# Updates in the Management of Chronic Constipation: Medications, Devices & Other Interventions

Satish SC Rao, MD, PhD, FRCP (Lon), FACG, AGAF
J. Harold Harrison, MD, Distinguished University Chair in Gastroenterology, Professor of Medicine
Director, Neurogastroenterology & Motility
Director, Digestive Health Clinical Research Center
Medical College of Georgia, Augusta, GA

AUGUSTA UNIVERSITY

# Disclosures

- Advisory Board/Honoraria:
  - Viatris Pharmaceuticals
  - Mylan Pharmaceuticals
  - Salix Pharmaceuticals
  - Ironwood Pharmaceuticals
  - Vibrant
  - Neurogut Inc
  - Ardelyx pharmaceuticals
- Research Support
  - National Institutes of Health, NIDDK
  - Vibrant

# OBJECTIVES

- Define constipation subtypes
- Understand its multifactorial pathophysiology
- Discuss clinical evaluation including APPs, DRE, and Diagnostic tests
- Review latest treatment options using a pathophysiologic-based approach

# Types of Constipation

1. Occasional Constipation
2. Chronic Constipation
   - *-Primary*
     - *-Slow transit constipation*
     - *-Dyssynergic Defecation*
     - *- IBS-C*
     - *-Rectal Hyposensitivity/Hypersensitivity*
   - *-Secondary*
   - *-Opioid induced constipation*

Rao S et al Nature Revs 2016; Rao SSC. Gastroenterol Clin N Am 36 (2007) 687-711

Bharucha A et al, Gastroenterology 2006;130:1514

# 52 yr old Dentist, Constipation- 6 months

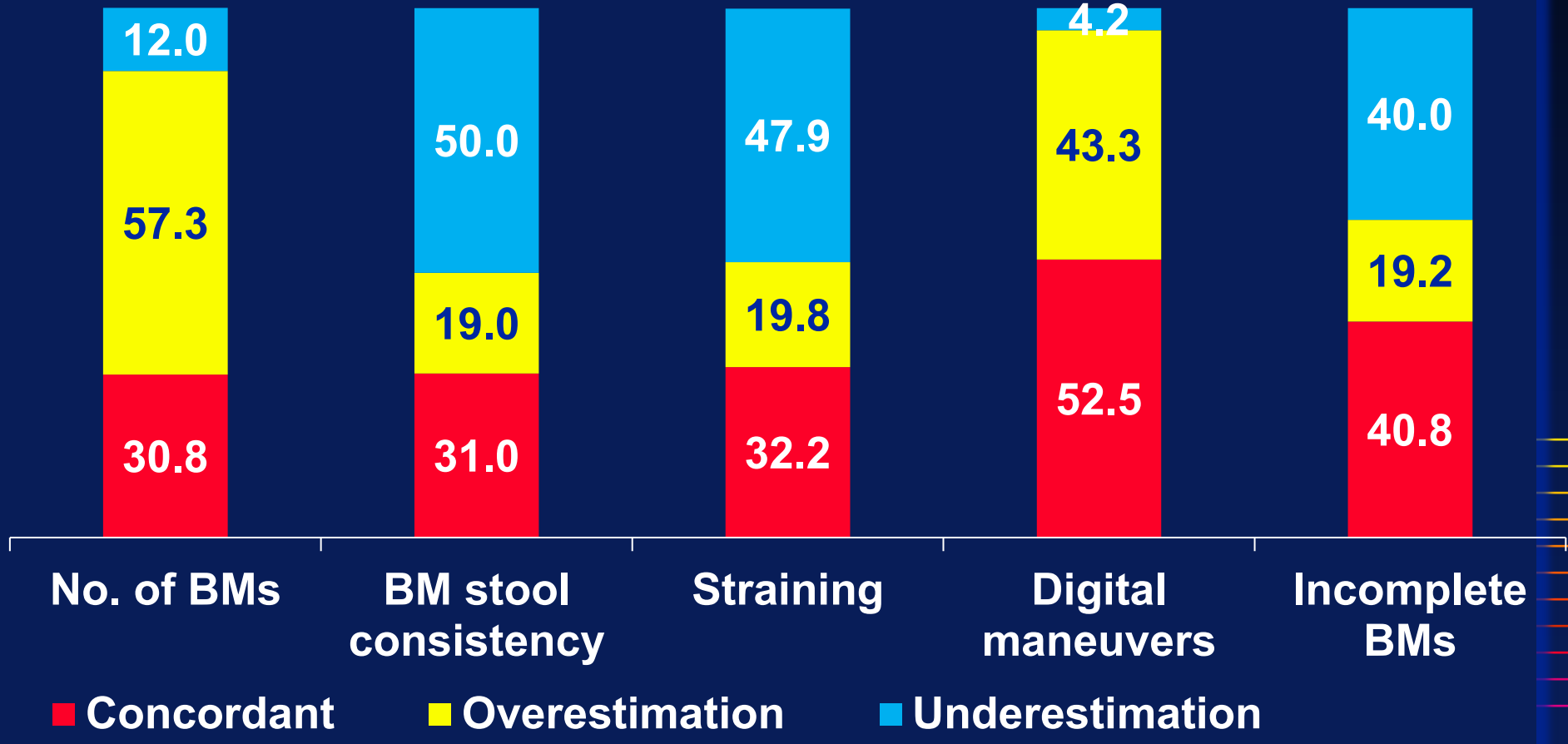
- B.M irregular 2-3 times a week, Type 1-4 stool, Straining +, FICE +, No blood
- Symptoms for 6 months
- Tried fiber and OTC laxatives- afraid to take because of unpredictable BMs
- Intermittent bloating, no wt loss
- Affects work , social engagements-QOL
- Past Hx: Hysterectomy, Normal colonoscopy-2 years ago
- What is the next step?

# Key Lesson

- Lumping all constipation as a one symptom disorder is wrong
  - Constipation is a polysymptomatic' heterogeneous disorder
  - Patient's recall of symptoms is poor
  - Hence prospective symptom evaluation is key
  - Use Rome IV Criteria

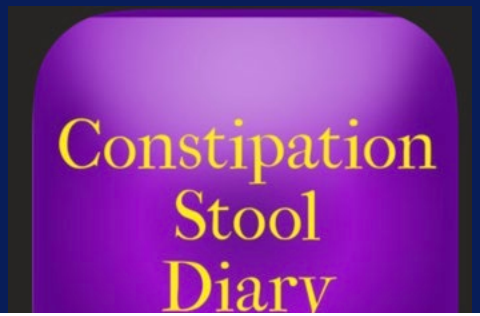
*Curtin B, Rao SS et al, JNM 2020;26:423-36*

# How accurate is constipation history? Recall vs Prospective Stool diary




Hudgi A, Yan Y, Rao SSC et al DDW 2022

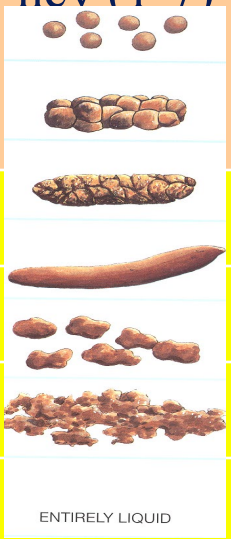
# Constipation: evaluating symptoms




App Store

Google

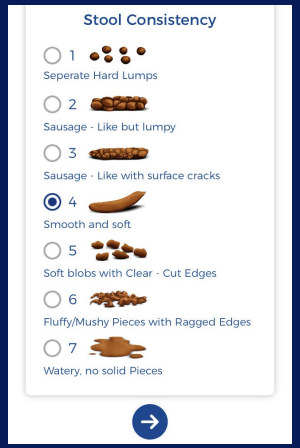
| Date | Time of Bowel Movement | Straining Yes/No | Feeling of incomplete BM Yes/No | Stool Consiste-ncy (1-7) | Urge Yes/No | Digita Yes/No | Drug | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

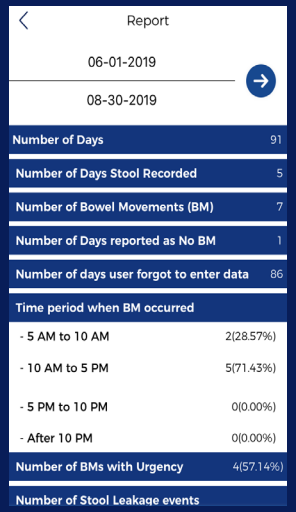



*Curtin B, Rao SS et al, JNM 2020;26:423-36*

# Components of Digital APP

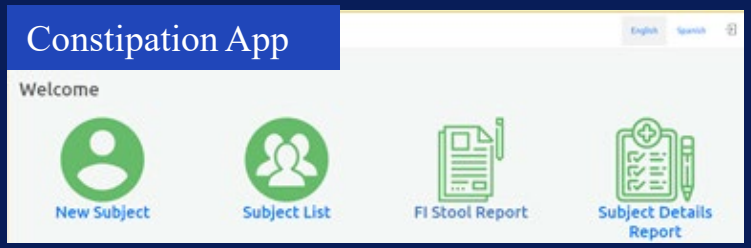
- **Clinician/Patient Use**


Check out in APP store

- Investigator Use



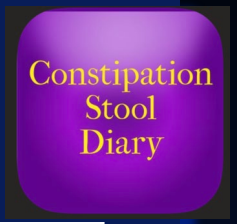

AUTN0006

| Date | Stool event | Time | Urgency | Leakage | Activity | Consistency | Sensation before | Pad use | BM induced | Complete Evacuation | Comments | Medications | Added By |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 08/15/2019 | 1 | 14:28 | Yes | None | | 6 | Normal Urge | No | Nothing | No | | | HH |
| 08/16/2019 | 1 | 03:44 | Yes | None | | 6 | Normal Urge | No | Nothing | Yes | | | HH |
| 08/16/2019 | 2 | 11:34 | No | Mild | Sitting or resting | 6 | Normal Urge | Yes | Nothing | Yes | | | HH |
| 08/16/2019 | 3 | 17:38 | Yes | Mild | Sitting or resting | 6 | Strong Urge | Yes | Nothing | Yes | | | HH |
| 08/16/2019 | 4 | 19:13 | Yes | None | | 6 | Strong Urge | No | Nothing | Yes | | | HH |
| 08/17/2019 | 1 | 12:26 | Yes | Mild | Household Chores | 5 | Normal Urge | Yes | Nothing | Yes | | | HH |
| 08/17/2019 | 2 | 13:16 | Yes | None | | 5 | Normal Urge | No | Nothing | No | | | HH |
| 08/17/2019 | 3 | 17:46 | Yes | Mild | Sitting or resting | 7 | Strong Urge | Yes | Nothing | No | | | HH |
| 08/18/2019 | 1 | 12:57 | No | None | | 5 | Normal Urge | No | Nothing | Yes | | | HH |
| 08/19/2019 | 1 | 10:48 | Yes | None | | 5 | Normal Urge | No | Nothing | Yes | | | HH |
| 08/20/2019 | 1 | 09:58 | No | None | | 5 | Normal Urge | No | Nothing | Yes | | | HH |
| 08/20/2019 | 2 | 16:39 | Yes | Mild | Sitting or resting | 7 | Strong Urge | Yes | Nothing | Yes | | | HH |
| 08/21/2019 | 1 | 12:41 | Yes | None | | 5 | Normal Urge | No | Nothing | Yes | | | HH |
| 08/21/2019 | 2 | 14:11 | No | Mild | Sitting or resting | 7 | Strong Urge | Yes | Nothing | Yes | | | HH |
| 08/21/2019 | 3 | 15:50 | Yes | None | | 6 | Strong Urge | No | Nothing | Yes | | | HH |
| 08/22/2019 | 1 | 03:36 | No | Excessive | Sitting or resting | 7 | No Awareness | Yes | Nothing | Yes | | | HH |
| 08/22/2019 | 2 | 12:39 | Yes | None | | 6 | Normal Urge | No | Nothing | Yes | | | HH |

