiLorenzo, M.Y. Berger, C. Faure, M.W. Langendam, S. Nurko, A. Staiano, Y. Vandenplas, and M.A. Benninga

- Evidence does <u>not</u> support:
  - Fibre supplements
  - Extra fluid intake
  - Pre- or probiotics
  - Behavioural therapy
- No RCTs to support:
  - Physical activity
  - Multidisciplinary treatment
  - Alternative medicine

Tabbers JPGN 2014

Pharmacological Management

Fecal disimpaction

- High-dose PEG +/- electrolytes daily for 3-6 days
- Enema once daily if PEG not available

Maintenance

- PEG +/- electrolytes; dose adjusted to clinical response
- Addition of enemas not recommended
- Lactulose if PEG not available

Additional or second line treatment

- Milk of magnesia, mineral oil, stimulant laxatives
- No RCTs in children for: prucalopride, lubiprostone, linaclotide

Tabbers JPGN 2014

Pharmacological Management

Oral Prucalopride in Children With Functional Constipation

*Harland S. Winter, †Carlo Di Lorenzo, ‡Marc A. Benninga, §Mark A. Gilger, ||Gregory L. Kearns, ¶Paul E. Hyman, #Lieve Vandeplassche, #Jannie Ausma, and #Mieke Hoppenbrouwers

JPGN • Volume 57, Number 2, August 2013

Methods: A single oral dose of 0.03 mg/kg prucalopride was administered to 38 children to characterize prucalopride pharmacokinetics (NCT01674166). Thereafter, 37 children entered an open-label extension period in which 0.01 to 0.03 mg/kg of prucalopride was administered once per day for 8 weeks to investigate efficacy, safety, and tolerability (NCT01670669).

Prucalopride Is No More Effective Than Placebo for Children With Functional Constipation

Suzanne M. Mugie,[1] Bartosz Korczowski,[2] Piroska Bodi,[3] Alexandra Green,[4] René Kerstens,[5] Jannie Ausma,[5] Magnus Ruth,[5] Amy Levine,[6] and Marc A. Benninga[1]

Gastroenterology 2014;147:1285–1295

Efficacy and safety were assessed in 213 children (106 prucalopride, 107 placebo)

Children < 50 kg given 0.04 mg/kg oral solution; Children > 50 kg were given a 2 mg tablet; once daily for 8 weeks

Pharmacological Management

Lubiprostone for the Treatment of Functional Constipation in Children

*Paul E. Hyman, †Carlo Di Lorenzo, ‡Laurel L. Prestridge, §Nader N. Youssef, and ||Ryuji Ueno

JPGN • Volume 58, Number 3, March 2014

Methods: Patients ≥12 kg, 17 years or younger, and with <3 spontaneous BMs (SBMs; ie, BMs that did not occur within 24 hours of rescue medication use) per week were enrolled at 22 US general pediatric and pediatric gastroenterology centers (January 2007–October 2008). Patients received 4 weeks of open-label lubiprostone at doses of 12 μg once daily (QD), 12 μg twice daily (BID), or 24 μg BID based on age and weight. The primary endpoint was SBM frequency during week 1 versus baseline.

Multicentre randomized placebo-controlled trial with lubiprostone in children is currently being carried out in Europe and North America (NCT02042183).

Linaclotide

Black box warning: contraindicated in pts <6 yo; deaths occurred due to dehydration w/in 24h in young juvenile mice in nonclinical studies; avoid use in pts 6-17 yo; safety and efficacy not established in pts <18 yo

Currently recruiting participants in a safety and efficacy study of a range of linaclotide doses administered orally to children aged 7-17 years, with irritable bowel syndrome with constipation (NCT02559817).

Differential Diagnoses

Celiac disease*
Hypothyroidism, hypercalcemia, hypokalemia*
Diabetes mellitus†
Dietary protein allergy*
Drugs, toxics
  Opiates, anticholinergics
  Antidepressants*
  Chemotherapy
  Heavy metal ingestion (lead)
Vitamin D intoxication*
Botulism
Cystic fibrosis*
HD*
Anal achalasia*
Colonic inertia†
Anatomic malformations
  Imperforate anus*
  Anal stenosis*
Pelvic mass (sacral teratoma)
Spinal cord anomalies, trauma, tethered cord*
Abnormal abdominal musculature (prune belly, gastroschisis, Down syndrome)*
Pseudoobstruction (visceral neuropathies, myopathies, mesenchymopathies)
Multiple endocrine neoplasia type 2B†

- **Celiac disease**
- **Hypothyrodism**
- **Congenital anomalies**

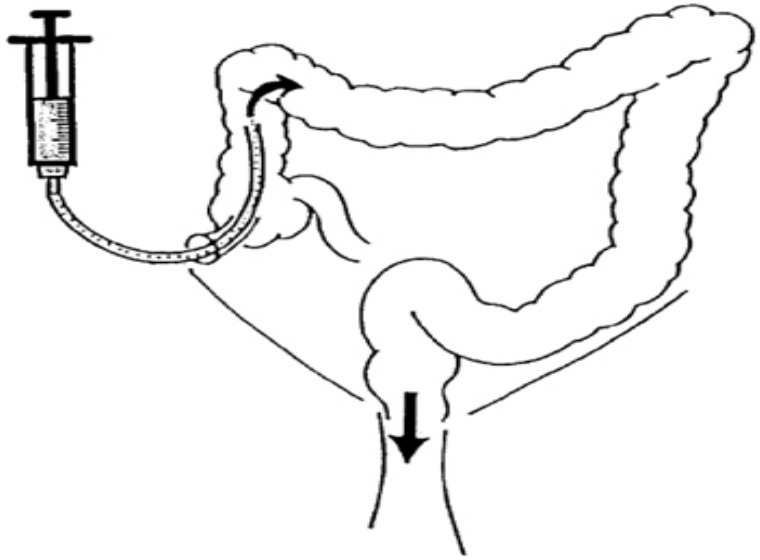
Tabbers JPGN 2014

Congenital Anomalies

Hirschsprung's disease	Delayed passage of meconium	Anorectal manometry; rectal biopsy
Anorectal malformations	Inspection of perianal region; associated congenital anomalies	Barium enema
Spinal malformations	Exam of lumbosacral region	MRI
Pseudoobstruction syndrome	Family history; associated anomalies	Abdominal ultrasound; colonic manometry

