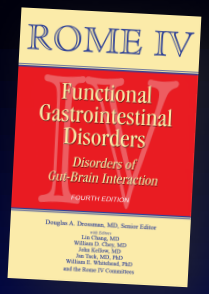
IBS: overview and assessment of pain outcomes and implications for inclusion criteria

William D. Chey, MD
Professor of Medicine
University of Michigan

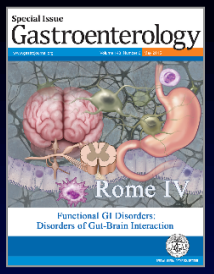
What is the Irritable Bowel Syndrome

- Symptom based condition defined by the presence of abdominal pain and altered defecation
- Affects 7-15% of adults
- Reduced quality of life and work productivity
- Increased heath care costs
  - Visits, tests, treatments, and surgeries
  - Up to $20 billion in annual direct and indirect costs

Chey et al, JAMA 2015;313:949



IBS: Rome IV Criteria*



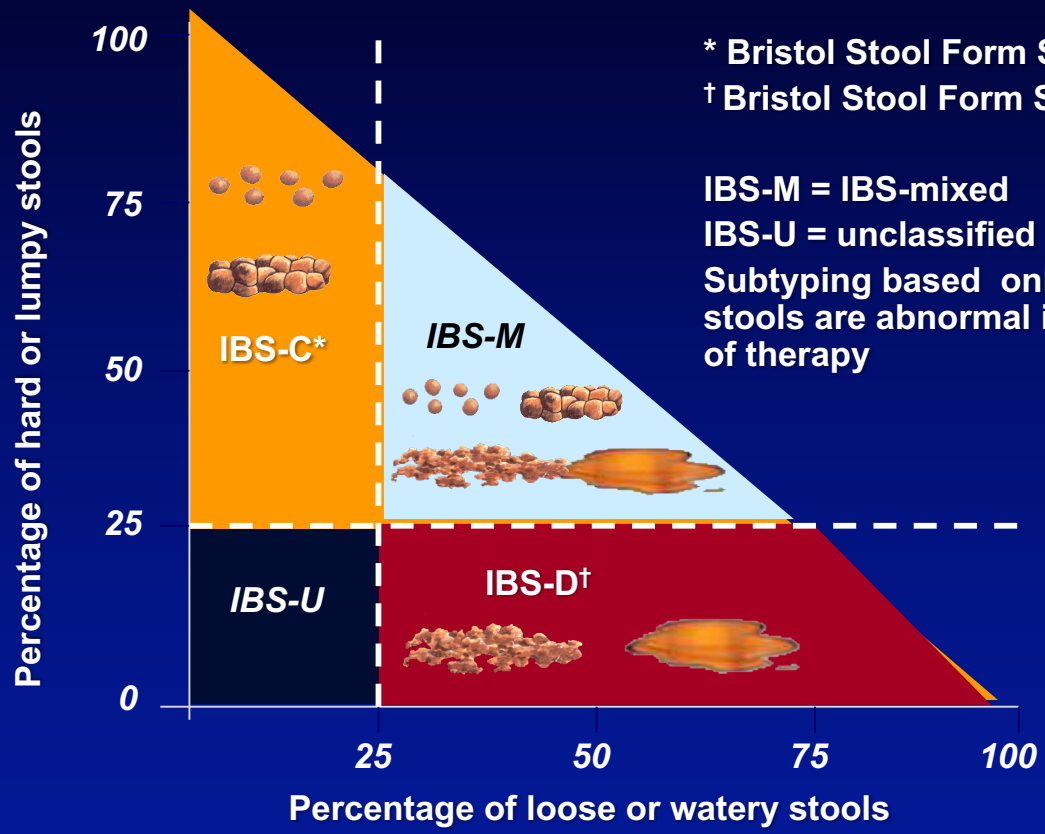
Recurrent abdominal pain 1 day per week associated with two or more of the following:

- **Related to defecation**
- **Onset associated with a change in the frequency of stool**
- **Onset associated with a change in the form of stool**