| Patient ID | Baseline Period | | End of Study Period | | Optional Study Period | |
|---|---|---|---|---|---|---|
| Stool Diary Parameters | Percentage or N | Number of Events | Percentage or N | Number of Events | Percentage or N | Number of Events |
| Study Duration | 09/10/2019-09/16/2019 | | 09/25/2019-10/01/2019 | | | |
| Number of Days (n) | 7 | 7 | 7 | 7 | | |
| Number of Days Stool recorded (n) | 7 | 7 | 6 | 6 | | |
| Number of Days reported as No BM (n) | 0 | 0 | 1 | 1 | | |
| Number of days Subject forgot to enter data (n) | 0 | 0 | 1 | 1 | | |
| Time of Bowel Movements/Leakage events | | | | | | |
| Number of BMs between 5 AM to 10 AM (%) | 30 | 3 | 0 | 0 | | |
| Number of BMs between 10 AM to 5 PM (%) | 30 | 3 | 75 | 9 | | |
| Number of BMs between 5 PM to 10 PM (%) | 30 | 3 | 25 | 3 | | |
| Number of BMs after 10 PM (%) | 10 | 1 | 0 | 0 | | |
| Number of Bowel Movements (n) | 10 | 10 | 12 | 12 | | |
| Number of BMs with Urgency (%) | 100 | 7 | 100 | 12 | | |
| Number of Stool Leakage events (n) | 8 | 8 | 4 | 4 | | |
| None (n) | 2 | 2 | 2 | 2 | | |
| Mild Severity (%) | 50 | 4 | 0 | 0 | | |
| Moderate Severity (%) | 25 | 2 | 100 | 4 | | |
| Excessive Severity (%) | 25 | 2 | 0 | 0 | | |
| Number of bowel movements without Leakage (n) | 2 | 2 | 2 | 2 | | |
| Where leakage occurred? | | | | | | |
| Sitting or Resting (%) | 100 | 0 | 100 | 4 | | |
| Household Chores (%) | 0 | 0 | 0 | 0 | | |
| Working (%) | 0 | 0 | 0 | 0 | | |
| Traveling (%) | 0 | 0 | 0 | 0 | | |
| Eating / Drinking (%) | 0 | 0 | 0 | 0 | | |
| Exercise (%) | 0 | 0 | 0 | 0 | | |

Yan Y, Rao SSC, et al. FNM 2020

# Constipation APP vs Paper Diary




| | Test-retest/Reliability (n=16) | | | | Validity (n=16), APP vs Paper | | | |
|---|---|---|---|---|---|---|---|---|
| | First week | Second week | ICC | P | APP | Paper | ICC | P |
| No. of BMs | 6.9 ± 1.0 | 5.2 ± 0.8 | 0.8 | <0.0001 | 12.1 ± 1.7 | 12.8 ±1.9 | 0.9 | <0.0001 |
| No. of SBMs | 4.4 ± 1.3 | 3.4 ± 0.9 | 0.9 | <0.0001 | 7.8 ± 2.1 | 10.3 ± 2.0 | 0.9 | <0.0001 |
| No. of CSBMs | 1.9 ± 0.9 | 1.6 ± 0.7 | 0.9 | <0.0001 | 3.5 ± 1.5 | 4.3 ± 1.6 | 0.9 | <0.0001 |
| Time on toilet (min) | 9.4 ± 1.9 | 9.0 ± 2.0 | 0.9 | <0.0001 | 9.1 ± 1.9 | 7.8 ± 1.8 | 0.9 | <0.0001 |
| No. of Type 1-2 stools | 1.4 ± 0.8 | 0.9 ± 0.3 | 0.07 | 0.445 | 2.3 ± 0.8 | 2.6 ± 1.0 | 0.9 | <0.0001 |
| No. of Type 3-5 stools | 3.2 ± 0.8 | 2.4 ± 0.7 | 0.2 | 0.345 | 5.6 ± 1.1 | 7.8 ± 2.1 | 0.8 | 0.0001 |
| Digital Use (n) | 2 | 2 | 0.6 | 0.043 | 3 | 3 | 1.0 | 1.000 |
| No. of Gas | 3.4 ± 0.8 | 2.4 ± 0.5 | 0.7 | 0.011 | 5.8 ± 1.2 | 8.4 ± 1.9 | 0.7 | 0.003 |
| No of Bloating | 5.1 ± 0.6 | 3.9 ± 0.6 | 0.8 | 0.003 | 9.1 ± 1.1 | 9.4 ± 1.8 | 0.8 | 0.004 |

Yan Y, Rao SSC. DDW 2020, Gastroenterology

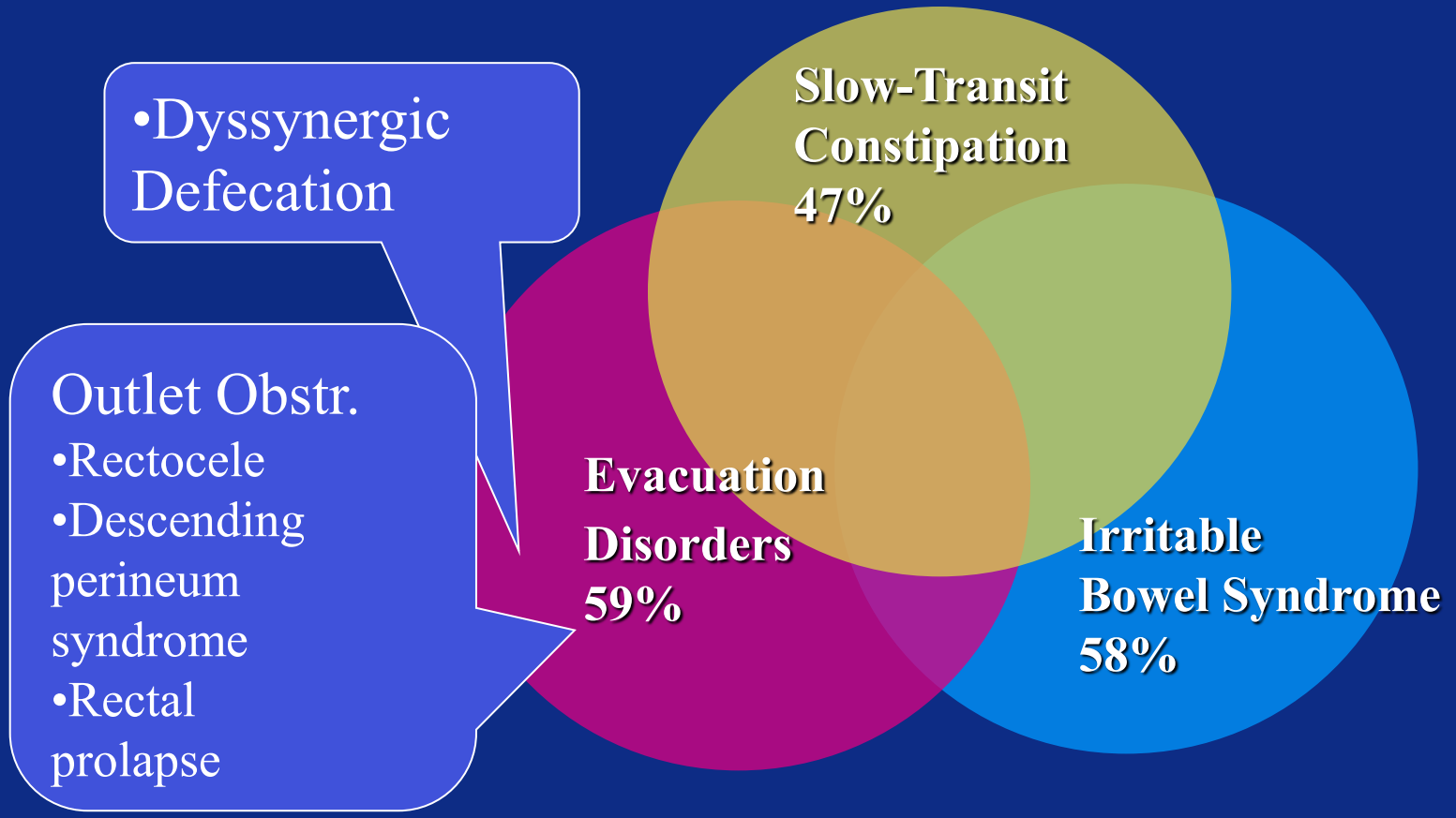
# Occasional Constipation- Definition

- Intermittent or occasional symptomatic alterations in bowel habit, in the absence of warning signs for more serious conditions
- Symptoms include
  - Bothersome reduction in stool frequency and/or
  - Difficulty with stool passage
- Symptoms last few days or weeks, and may require
  - Modification of lifestyle, dietary habits and/or
  - Use of OTC laxatives or bulking agents to restore bowel habit

- *Warning features: Blood in stool, Weight loss, abdominal pain, Hx of colon cancer, Recent new meds- Consult Physician*
- *Prevalence: 15-29.5%*