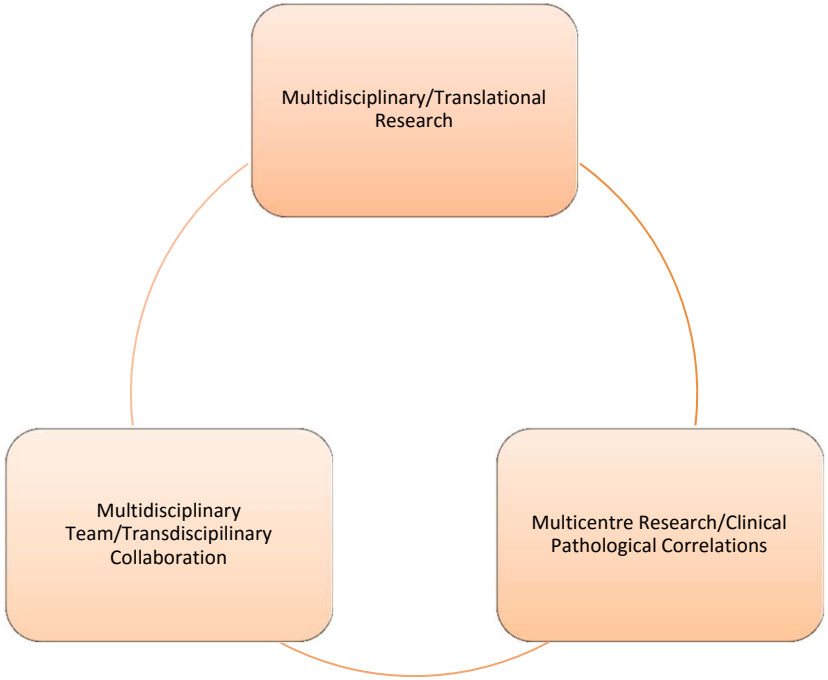
Intractable Constipation

- Anterograde continence enema (ACE)
  - No RCTs; 6 open retrospective studies
  - Option when maximal conventional therapy not successful
  - Potential complications: granulation tissue, leakage, dislodgement, skin infection, stoma stenosis



Tabbers JPGN 2014

Future Directions



Management of Difficult Constipation in Adult

http://www.qmedicine.co.in/top%20health%20topics/C/Constipation%20in%20Adults.html

Louis W.C. Liu
MD, PhD, FRCP(C)

Head of Gastroenterology, University Health Network and Sinai Health System
Director of Motility Unit, University Health Network

Learning Objectives

By the end of this session, the attendances will be able to:

1. identify the different etiologies of constipation between children and adults
2. apply the evidence for current therapies to manage constipation in children and adults

Case

- 37 yr-old healthy female, constipated since teenage years starting in high school.
- Tried various laxatives, all worked initially and then stopped working.
- Now using stimulant laxatives prn, often 6 to 8 tablets required “to go” with un-predictable response and caused abdominal pain.
- Tried to increase “fiber” intake but get cramps and bloating
- Referred to GI for refractory constipation and bloating

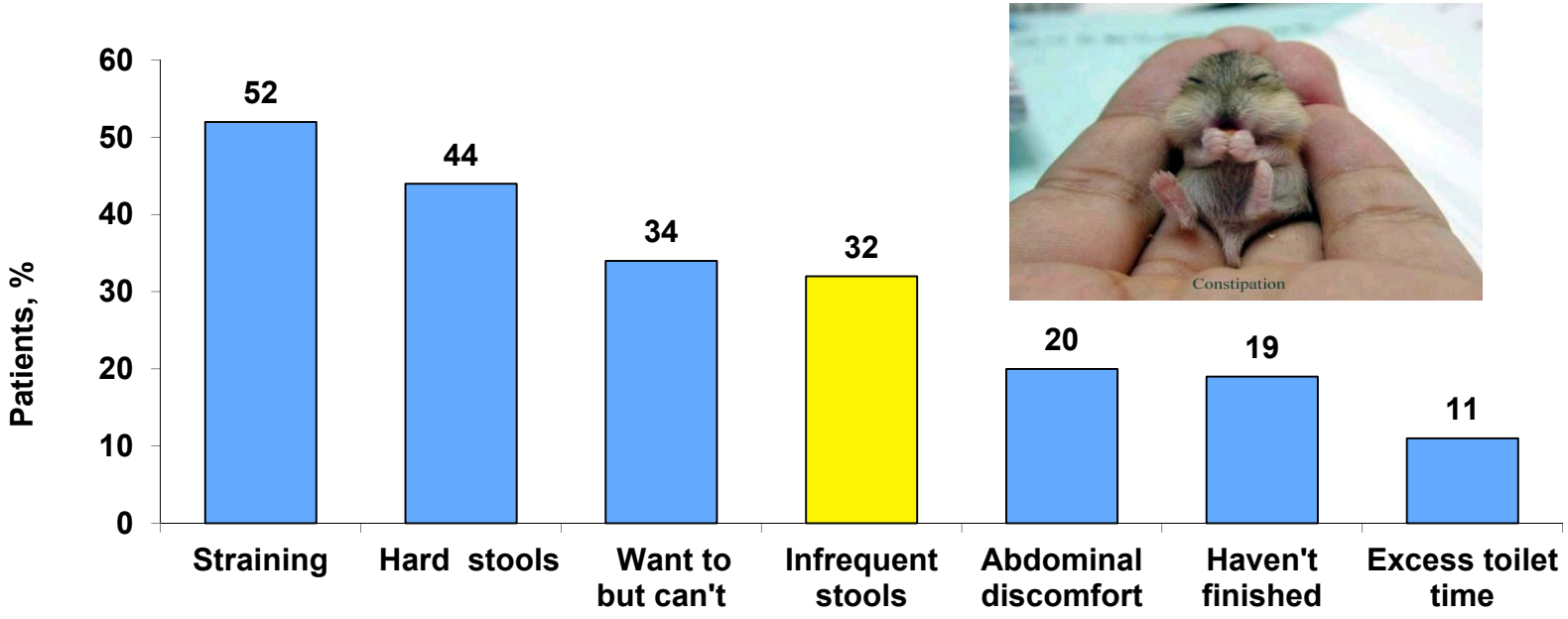
https://www.ayurvediccure.com/best-home-remedies-for-constipation/

http://www.clipartpanda.com/clipart_images/this-week-s-wth-moments-46388142

http://sbrownehr.com/wp-content/uploads/2014/03/Approach.png

Constipation means more than infrequent BM

n = 1128 (60% university students, 32% hospital employees, 8% medical students)