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

Mearin et al, Gastroenterol May 2016

IBS Subtypes Are Based on Stool Consistency



* Bristol Stool Form Scale 1-2

† Bristol Stool Form Scale 6-7

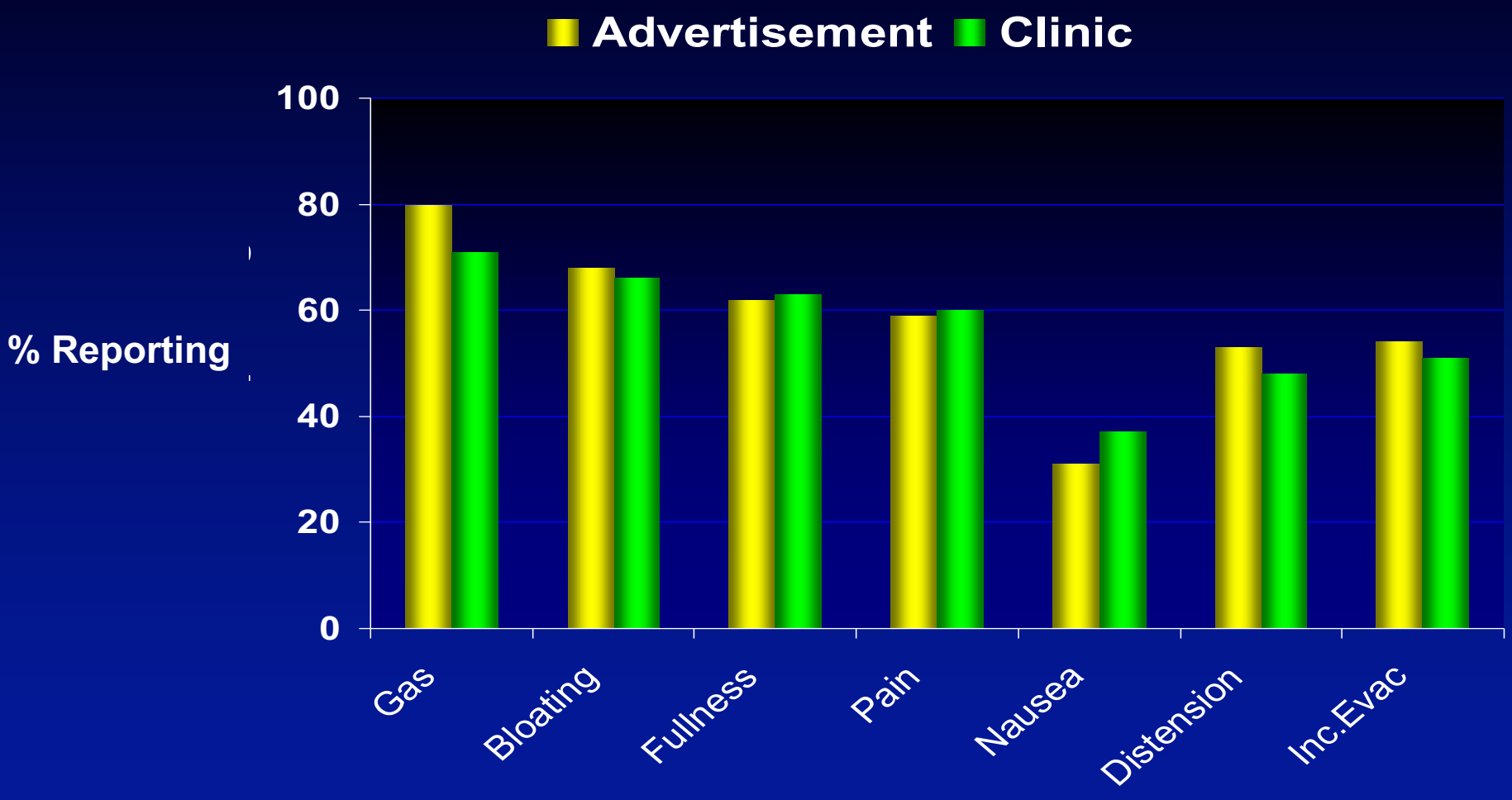
IBS-M = IBS-mixed

IBS-U = unclassified IBS

Subtyping based only on when stools are abnormal in the absence of therapy

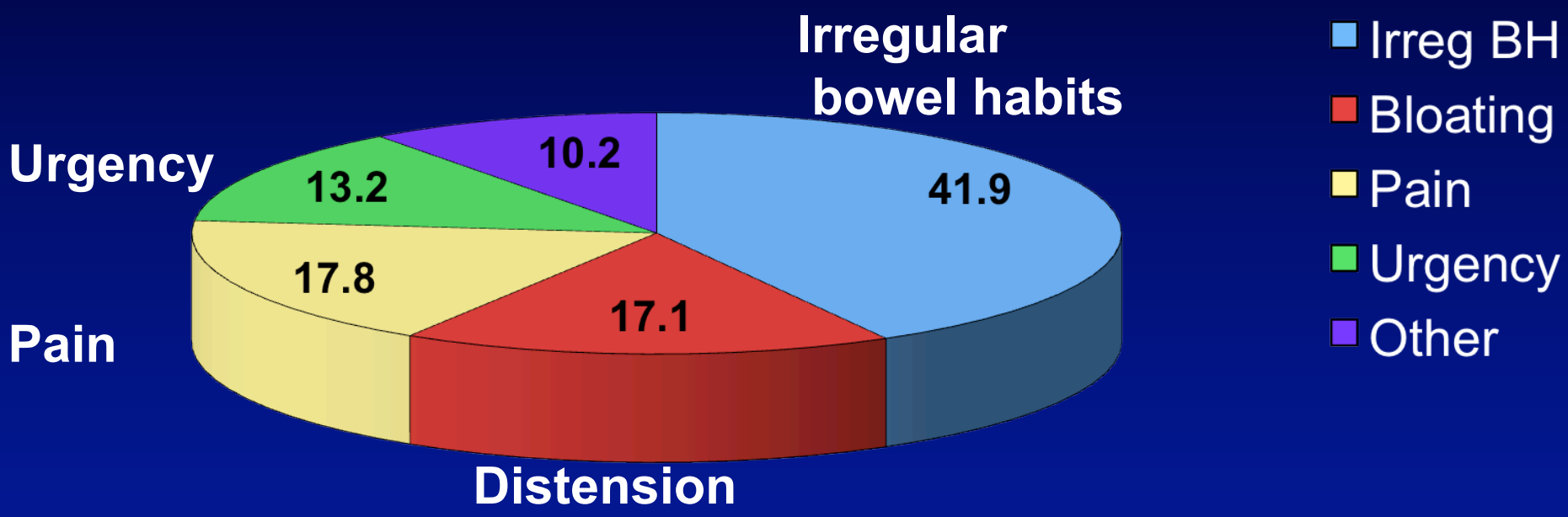
Mearin et al. Gastroenterology. May 2016