- Rao SSC Quigley EMM et al Am J Gastro 2022; doi.org./10.14309

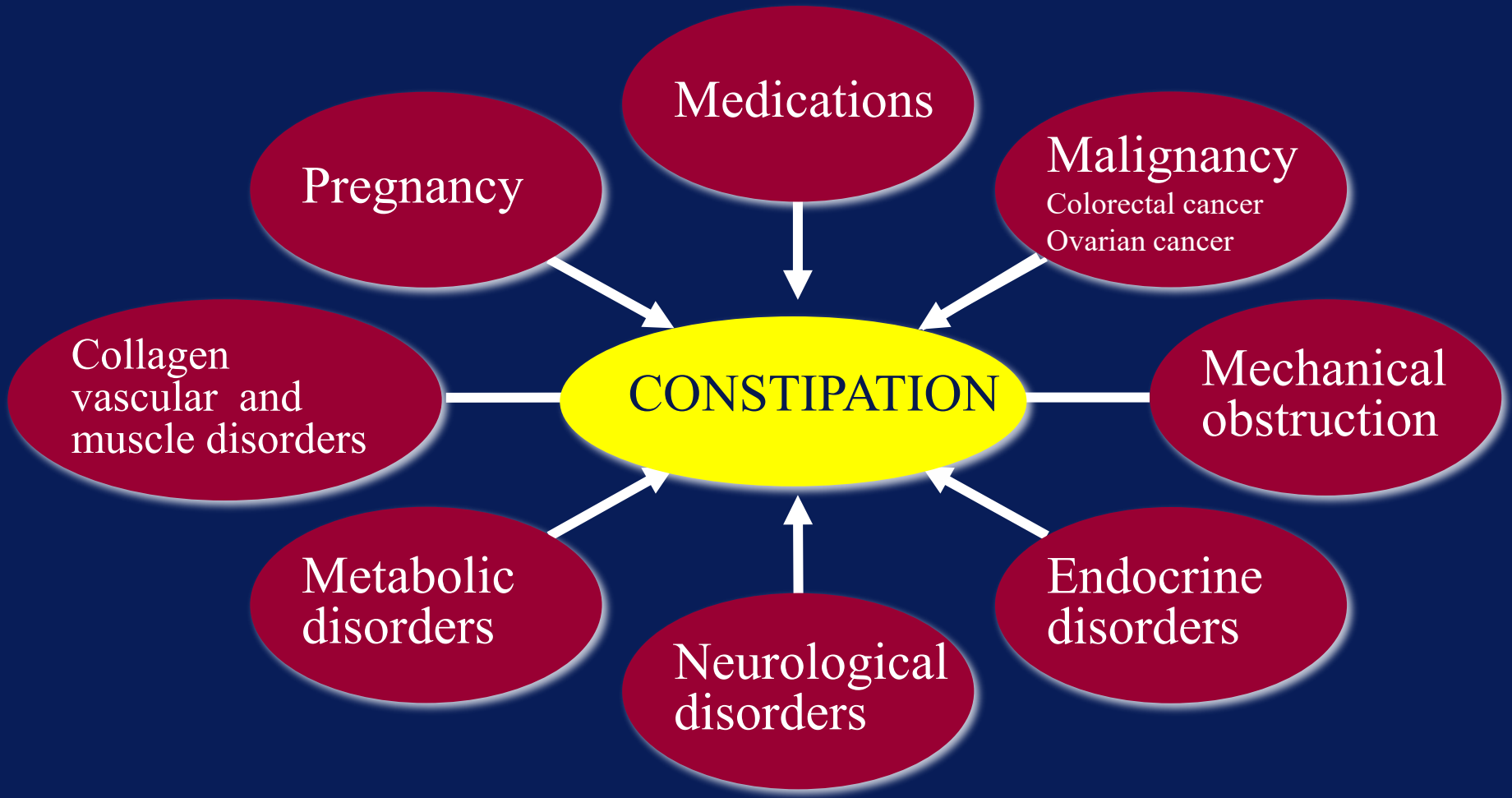
# Primary Constipation: Subtypes




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

Rao et al Nat Rev Gastro 2016
Mertz H, et al. Am J Gastroenterol. 1999;94:609.

# Secondary Causes of Constipation




Rao SSC. Nat Rev . Gastro Hepatol 2016; 13: 295-305

# 52 yr old Dentist, Chronic Constipation

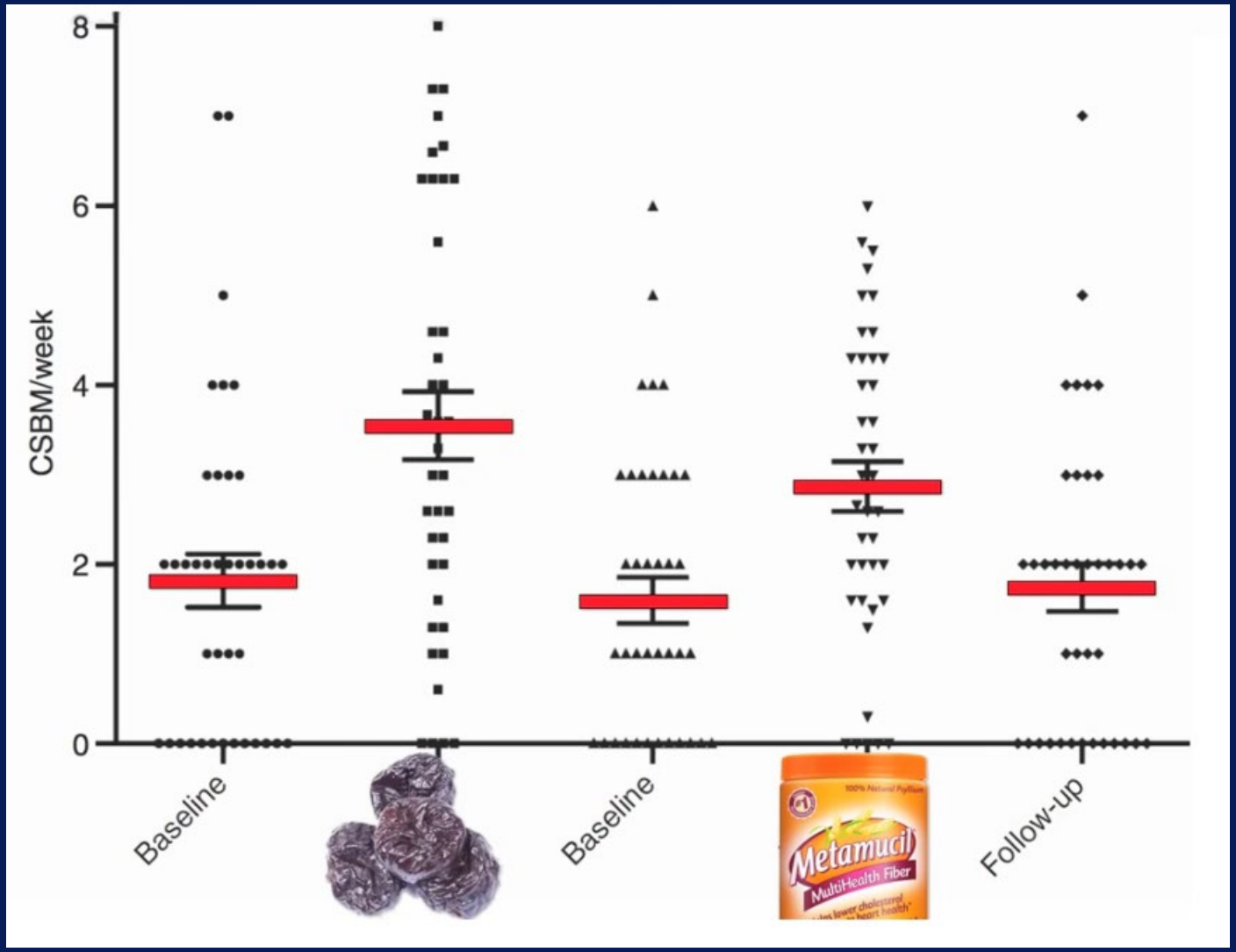
- Meds: Psyllium, Aloe vera, Probiotics
- O/E: General Exam normal, tender LLQ, stool +

## What would you do next?

# 52 yr old Dentist, Constipation- Treatment Plan

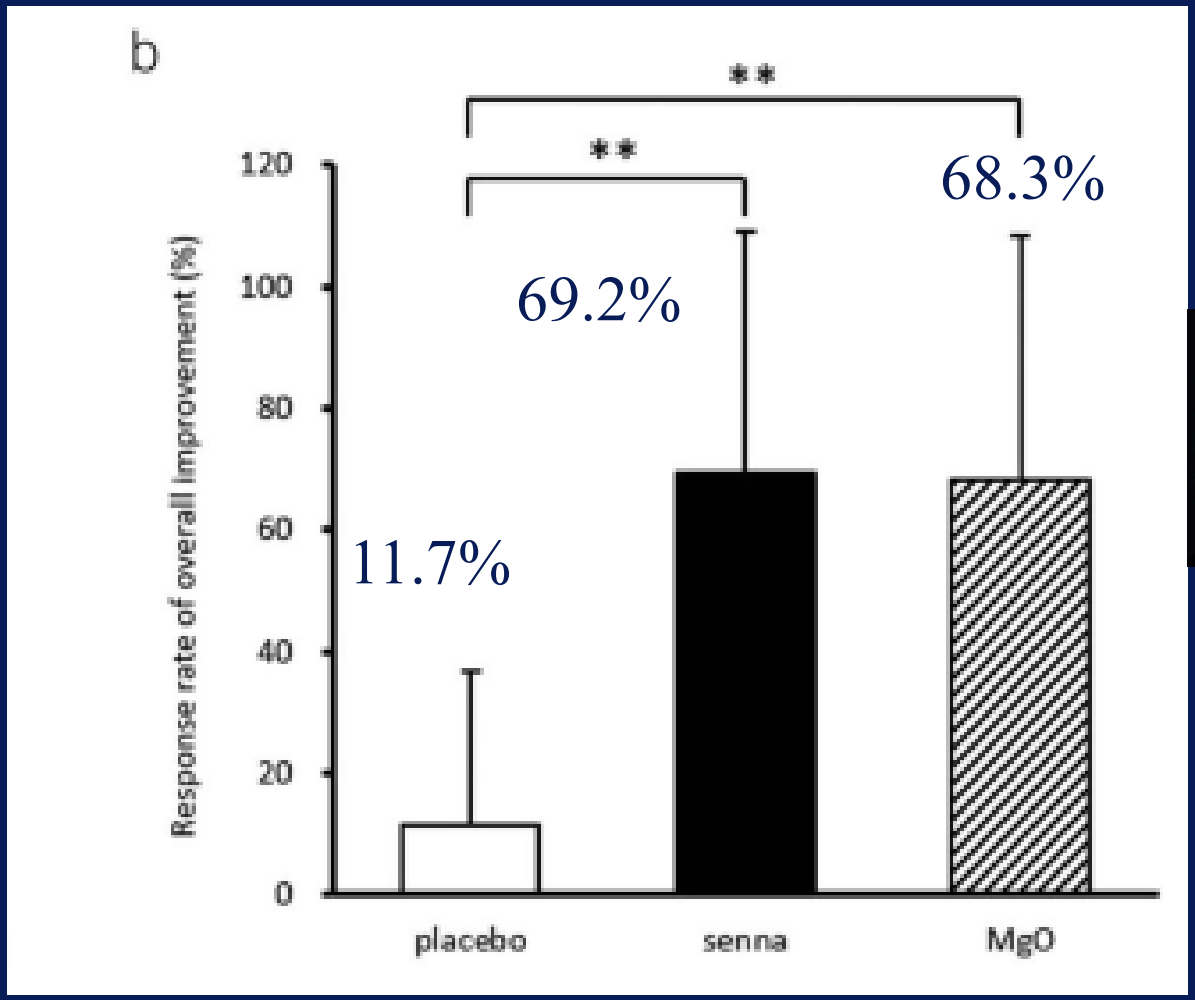
- Habit training
  - Timed toileting & ritualizing bowel habit-am/pm
  - Diaphragmatic breathing, Squatty potty
- Capitalize on physiological stimulants
  - Waking up, Meal (gastrocolonic response), coffee, exercise
- Diet
  - Three meals/day, breakfast most important, Adequate fiber, 20-30 g/day, Gradual increase, fluids
- Fiber supplements
  - Suprafiber, Prunes
- Laxatives: Senna for 4 weeks then titrate need