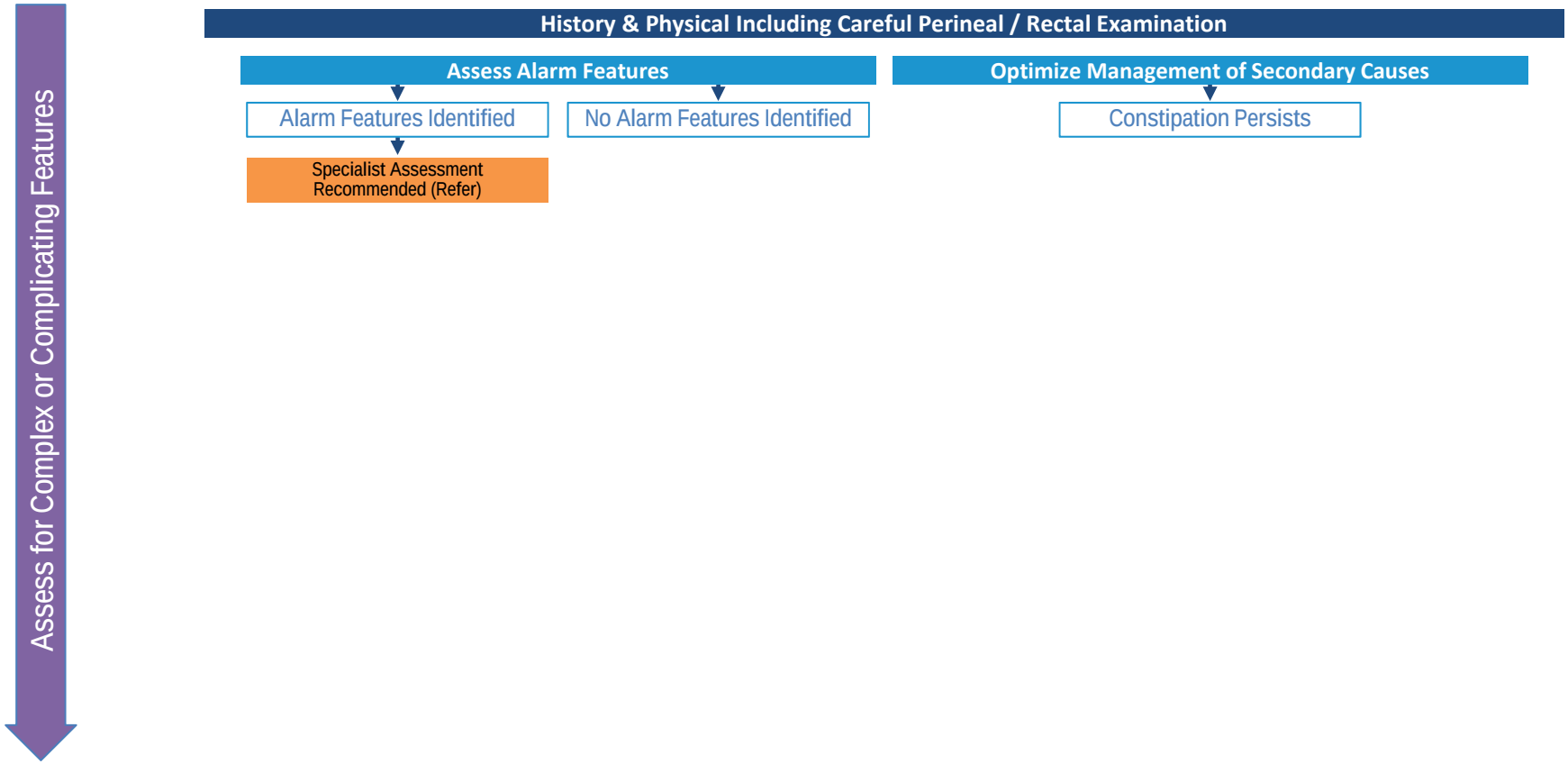


Sandler RS, et al. *Dig Dis Sci.* 1987;32:841-845.

Chronic Constipation Treatment Algorithm

Louis Liu, Chris Andrews, David Armstrong, Alain Bitton, Brian Bressler, John Marshall

Contributing faculty members involved in the development of the algorithm



Tse Y et al CJGH 2017, in press

Constipation

Red Flags for Organic Causes

- > 50 yr, recent onset in symptoms
- Acute severe symptoms
- Rectal bleeding
- Fever or wt loss
- Unremitting or nocturnal symptoms
- Abnormal blood test
  - Fe def anemia
- Positive family hx
  - IBD, CRC
- Abnormal physical exam
  - Abd mass
  - skin/joints

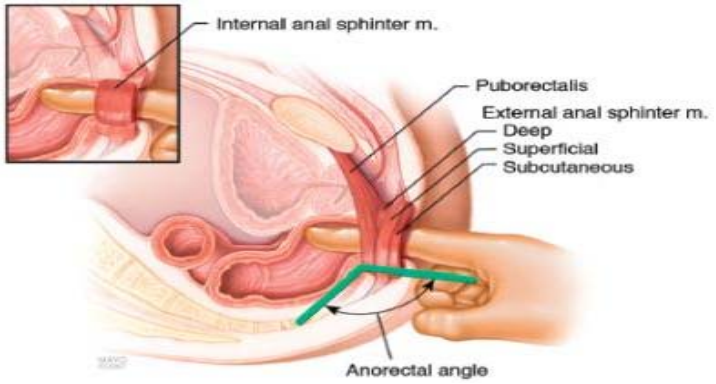
PPV 98-100%, NPV 68-76%

Utility of Digital Rectal Examination

Table 2. Performance Characteristics of DRE in the Diagnosis of Dyssynergia in Patients With Chronic Constipation

	Estimated value	95% CI Lower limit	95% CI Upper limit
Sensitivity	0.75	0.68	0.81
Specificity	0.87	0.68	0.96
For any particular positive test result, the probability that it is:			
True positive	0.97	0.92	0.9
False positive	0.03	0.01	0.08

1. Tantiphlachiva K et al. Clin Gastro Hep 2010



Talley NJ. Am J Gastroenterol. 2008;103(4): 820-2

- In trained examiners, DRE
  - Has a high PPV to identify DD in patients with constipation[1,2] and probably in FI[2]
  - Is poor in identifying abnormal sphincter tone[1,2]

2. Soh, JS et al The diagnostic value of a digital rectal examination compared with high-resolution anorectal manometry in patients with chronic constipation and fecal incontinence. AJG Aug 2015; 110:1197–1204

Basic Investigations

- Screening Blood work TSH, Calcium, renal function, CBC, and screen for diabetes
- Abdominal flat plate often enough to see how much stool in the colon and if the colon looks dilated

Courtesy of Dr. Geoffrey Turnbull

She is worried about a blockage and wants to have a colonoscopy.

What would you do?

Colonoscopy is not recommended as a routine investigation for constipation

Choosing Wisely Canada

4 **Avoid performing a colonoscopy for constipation in those under the age of 50 years without family history of colon cancer or alarm features.**

Constipation is a common problem and systematic review data suggests this is not an accurate symptom in diagnosing organic disease. If the patient is also under the age of 50 and does not have a family history of colon cancer and there are no alarm features such as anemia or weight loss, then the risk of colorectal cancer is very low and the risks of colonoscopy usually outweigh the benefits in these patients.