Multiple Symptoms Reported by IBS Patients



Lee OY et al. Aliment Pharmacol Ther 2000;13:1631-1638

IBS: Most Bothersome Symptoms



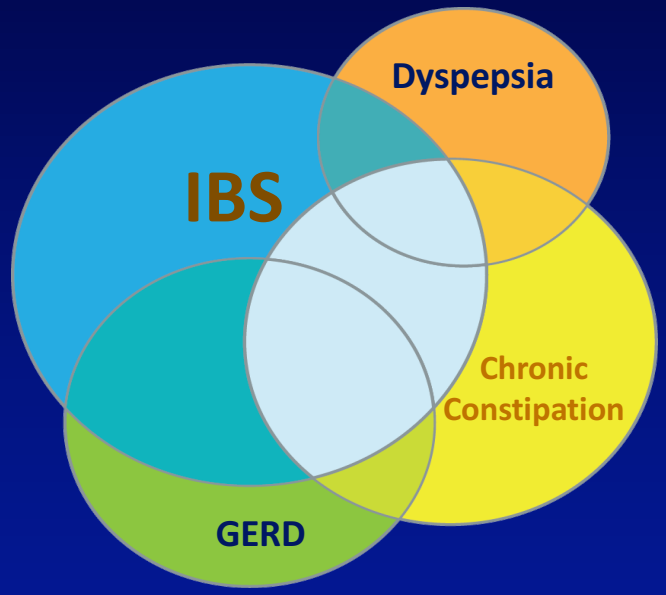
Difficulties in Diagnosing IBS

Common Comorbidities in IBS[1,2]

- Major depression
- Fibromyalgia
- Chronic fatigue syndrome
- Anxiety
- TMJ disorder
- Chronic pelvic pain
- Painful bladder syndrome/ interstitial cystitis
- Somatoform disorders