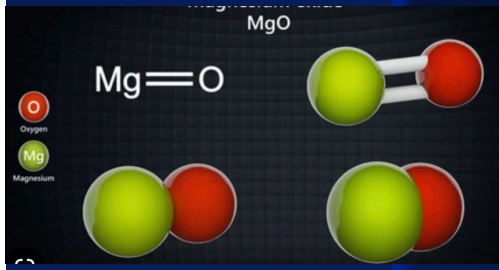
# Dried Plums (prunes) vs Psylium: RCT




Attaluri A, Rao SSC et al Alim Pharmacol Therap 2010

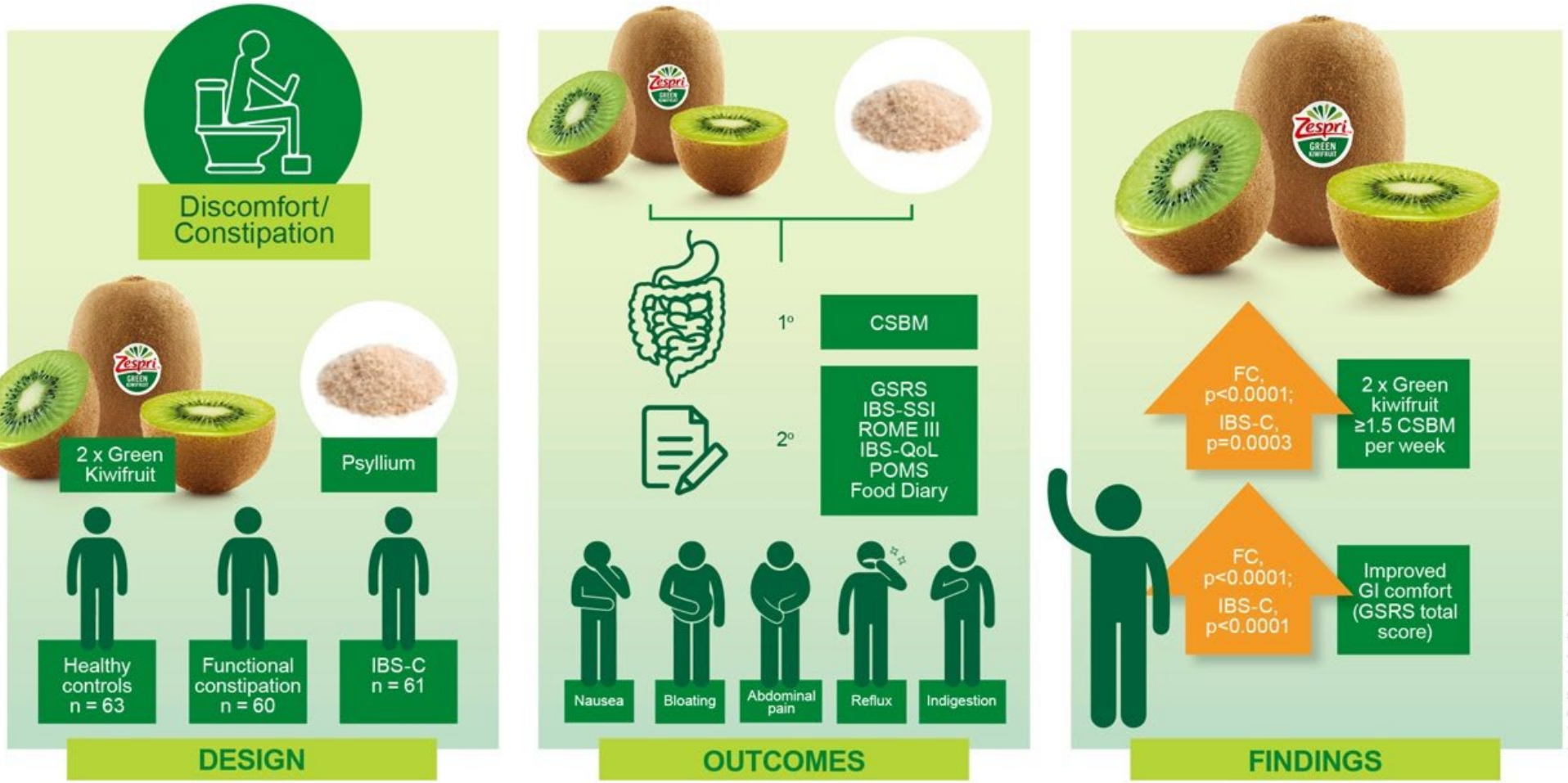
# Efficacy of Senna vs Magnesium vs Placebo, RCT, C.Constipation, n= 90




Morishita D, Miwa H et al Am J Gastroenterol 2021; 116:152-61

# Green kiwifruit improves constipation and gastrointestinal comfort – RCT




Gearry et al. *Am J Gastroenterol.* 2022. doi:10.14309/ajg.0000000000002124

AJG The American Journal of GASTROENTEROLOGY
OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF GASTROENTEROLOGY | ACG

# OTC Therapies for Constipation-2022

| OTC Products | Ramkumar/Rao, 1966-2004 | | Current Review, 2004-2020 | |
|---|---|---|---|---|
| | Level of Evidence | Recommend. Grade | Level of Evidence | Recommend. Grade |
| **Osmotic Laxatives** | | | | |
| PEG | I | A | I | A |
| **Stimulants** | | | | |
| Senna | III | C | I | A |
| Bisacodyl | III | C | I | B |
| Sodium picosulfate | III | C | I | B |
| **Magnesium** | | | | |
| Magnesium hydroxide | III | C | NA | NA |
| Magnesium-rich water | NA | NA | I | B |
| Magnesium oxide | NA | NA | I | B |
| **Fruit-Based Laxatives and Foods with Prebiotics** | | | | |
| Kiwi | NA | NA | I | B |
| Mango | NA | NA | II | B |
| Ficus | NA | NA | II | B |
| Prunes | NA | NA | II | B |
| Rye bread with yogurt | NA | NA | III | C |
| Yogurt+galacto+ prunes + linseed oil | NA | NA | II | B |

Rao SSC, Brenner D. Am J Gastroenterol 2021

# OTC Therapies for Constipation-2022

| OTC Products | Ramkumar/Rao, 1966-2004 | | Current Review, 2004-2020 | |
|---|---|---|---|---|
| | Level of Evidence | Recommend. Grade | Level of Evidence | Recommend. Grade |
| **Fiber-Containing Products** | | | | |
| **Psyllium** | II | B | II | B |
| **Polydextrose** | NA | NA | I | Insufficient |
| **Inulin** | NA | NA | I | Insufficient |
| **Bran, methylcellulose** | III | C | NA | NA |
| **SupraFiber®** | NA | NA | II | B |
| **Miscellaneous** | | | | |
| **Flaxseed oil** | NA | NA | II | C |
| **Fructo-oligosaccharide** | NA | NA | III | Insufficient |
| **Surfactants** | | | | |
| **Docusate** | III | C | NA | NA |

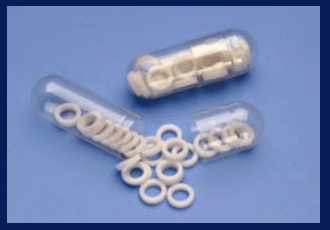
Rao SSC, Brenner D. Am J Gastroenterol 2021; 116: 1156-81

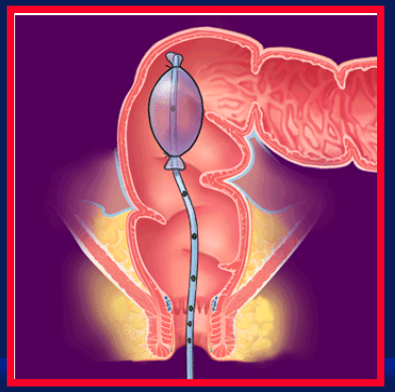
# Case Study
# 31-yr-old school teacher

- Increasing constipation- 9 years
  - B.M once every 2 weeks, hard, pellet-like stool only after Fleet's enema + Suppository and laxatives
  - Frequent digital maneuvers, excessive straining, and incomplete evacuation
  - Tried OTC laxatives, MOM, PEG-no relief
  - DRE: paradoxical anal contraction-?dyssynergia
  - What would you do Next?

# Diagnostic Tools for Constipation

- History
- Stool diary
- Digital Rectal Exam
- Colonoscopy (particularly if aged > 50 years)
- Colonic transit study
  - Radiopaque markers,
  - Scintigraphy
  - Wireless pH/Motility (SmartPill)
- Balloon expulsion test
- Defecography/MRI defecography
- Anorectal manometry
- Colonic manometry

Rao SSC, et al. Am J Gastroenterol. 2005;100:1605.

HOW I APPROACH IT

# Rectal Exam: Yes, it can and should be done in a busy practice!

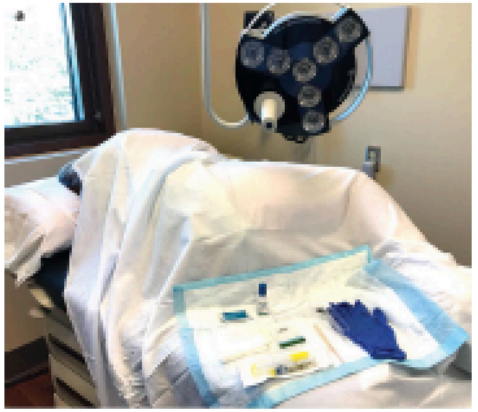
Satish S.C. Rao, MD, PhD, FRCP(LON), FACG, AGAF

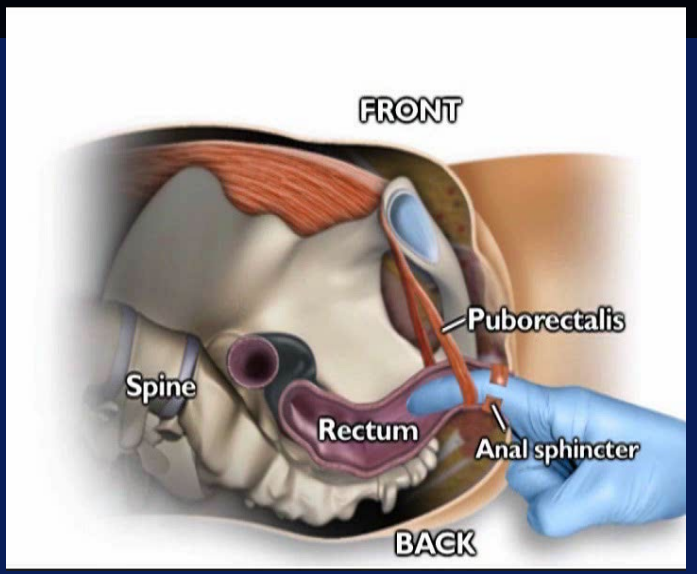
*Am J Gastroenterol* (2018) 113:635–638. https://doi.org/10.1038/s41395-018-0006-y