http://www.choosingwiselycanada.org/recommendations/gastroenterology-2/

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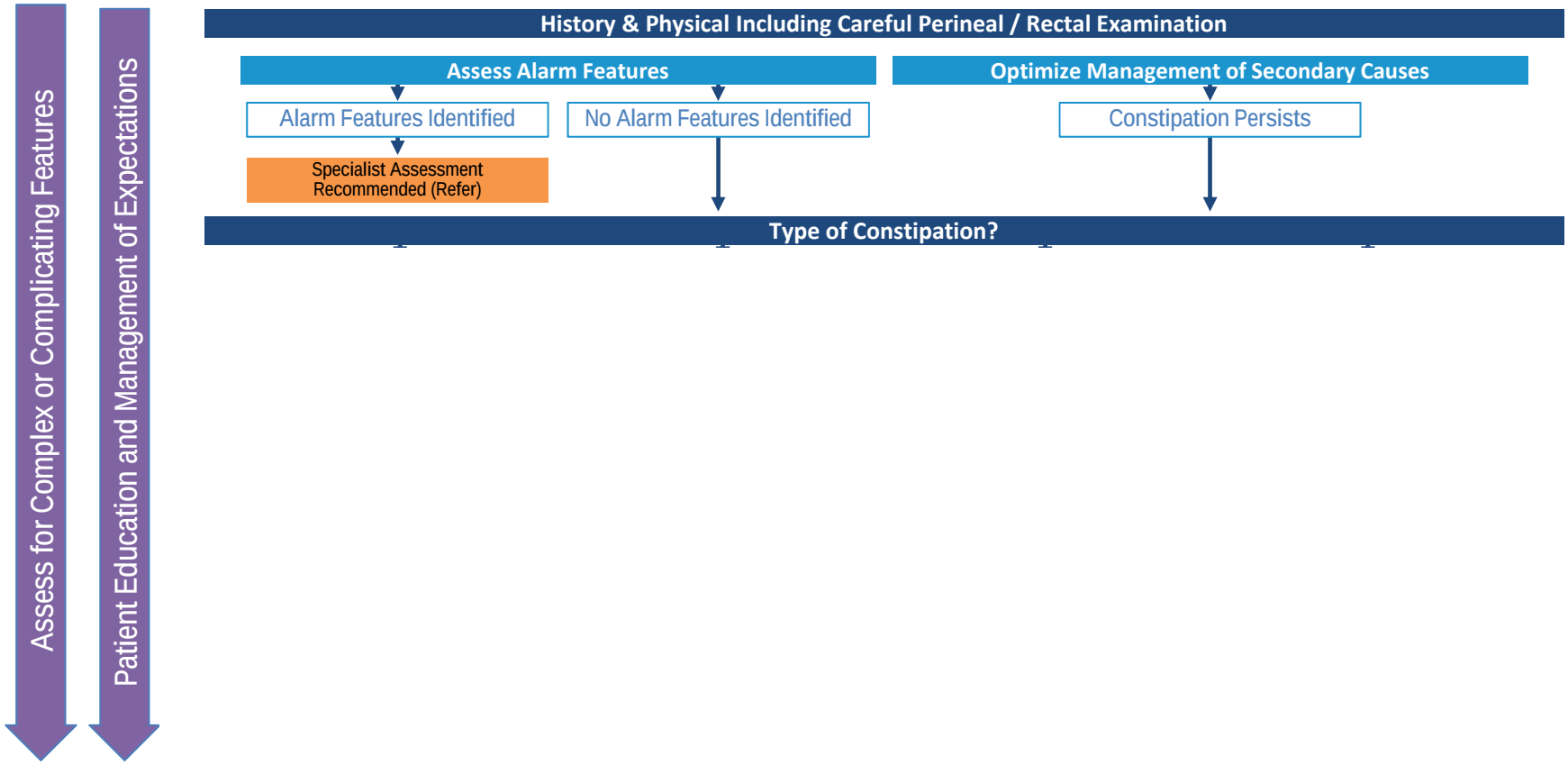
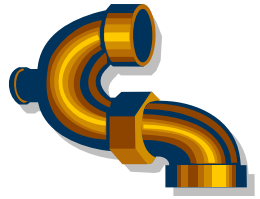
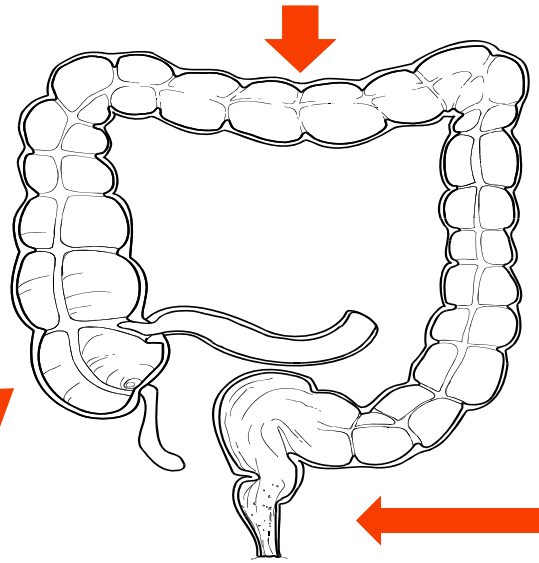


Tse Y et al CJGH 2017, in press

Conceptual approach to constipation



LOSS OF PERISTALTIC CONTRACTIONS
"PUMP FAILURE"

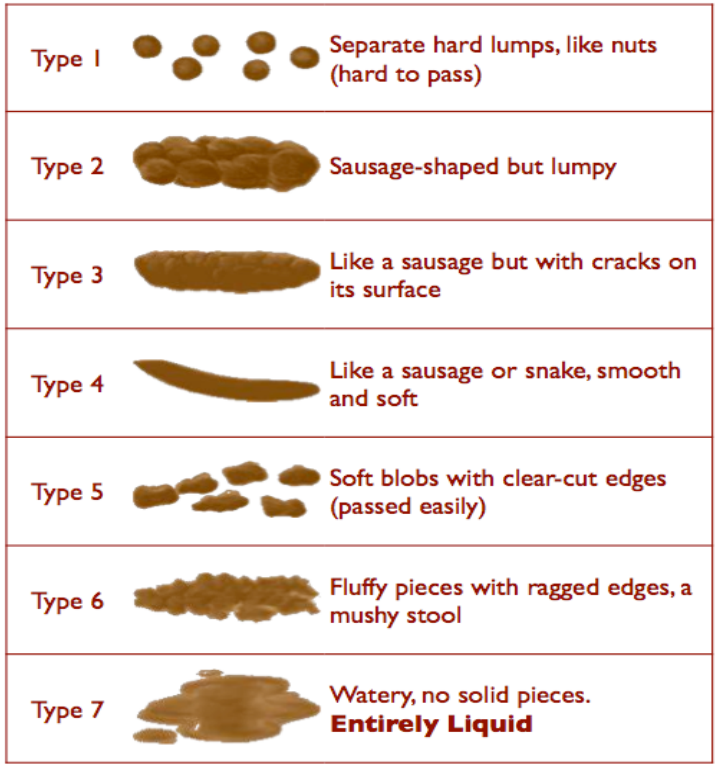


POOR INTAKE
WATER/FIBER

OUTLET PROBLEMS
"FAILURE SPHINCTER RELAXATION"

Quigley, EM., Ther Adv Gastroenterol (2011) 5(1) 23-30

Bristol Stool Chart



- designed to classify stool consistency into seven categories
- Types 1 and 2 indicate slow transit constipation

Lewis SJ, Heaton KW. *Scan J Gastroenterol* 1997;32(9):920–924

FBDs are a Continuum in Clinical Practice

Less Abdominal Pain **More Abdominal Pain**

Pain is an important therapeutic target to manage

Symptom-based criteria for CIC and IBS-C
overlap and **transition** between diagnosis overtime

1. Rey et al. AJG 2014; 109: 876 – 884.
2. Thompson WG et al, Gut 1999; 45: SII43.
3. Wong et al. AJG 2010; 105: 2228 – 2234.
4. Palsson, O. S., Baggish, J., & Whitehead, W. E. AJG: 2014, 109(9), 1450-1460.