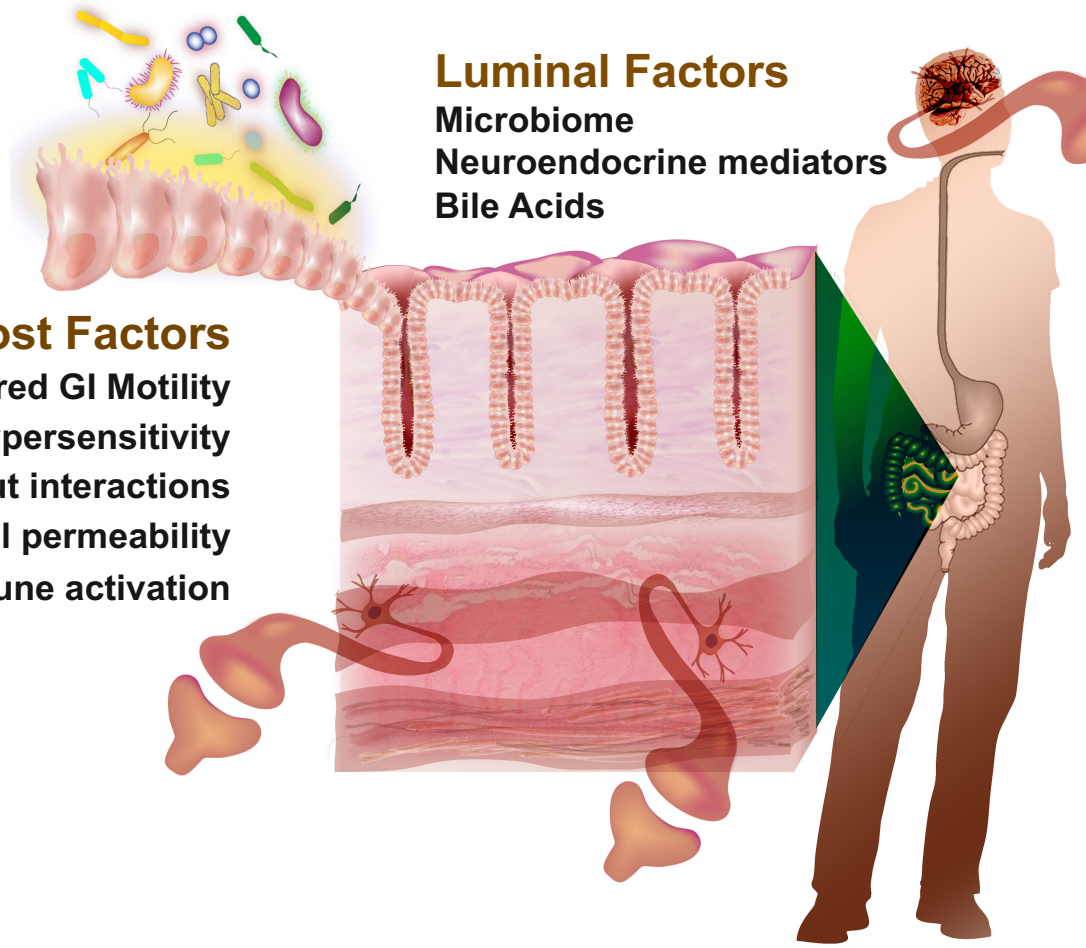
GERD=gastroesophageal reflux disease; IBD=inflammatory bowel disease; TMJ=temporomandibular joint .

IBS and Symptom Overlap[3]



1. Whitehead WE, et al. *Gastroenterology*. 2002;122:1140-1156.
2. Levy RL, et al. *Gastroenterology*. 2006;130:1447-1458.
3. Frissora CL, Koch KL. *Curr Gastroenterol Rep*. 2005;7:264-271.

Overview of IBS Pathophysiology



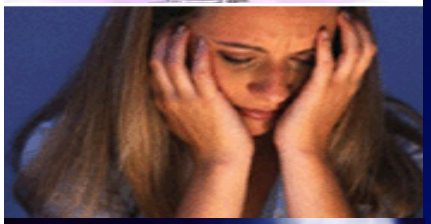
Luminal Factors
Microbiome
Neuroendocrine mediators
Bile Acids

Host Factors
Altered GI Motility
Visceral hypersensitivity
Altered brain-gut interactions
Increased intestinal permeability
Gut mucosal immune activation

Environmental Factors
Psychosocial distress
Food
Antibiotics
Enteric infection

Chey WD, et al. *JAMA*. 2015;313(9):949-958.