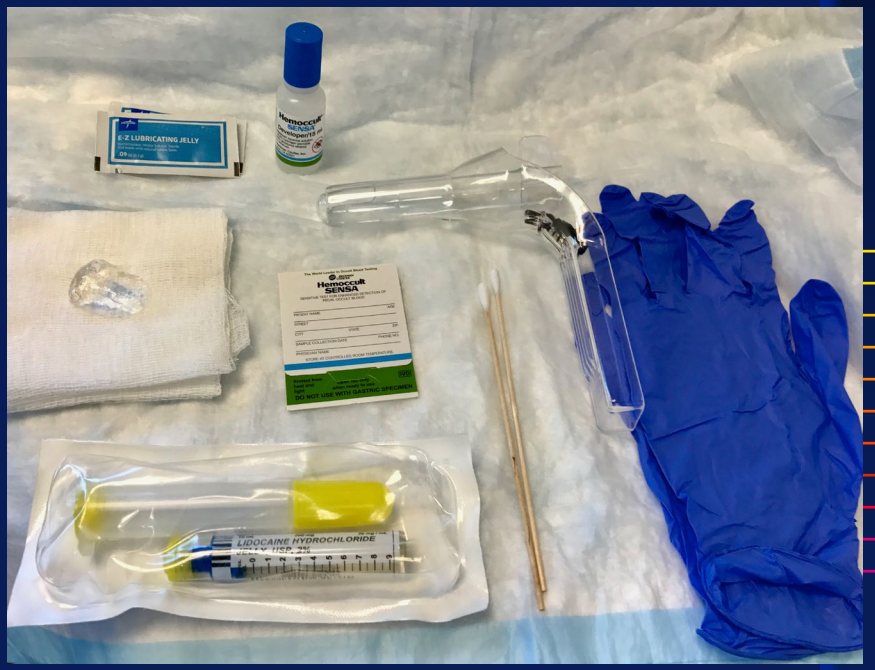
"Dr, I am constipated and feel tied to the bathroom" said Mrs. Smith during an office consultation. "Let's arrange a colonoscopy to check your colon", said her gastroenterologist. At follow-up, "Mrs. Smith, good news, your colonoscopy is normal". "But Dr, I am very constipated". "Well, I suggest you take polyethylene glycol daily". And that was it! 1 year later, she was referred to another specialist, who performed a digital rectal examination (DRE), whose findings (summarized below) changed the course of her management.

Dyssynergic defecation, fecal incontinence (FI), and other anorectal disorders are common problems that affect one third of the US population [1]. DRE is a key component of physical examination [2, 3], but is rarely performed, except for perhaps a cursory exam prior to colonoscopy [4]. This problem is further compounded by a lack of knowledge on how to perform a comprehensive DRE.

A survey of 256 final-year medical students revealed that 17% had never performed a DRE, and 48% were unsure of their find-



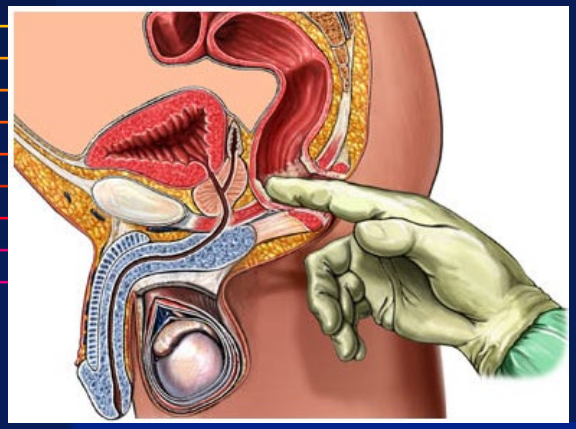



Rao S. Am J Gastroenterol 2018;112:635-38

# 3-step DRE-PROTOCOL

1) **Inspection**
2) **Perianal sensation & anocutaneous reflex:**
   - normal, impaired, absent
3) **Digital maneuvers: mass, tenderness, stool**
   - Squeeze x 2: normal, weak, increased
   - Bearing down x 2
     - push effort, sphincter relaxation, perineal descent



Clinically dyssynergia *if* ... any 2;

- inability to
  - •contract abdominal muscles
  - •relax anal sphincter
- paradoxical contraction of anal sphincter
- absence of perineal descent

*Tantiphlachiva, Rao et al, CGH 2010*

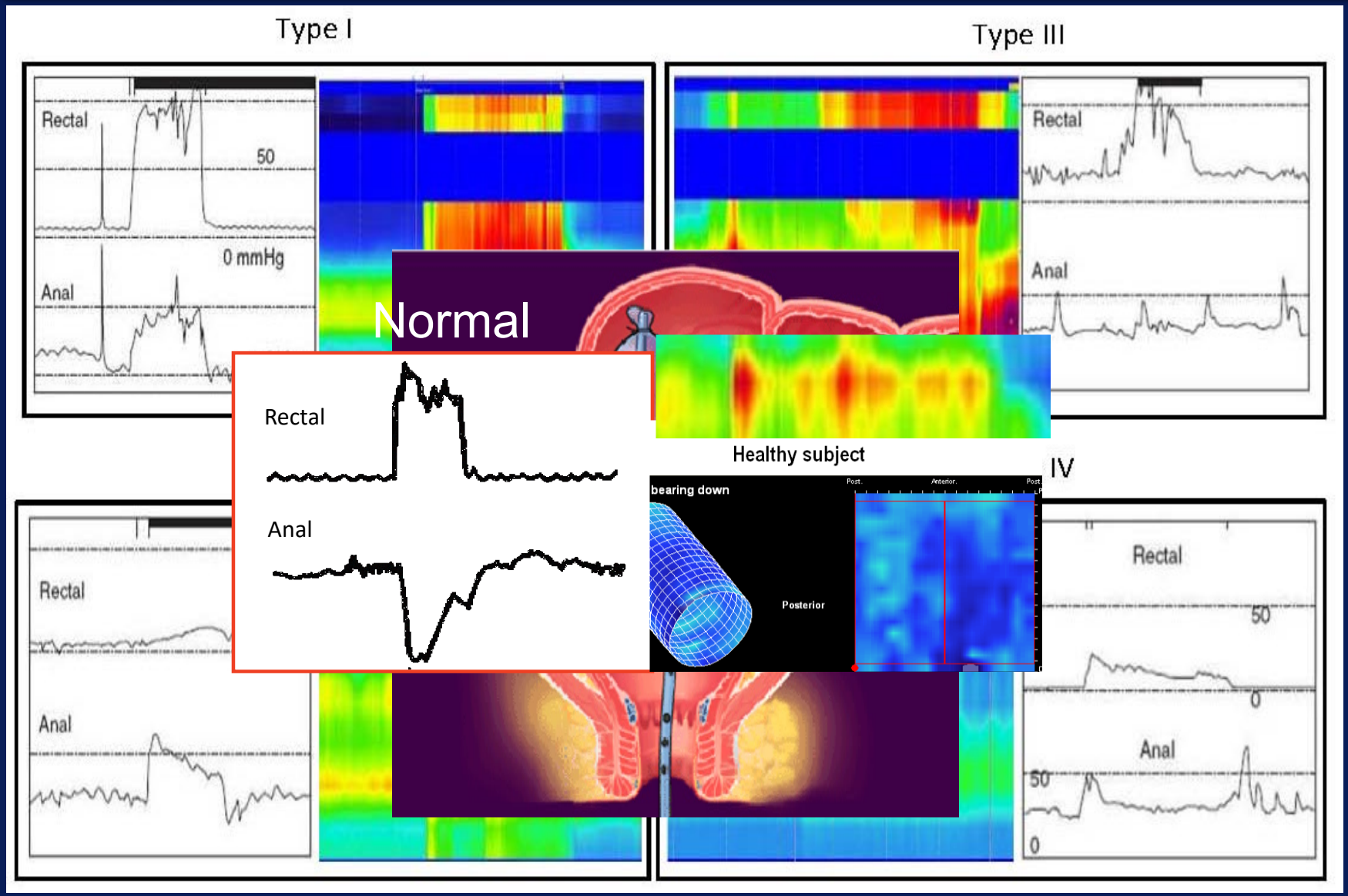
# Yield of rectal exam in dyssynergia, n=209

- All patients had DRE and anorectal manometry and BET

| Parameter | Sensitivity (%) | Specificity (%) |
|---|---|---|
| Dyssynergia from DRE | 75% | 87% |
| Balloon expulsion test | 49 | 90% |

Tantiphlachiva K, Rao P, Attaluri A, Rao S, CGH 2010

# Types of Dyssynergic Defecation




*Rao et al, Neurogastroenterol Motil 2004; 16: 589*

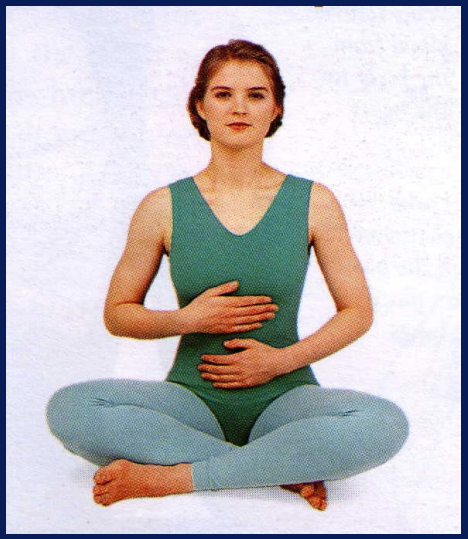
# How to Treat Dyssynergic Defecation ?