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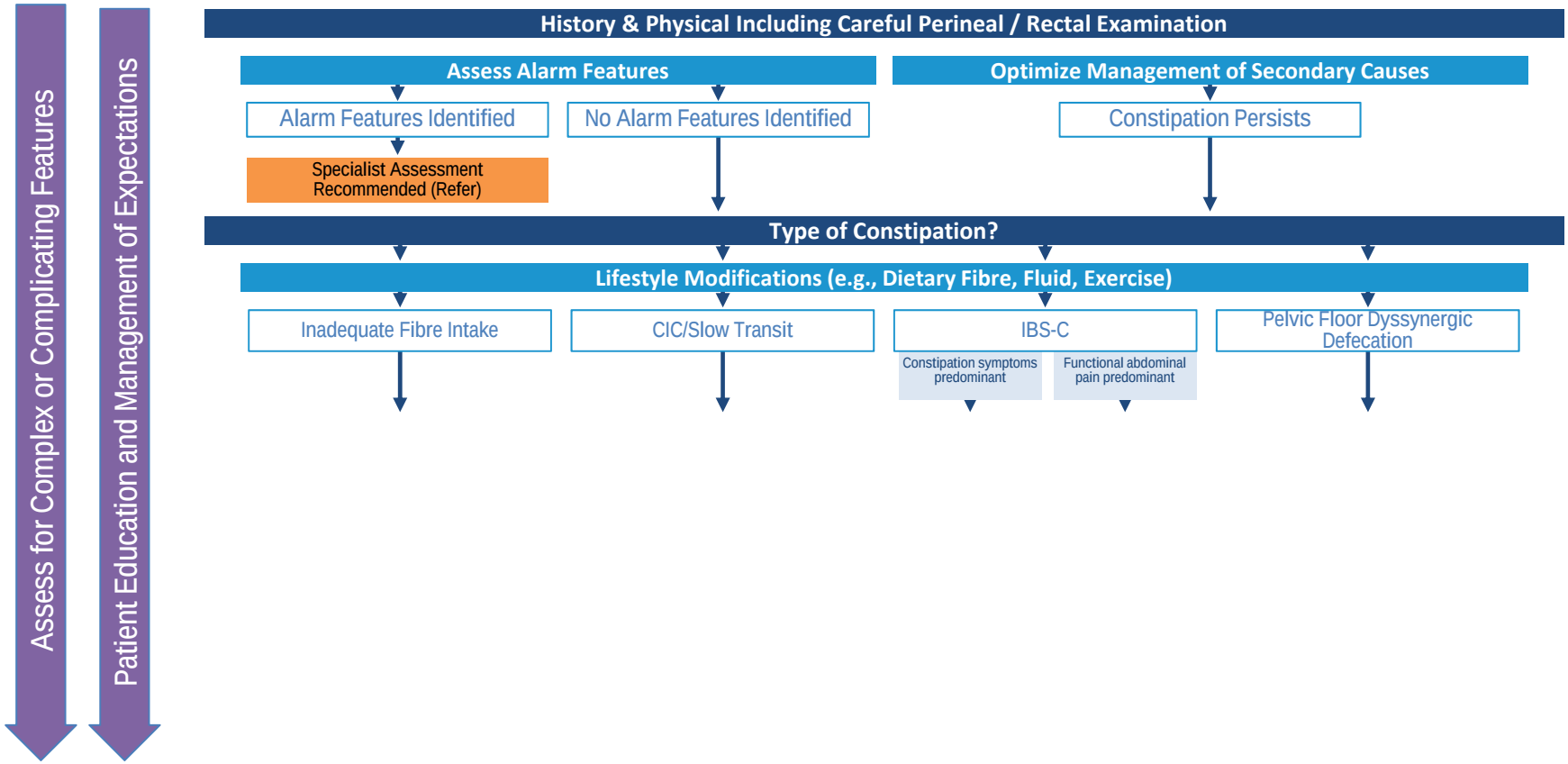

Tse Y et al CJGH 2017, in press

ACG Monograph on the Management of CIC – Abbreviated Table

Treatment	No. of Trials	No. of Patients	Recommendation	Quality of Evidence
Fiber	3	293	Strong	Low
PEG	4	573	Strong	High
Lactulose	2	148	Strong	Low
Stimulant Laxatives	2	735	Strong	Moderate
Prucalopride	8	3140	Strong	Moderate
Linaclotide	3	1582	Strong	High
Lubiprostone	4	651	Strong	High

Grading of Recommendations Assessment, Development and Evaluation (GRADE)
Quality of Evidence Grading : High, Moderate, Low or Very Low
Recommendations : Strong or Weak
Ford et al, Am J Gastroenterology 2014.