IBS Pain is Multi-Dimensional

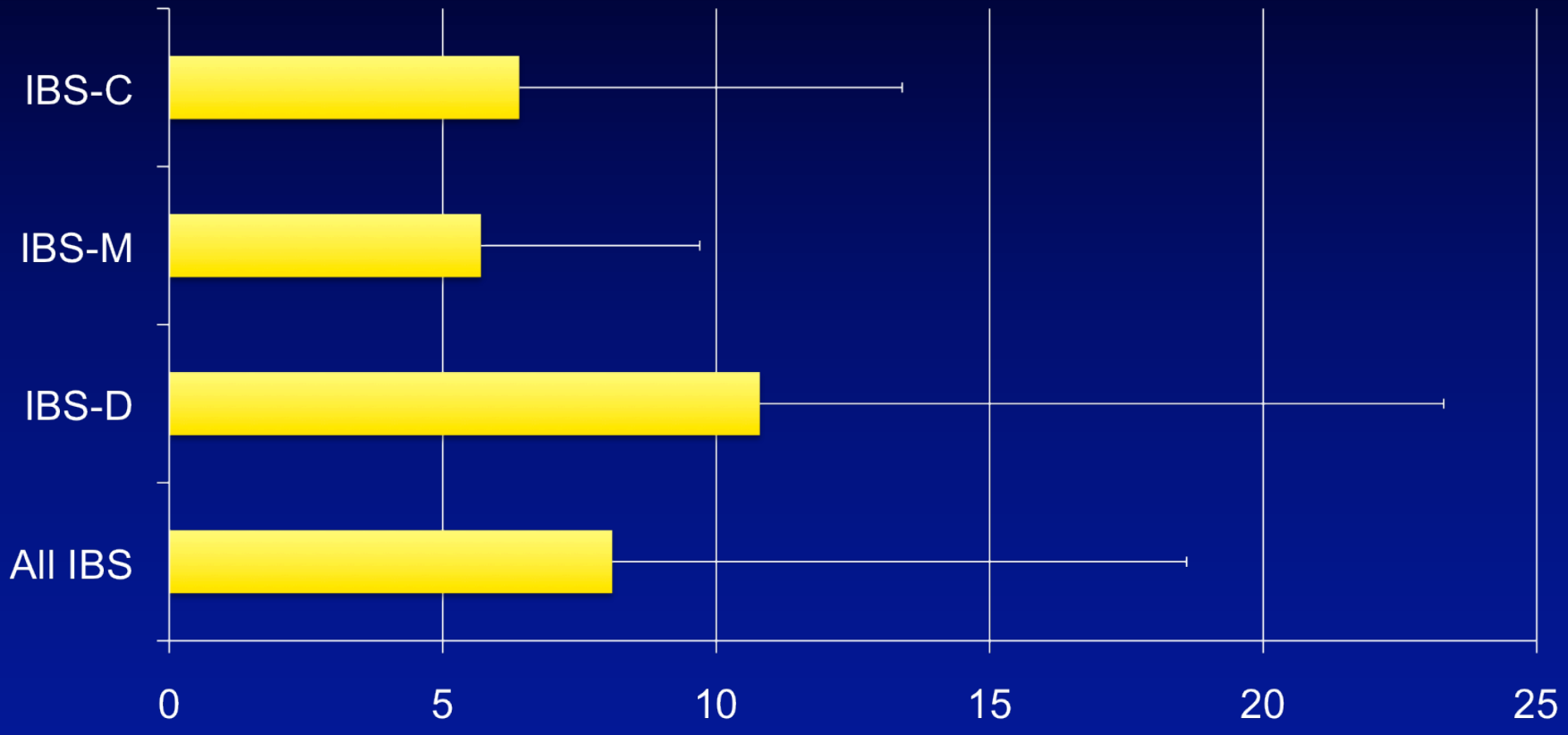
- IBS pain is complex and multifaceted – not a unidimensional symptom
  - Pain is typically measured by intensity alone
- Intensity is predictive of IBS severity, but less is known about the incremental value of other dimensions:
  - Frequency, duration, bothersomeness, predictability, speed of onset
- Understanding the impact of different pain dimensions is important:

  … to guide PRO development for future clinical trials

  … to define inclusion criteria for these trials in the first place.