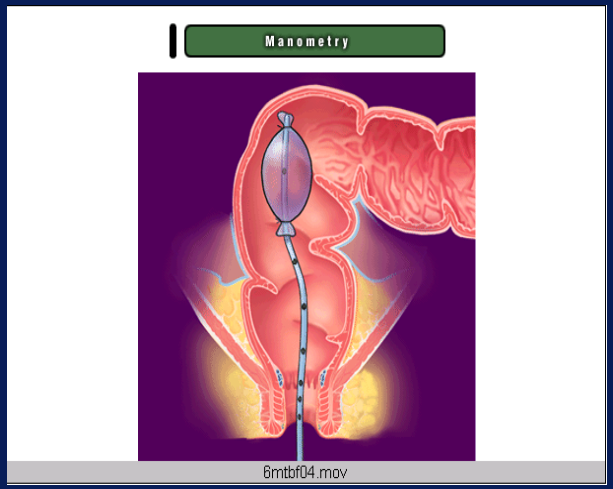
- General Measures
  - Diet, exercise, fluids & habit training
  - Laxatives/Prokinetics
- Specific Treatment
  - Botox injection
  - Biofeedback therapy
  - Cognitive Behavioral Therapy
  - Surgery
    - Myectomy- 30% improvement
    - Colostomy

Rao et al, Gastro Clin N Am 2009

# Biofeedback-Dyssynergia

- **Goals of Therapy :**
  - A) Teach Diaphragmatic breathing exercise
  - B) Teach anal sphincter & pelvic floor relaxation
  - C) Improve Rectal Sensation
  - D) Eliminate Sensory Delay
  - E) Improve Recto-anal Coordination





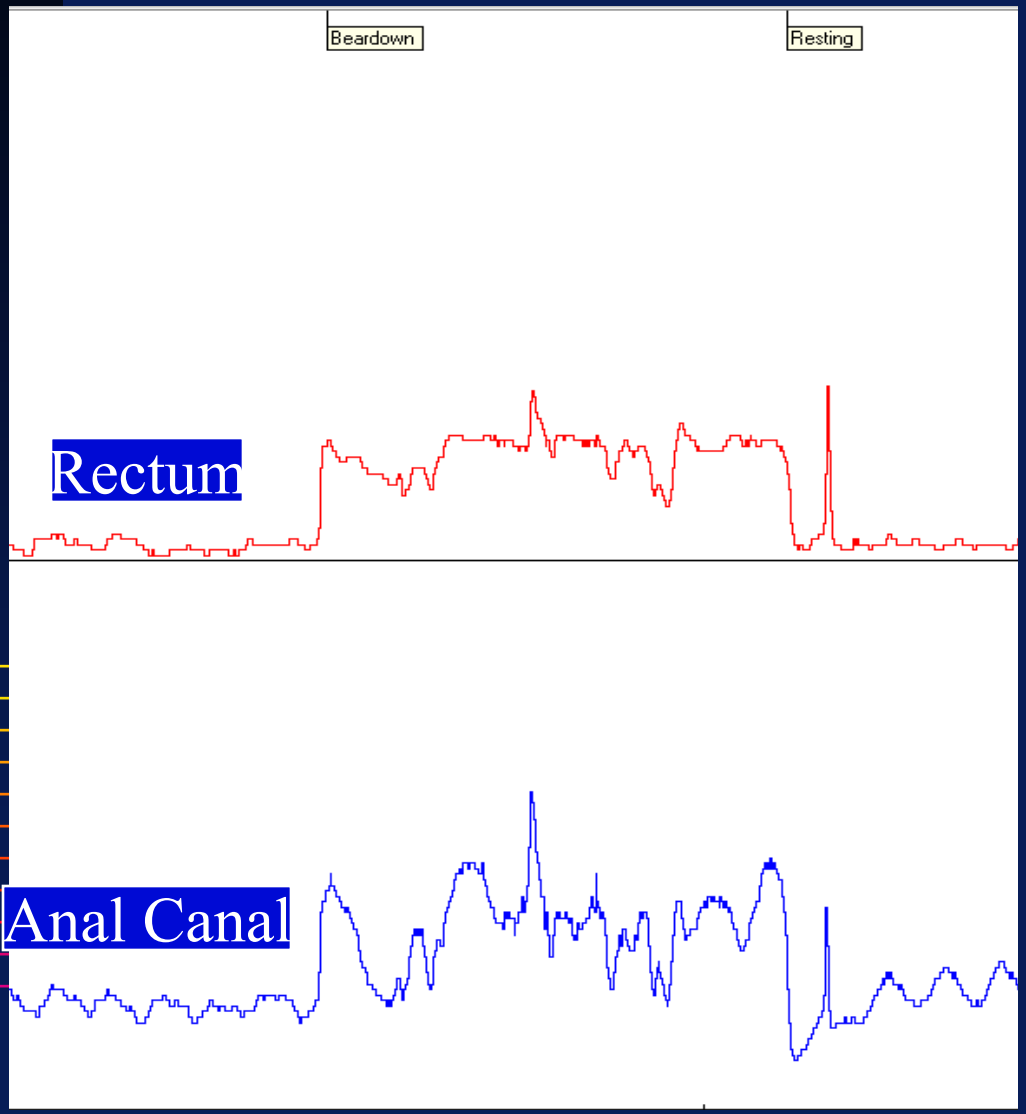

Rao et al, Gastro Clin N Am 2009

# Biofeedback Therapy-RCTs

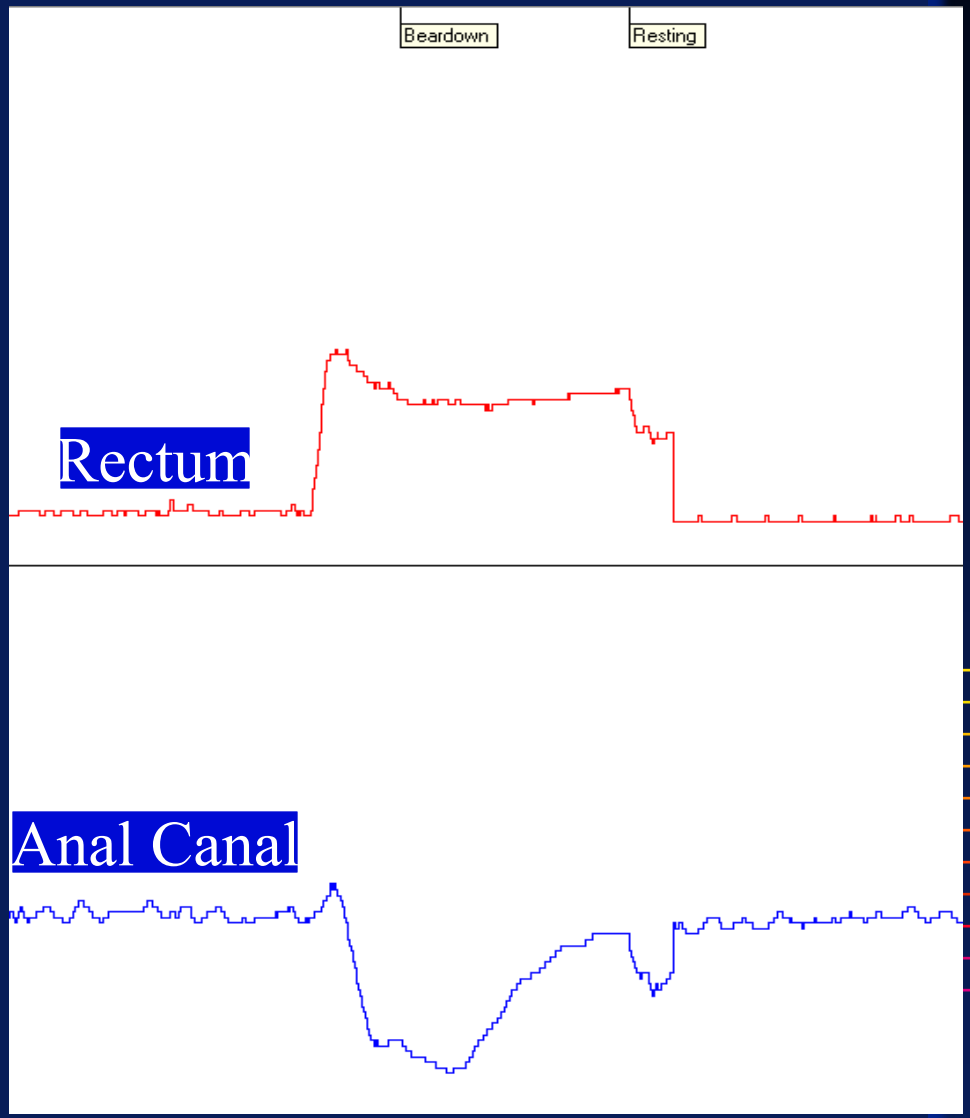
- Biofeedback Vs PEG 14.6 g for Dyssynergia
  - *Chiarioni et al, Gastroenterology 2006; 130: 657-64*
- Biofeedback vs Diazepam for Dyssynergia
  - Heymen et al, Dis Col Rectum 2007
- Biofeedback vs Sham Therapy vs Standard Therapy
  - *Rao et al CGH 2007*
- Biofeedback vs Standard Therapy-One Year outcome
  - *Rao et al Am J Gastroenterol 2010*
- *Home vs Office Biofeedback Therapy-Efficacy & Cost Effectiveness*
  - *Rao et al, Go et al, DDW 2011*