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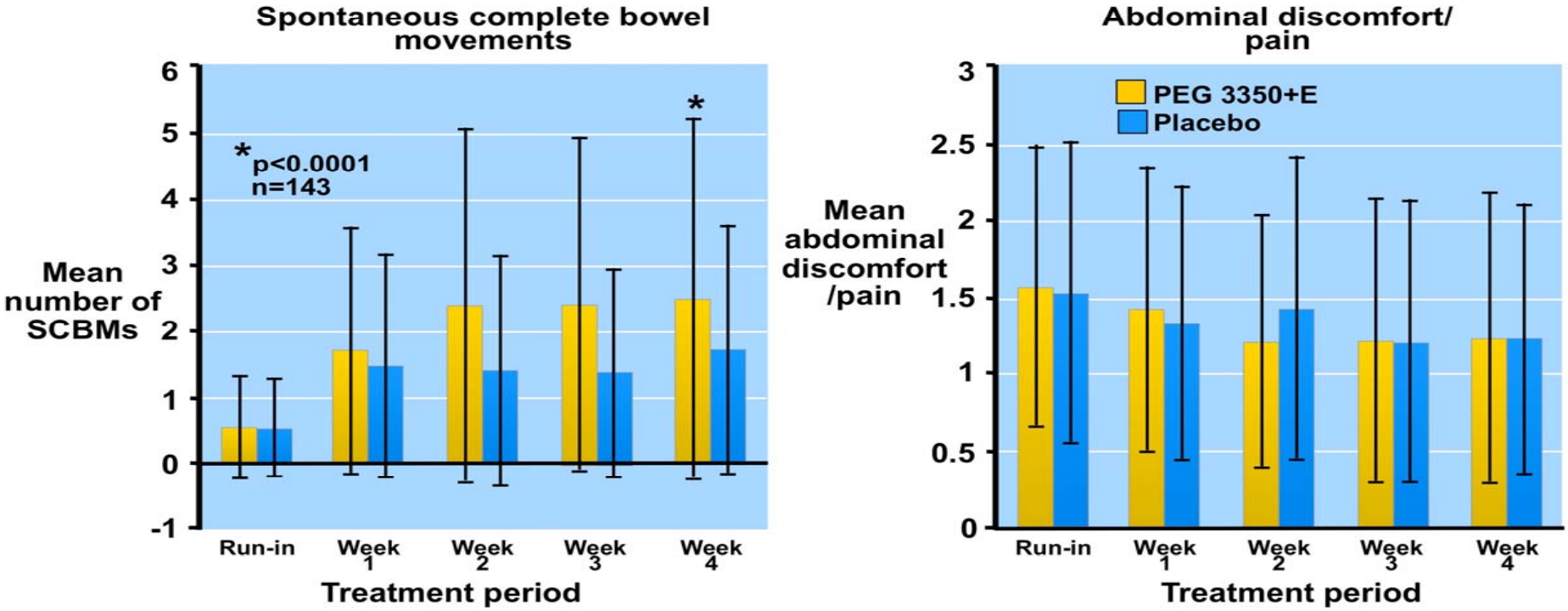
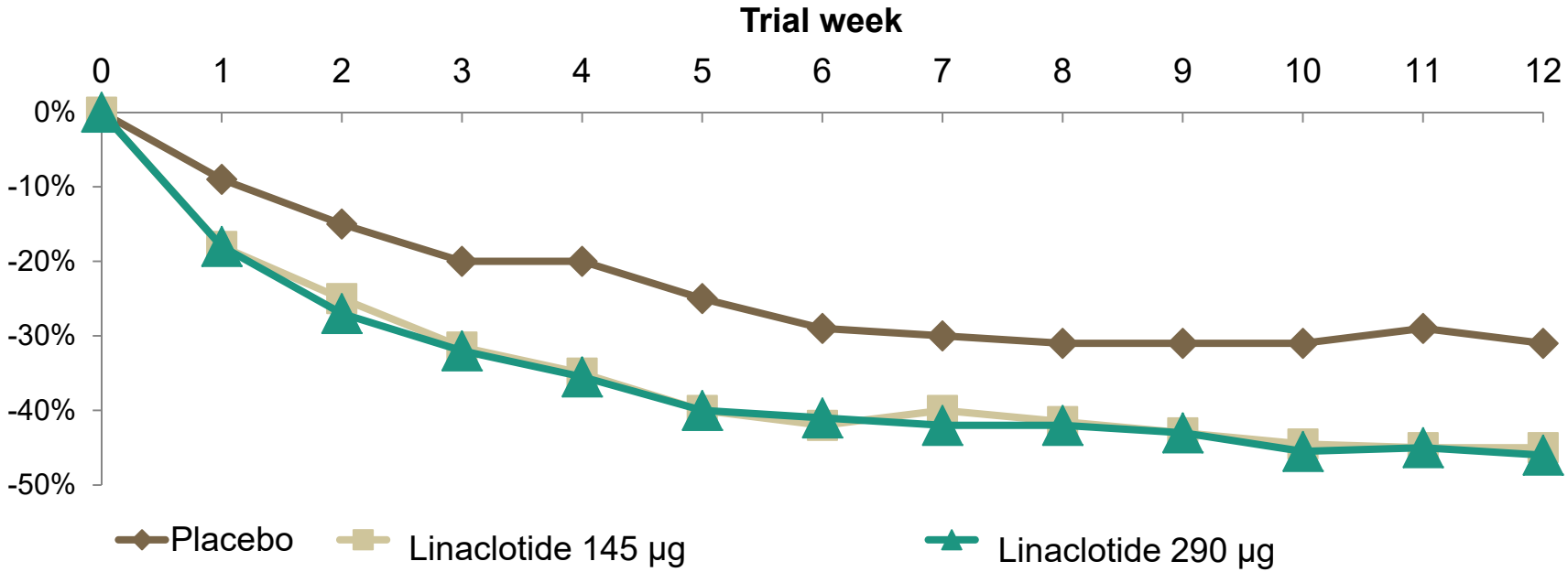
Task Force on the Management of Functional Bowel Disorders

Polyethylene Glycol for IBS-C: Results from an RCT



ACG Task Force Recommendation:
There is no evidence that PEG improves overall symptoms and pain in patients with IBS
Recommendation: weak; Quality of evidence: very low

Percent Change from Baseline in Abdominal Bloating by Week in CIC



Significant improvements noted at week 1 and sustained thereafter

($p<0.05$ vs. placebo for all time points)

Lacy et al. (2015). PLoS One, 10(7), e0134349.

ACG Monograph on the Management of IBS-C – Abbreviated Table

Treatment	No. of Trials	No	NNT	Recommendation	Quality of Evidence
Specialized diet	3	203	NA	Weak	Very Low
Psyllium, not bran	7	499	7 (4-25)	Weak	Moderate
Probiotics	23	2575	7 (4-12.5)	Weak	Low
Antispasmodics	23	2154	5 (4-9)	Weak	Low
Peppermint Oil	5	482	3 (2-4)	Weak	Moderate
Antidepressants	17	1084	4 (3-6)	Weak	High
Linaclotide	3	2028	6 (5-8)	Strong	High
Lubiprostone	3	1366	12.5 (8-25)	Strong	Moderate
PEG	2	166	NA	Weak	Very Low

- Quality of Evidence Grading: High, Moderate, Low or Very Low
- Recommendation Grading: Strong or Weak

Grading of Recommendations Assessment, Development and Evaluation (GRADE)
Ford et al. Am J Gastroenterol 2014; 109:S2-S26

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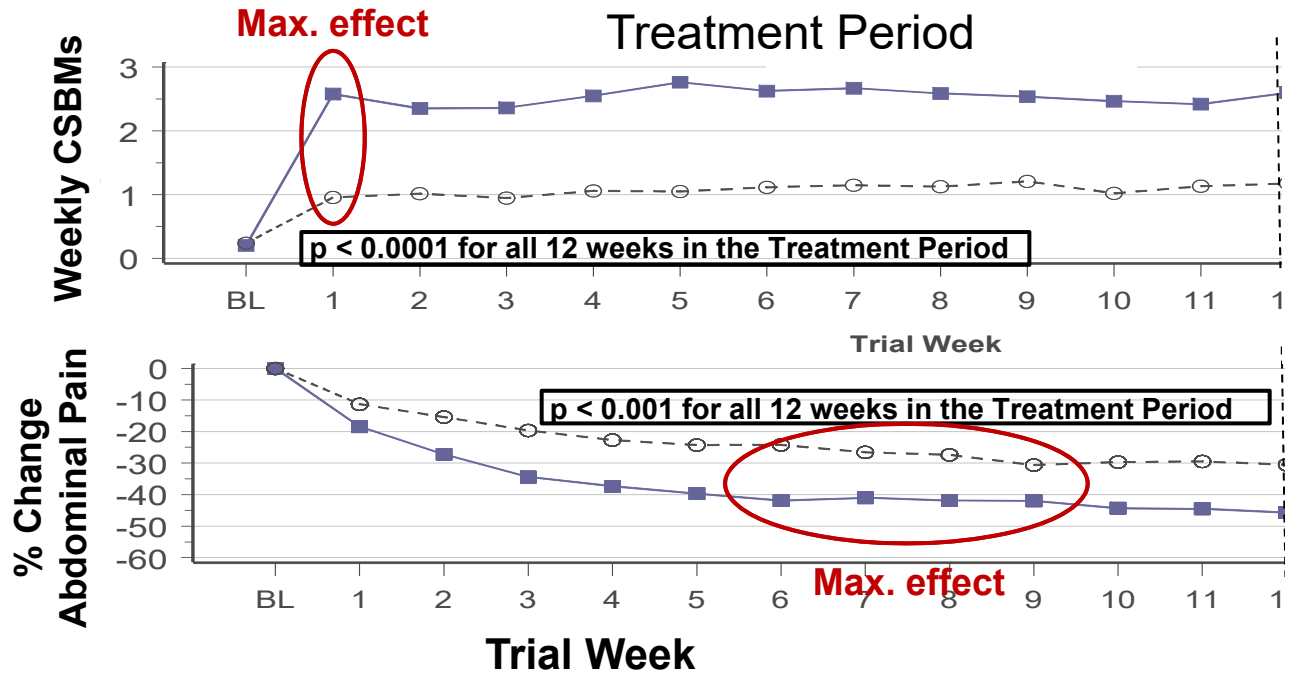
Task Force on the Management of Functional Bowel Disorders