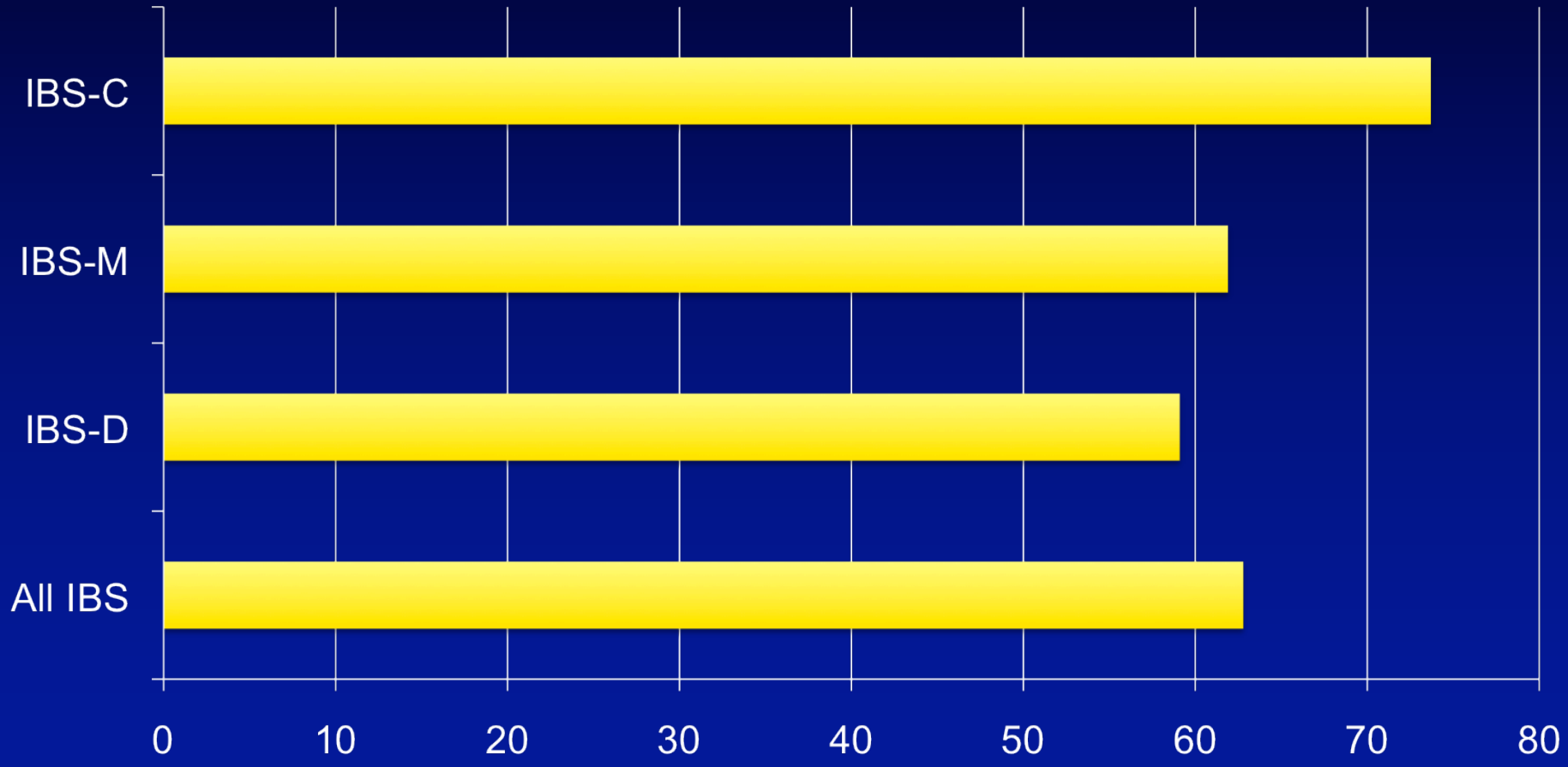
Lembo A, et al *CGH* 2005;3:717
Spiegel et al. *APT* 2009;30:1159