# Dyssynergic Defecation-Effects of Biofeedback

## BEFORE

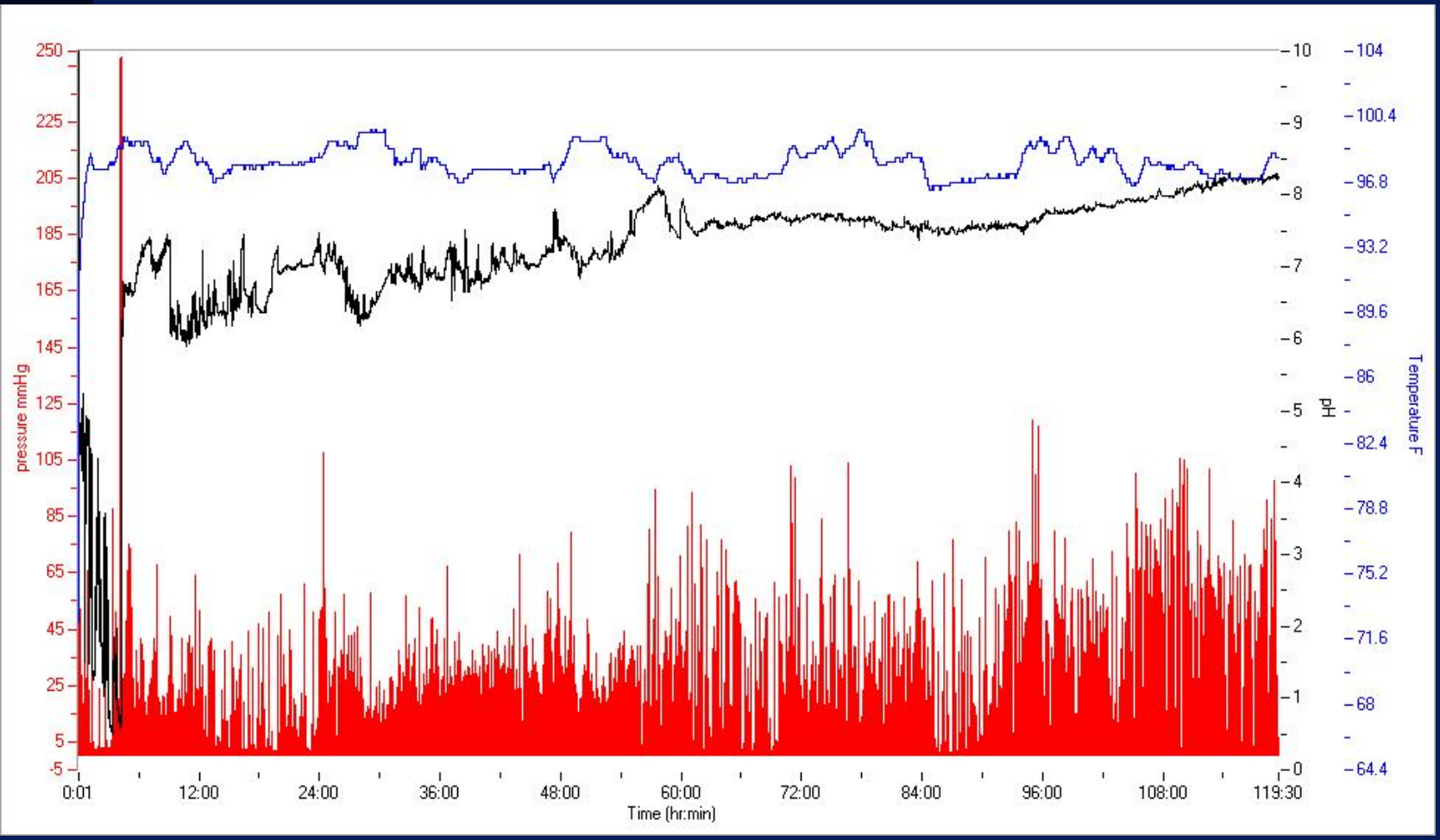


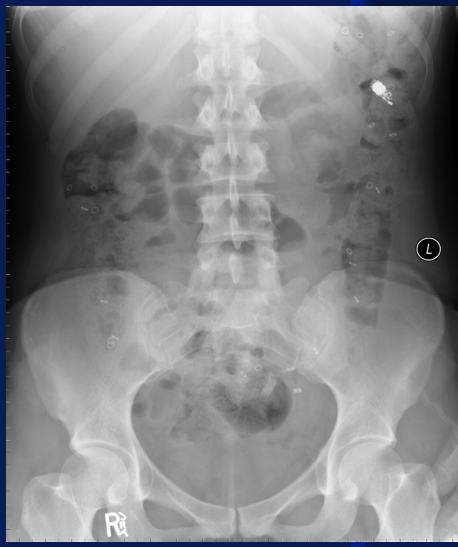

## AFTER




Courtesy of Rao SS

# 40 yr old Nurse, Severe Constipation, pain, gas & bloating- worse 2 yrs, On depo Provera Refractory to laxatives; ? Colectomy

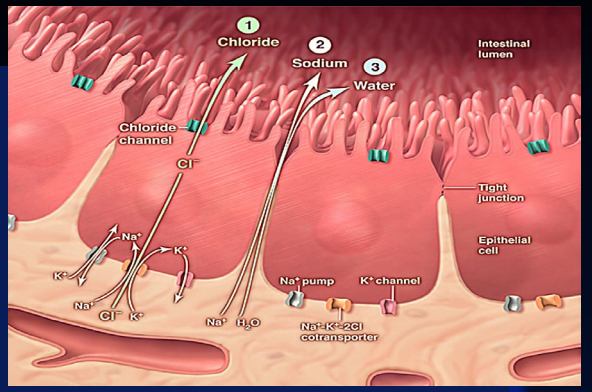


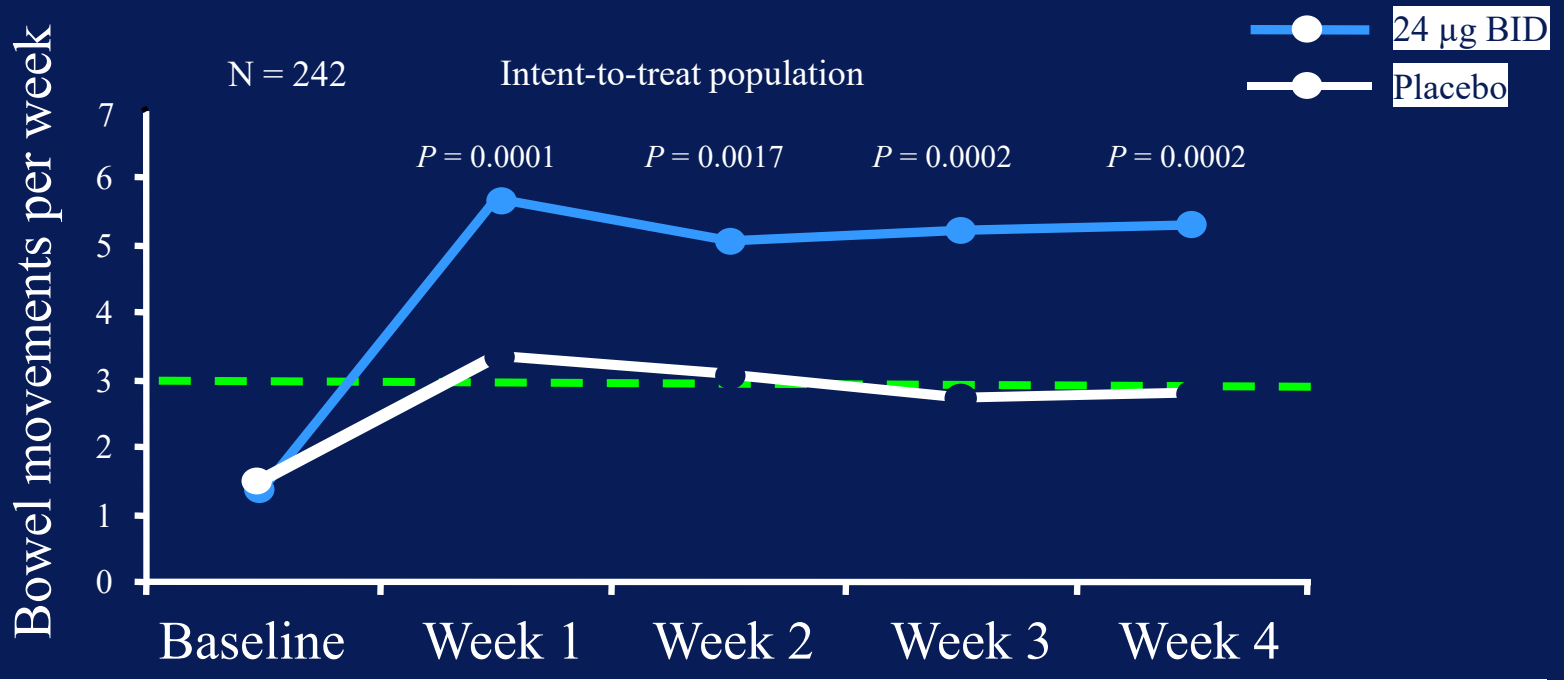



# Wireless Motility capsule Test

| | Subject | Normal Range |
|---|---|---|
| Gastric Emptying Time | 6 hrs 32 mins | 2.4- 5 hours |
| Small Bowel Transit Time | 5 hrs 23 mins | 3-6 hours |
| Colonic Transit Time | >111hours | 17-59 hours |
| Whole Gut Transit Time | >122 hours | 26-71 hours |

# Effects of Lubiprostone on Number of Spontaneous Bowel Movements



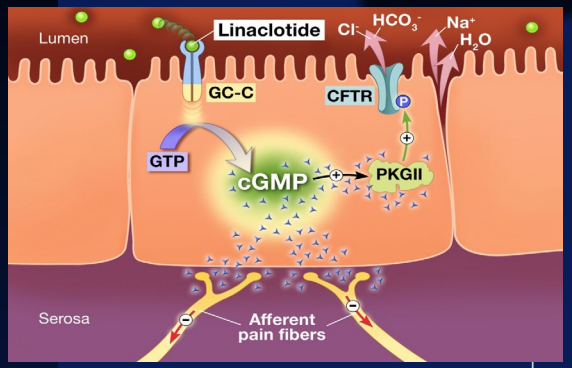




- Onset of action was within 24 hours in the majority of subjects
- Most common adverse events were nausea, diarrhea, and headache
- 9 subjects taking lubiprostone withdrew due to adverse events

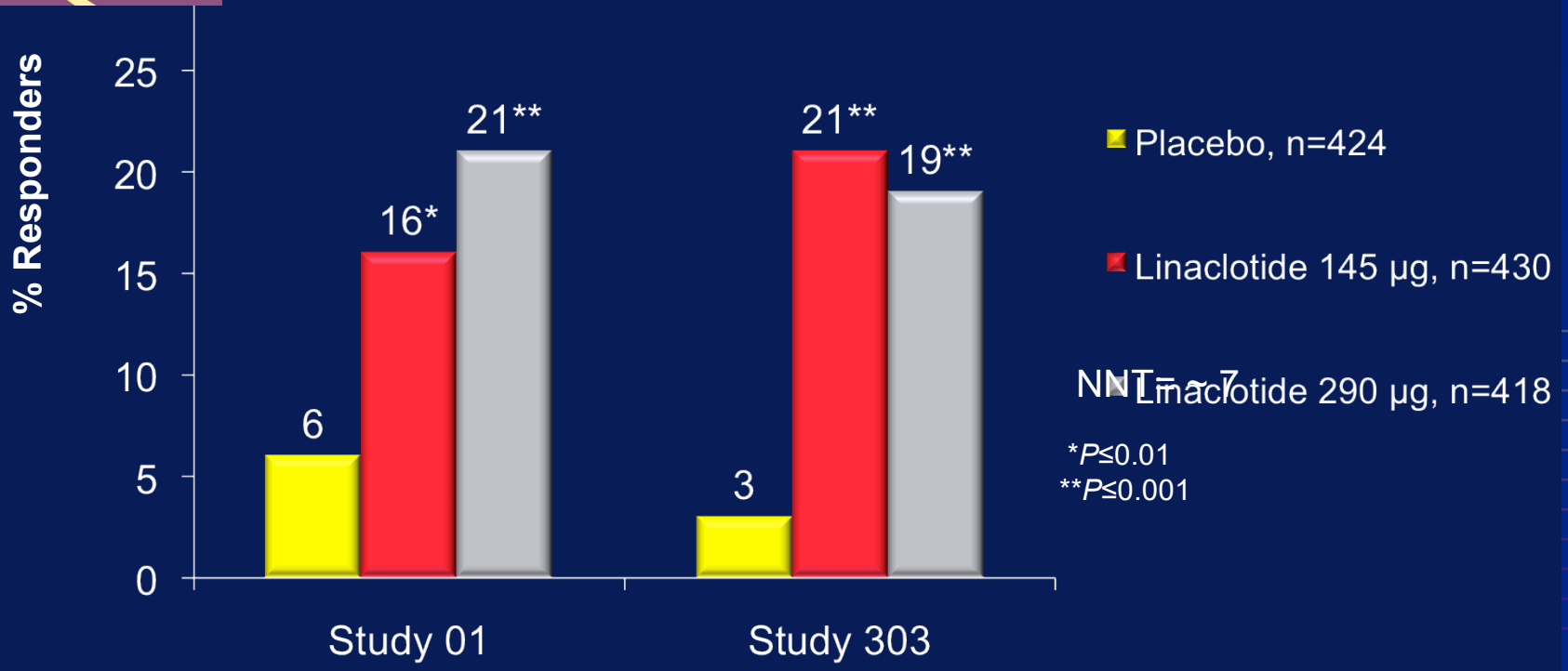
N = 242

*Johanssen et al Am J Gastroenterol* 2008;103:170-7.