Weekly CSBMs and abdominal pain responses in linaclotide group



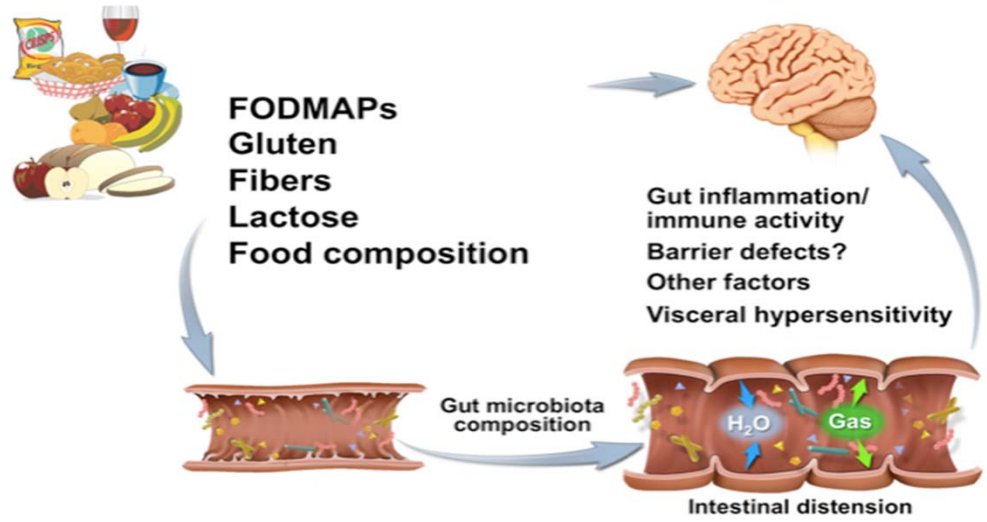
Complete Spontaneous Bowel Movement (CSBM) – A spontaneous bowel movement that gives a sense of complete evacuation

Treatment Groups
290 µg linaclotide ○ Placebo

Rao S et al. *Am J Gastroenterol,* 2012

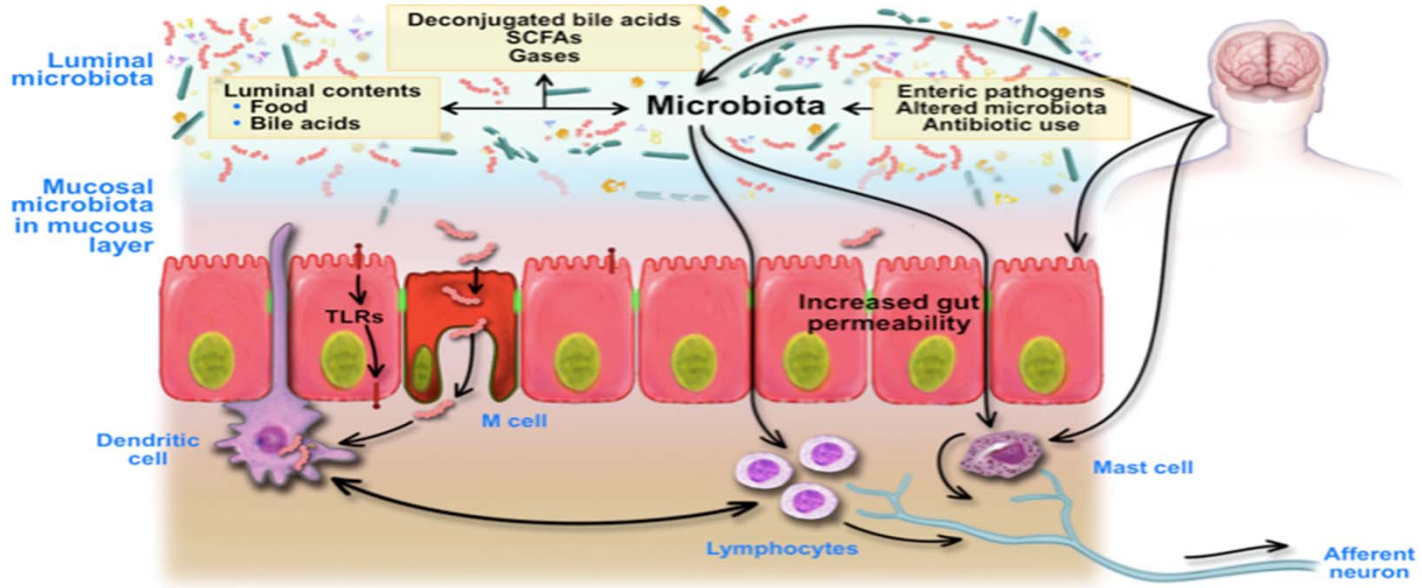
Diet and IBS symptoms

- Low FODMAP diet is better than typical Austrian diet[1]
- Low FODMAP diet is no different from the convention IBS diet[2]



1. Halmos, E. P., Power, V. A., Shepherd, S. J., Gibson, P. R., & Muir, J. G. (2014). A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. Gastroenterology, 146(1), 67-75.e5
2. Böhn, L., Störsrud, S., Liljebo, T., Collin, L., Lindfors, P., Törnblom, H. et al. (2015). Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. Gastroenterology, 149(6), 1399-1407.e2