# Efficacy of Linaclotide in Chronic Constipation




**Responder: ≥3 CSBM/wk & Increase of ≥1 CSBM/wk for ≥9/12 wks**




NNT = ~7

*$P \leq 0.01$
**$P \leq 0.001$

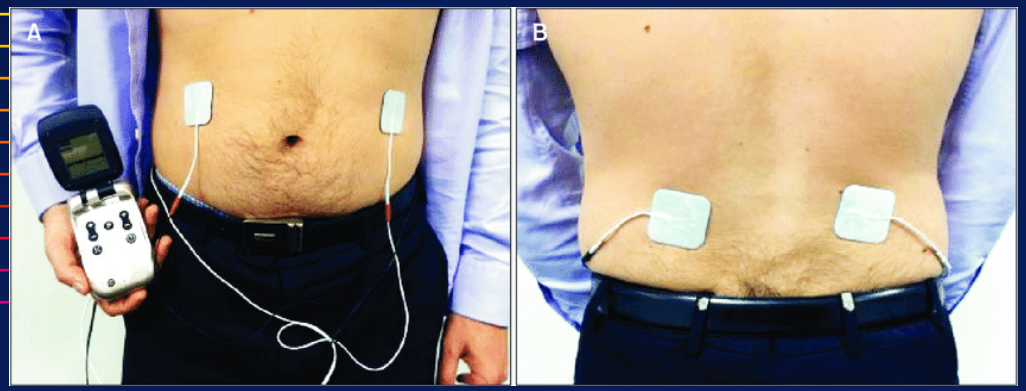
Most common AE diarrhea (14%-16% vs 4.7%);
Discontinuation (4% vs 0.5%).

CSBM=complete spontaneous bowel movement.

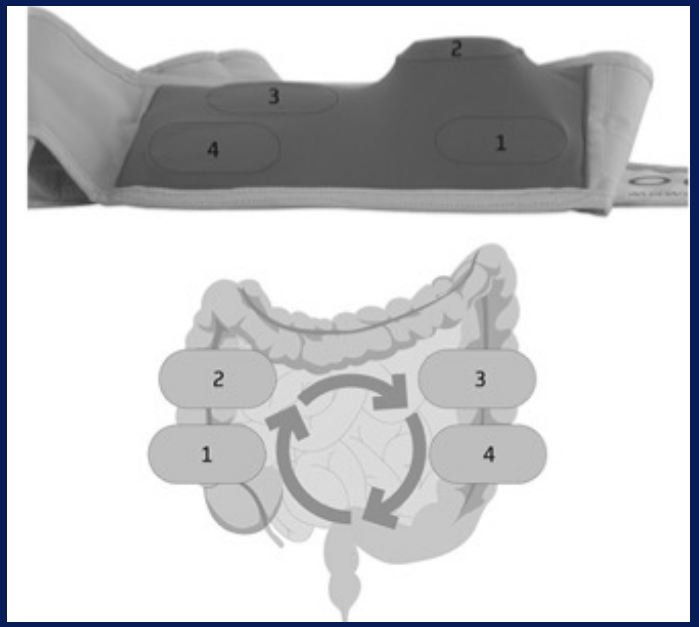
Lembo AJ, et al. *N Engl J Med*. 2011;365:527-536.

# Novel Constipation Device Therapies






Abdominal Interferential Therapy




*Intestinal Colonic Exoperistalsis*

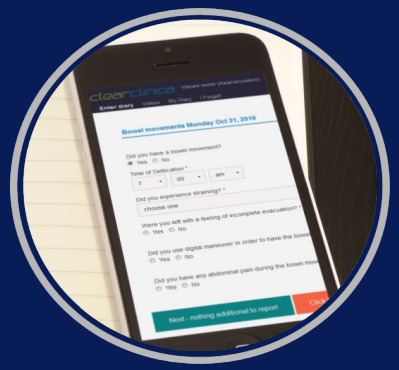
# Vibrating Capsule for Chronic Constipation

**Vibration Capsule Program**
Two Stimulation Cycles, each ~ 2 hours:
Each Vibration cycle: 3 seconds on and 16s rest

**Vibrating capsule**

**Activation POD:**

- **Used for activating the capsule**




**E-Diary: Patient Reporting APP**

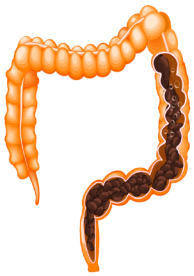
- Daily stool data
- Symptoms
- Capsule ingestion information
- Compliance
- Rescue
- Adverse Events

Rao SSC, et al. *Gastroenterology 2023;164:1202-10.*

# Efficacy of Vibrating Capsule

## Vibrating Capsule Treatment for Chronic Constipation

Phase 3, Double Blind, Multicenter, Placebo controlled trial



312 patients with Chronic Constipation

Randomized

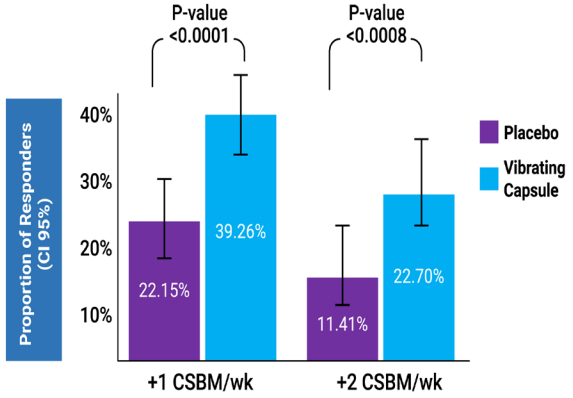
Vibrating Capsule, n=163

Placebo Capsule, n=149

- Patients ingested one capsule at bedtime daily for 5 days a week
- Duration of study= 8 weeks

**Primary Outcome Measures:** Increase in one or more or two or more complete spontaneous bowel movements (CSBM) per week over baseline in 6 out of 8 weeks

**Effect of Vibrating Capsule on CSBM, Primary Outcomes**



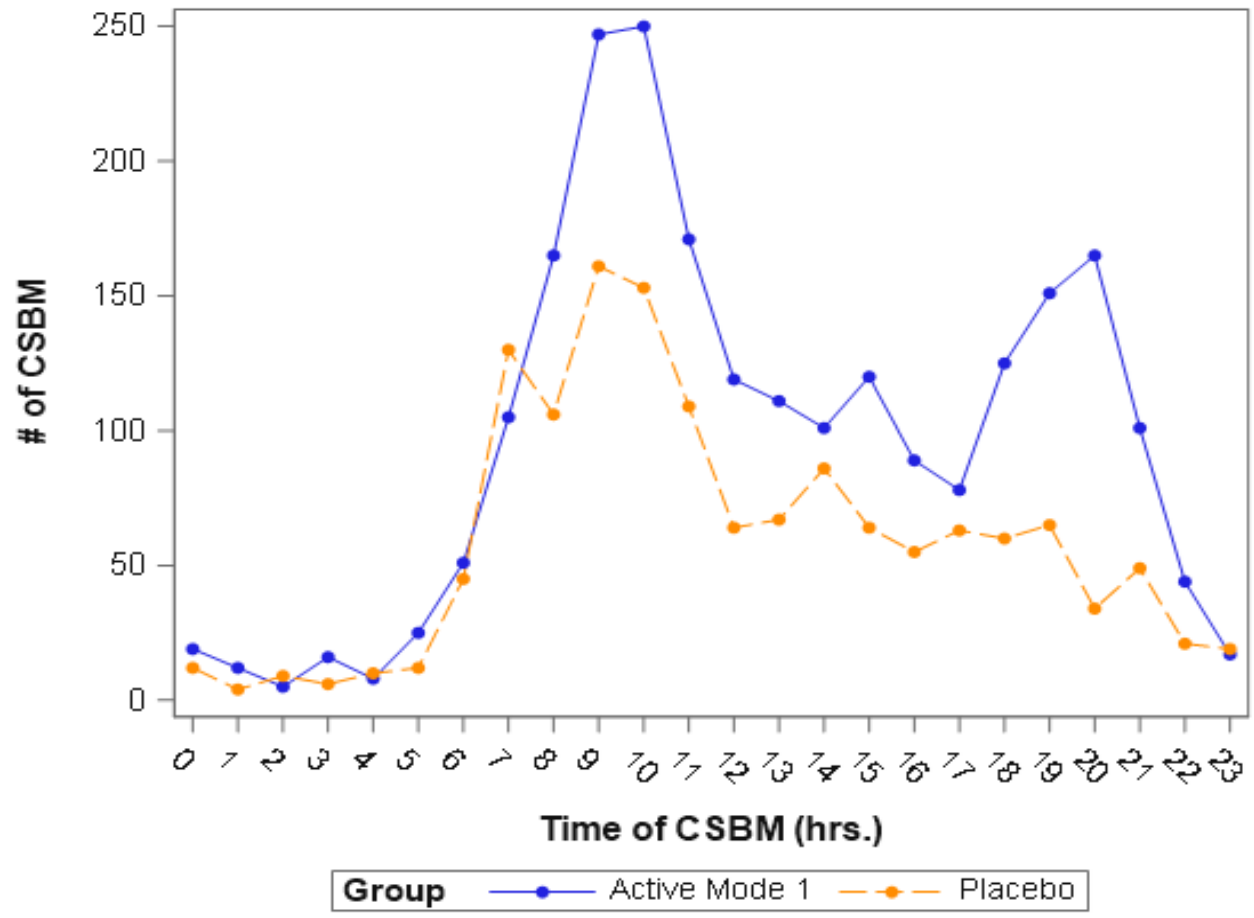

Incremental CSBM (Complete Spontaneous Bowel Movement)

Vibrating Capsule was superior to Placebo capsule in improving constipation symptoms and quality of life, and was safe and well tolerated

Gastroenterology

Rao SSC, et al. *Gastroenterology 2023;164:1202-10*

# Vibrating Capsule Enhances circadian rhythm
# Distribution of CSBMs Over 24h During 8-week Phase III Trial: Severe Constipation




Lembo A, Rao SSC, et al. DDW 2023

# 40 yr old Nurse, Severe Constipation MANAGEMENT

- Lactose exclusion diet
- Reassure- evidence of colonic myopathy but no neuropathy, mild generalized dysmotility
- Explain Slow Transit Constipation
- Life style + Behavioral + Diet
- D/C Depo Provera
- Vibrating Capsule 5 caps/week
- F.up 6 weeks- BM every 2-3 days, Type 4 stool

# Take Home Points- Generalist


- Chronic constipation involves multiple overlapping subtypes
- Detailed History, Physical & DRE important
- DRE is a useful bedside clinical tool
- Dyssynergic defecation is common
- Prunes, Suprafiber effective in mild constipation

Rao S et al Nature Revs 2016  Curtin B, Rao S et al JNM 2020

# Take Home Points- Specialist

- Investigation is key:
  - Colonic Transit, WMC, ARM, defecography, Colonic manometry are complementary & helpful
- Recognize comorbid illnesses, Burden & QOL
- Therapeutic options will depend on a clear understanding of pathophysiology
  - STC/CIC: Vibrating Capsule, Lubiprostone, Linaclotide, Prucalopride
  - OIC: Naloxegol, Methyl naltrexone
  - Dyssynergic Defecation: Biofeedback therapy