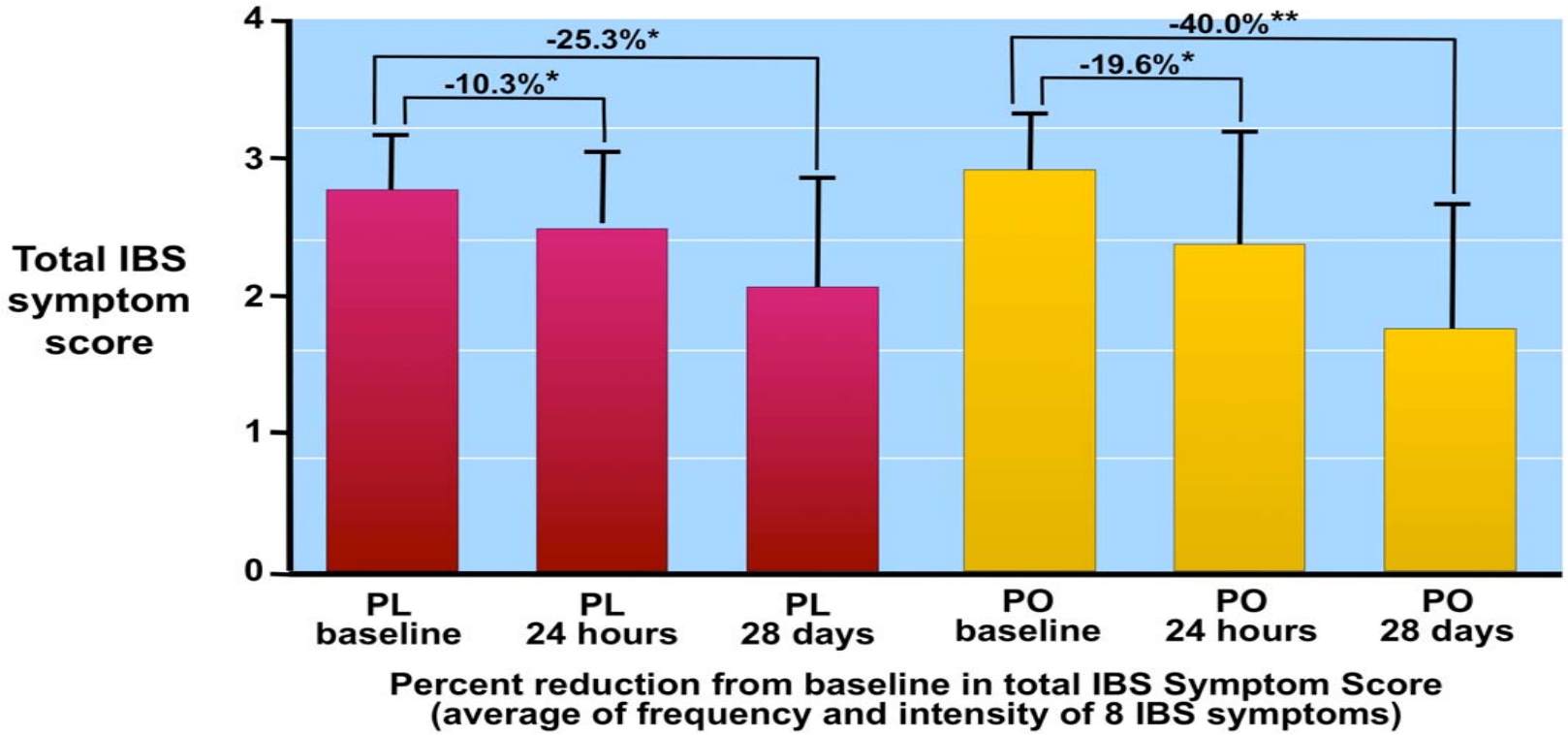
Probiotic reduces IBS symptoms



- Meta-analysis included 21 trials – improves overall abdominal symptoms and QoL, but not individual abdominal symptoms
- No significant improvement in abdominal pain

Zhang, Y., Li, L., Guo, C., Mu, D., Feng, B., Zuo, X. et al. (2016). Effects of probiotic type, dose and treatment duration on irritable bowel syndrome diagnosed by Rome III criteria: a meta-analysis. BMC Gastroenterol, 16(1), 62
Figure extracted from the ROME IV slide deck, 2016

Sustained Release Peppermint Oil Improves IBS Symptoms



Enteric coated delayed release (IBgard®)

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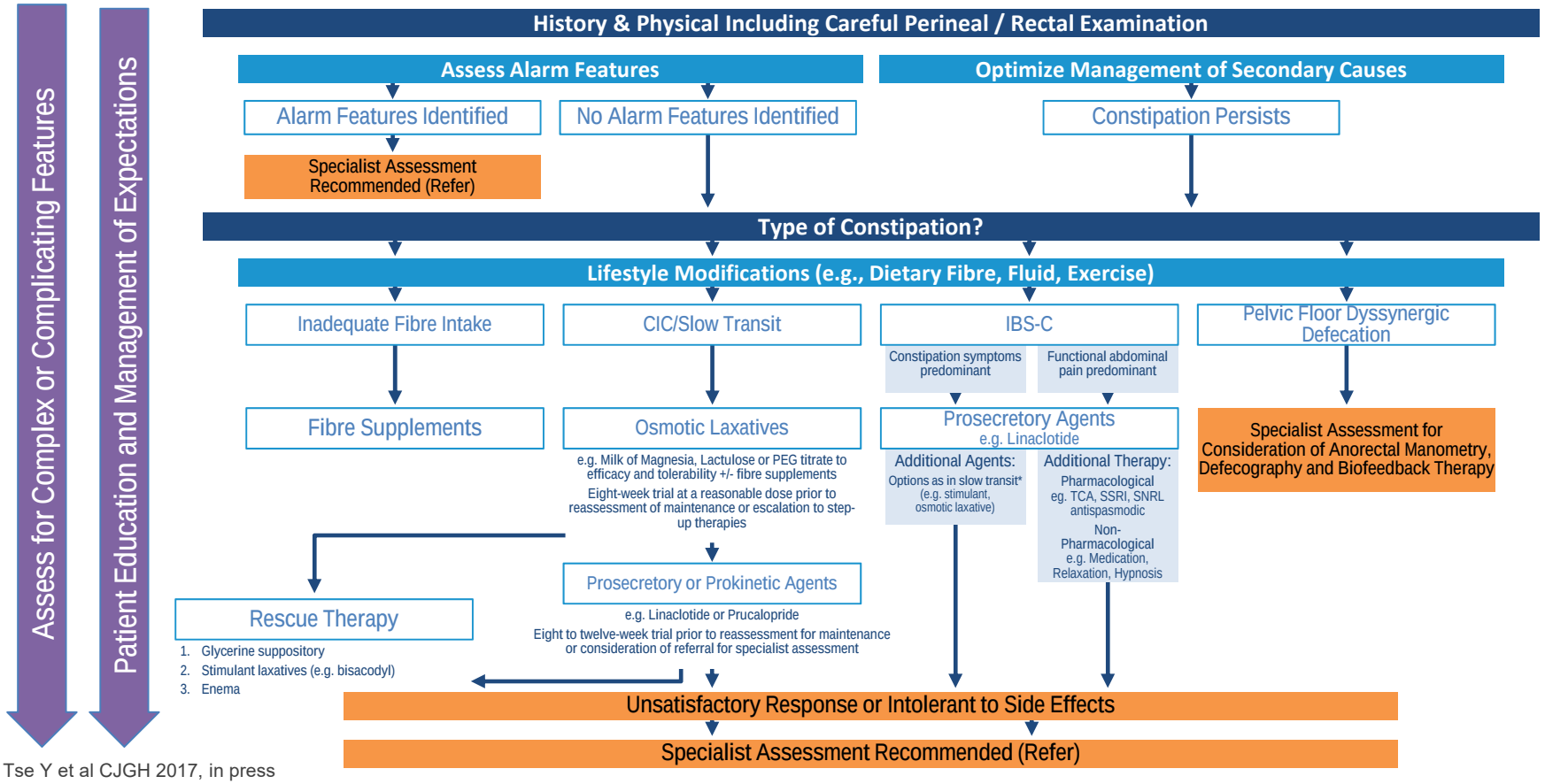

Tse Y et al CJGH 2017, in press

Overcoming the challenges in managing difficult constipation

- Validate and educate
  - Normal variation of bowel function
  - Ensure adequate and appropriate trials of treatment agents
- Manage expectations
- Empower and engage patients
- Choose therapy targets predominant symptoms
  - Align patients' belief and acceptance
- Patient-physician relationship

http://www.clipartkid.com/overcome-challenge-concept-with-3d-man-figure-jumping-over-text-on-eCNF33-clipart/

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