Mean Frequency of Pain Attacks in IBS

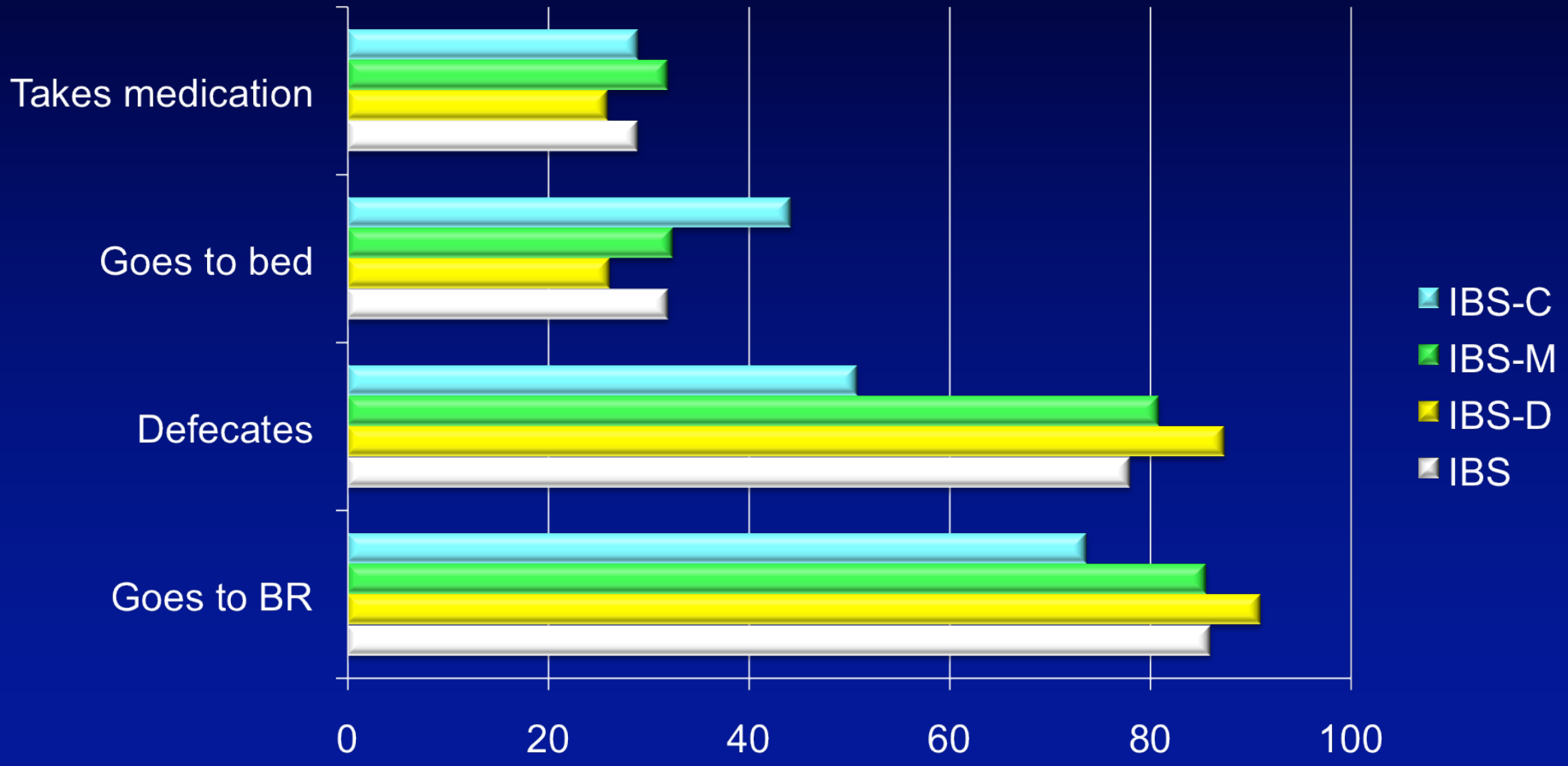


Mean pain intensity at the start of the attack was 6.9±1.4 (0-10 scale)

Proportion of Pain Attacks Interfering with Work and Daily Activities



Behaviors during Pain Attacks



Abdominal pain severity, bothersomeness, and frequency stratified by IBS subtypes

	IBS with diarrhea (n=245)	IBS with constipation (n=232)	Mixed-type IBS (n=681)
Abdominal pain GI PROMIS® score, 0 to 100 [b]	68.3 ± 25.8 (reference)	75.9 ± 20.9 (p<0.001 vs IBS-D)	70.8 ± 25.0 (p=0.16 vs IBS-D)
Abdominal pain severity rating at its worst, 5-point Likert scale (0=not bad at all; 4=very bad) [b]	2.3 ± 1.0 (reference)	2.5 ± 0.9 (p=0.07 vs IBS-D)	2.4 ± 1.0 (p=0.38 vs IBS-D)
Abdominal pain bothersomeness, 5-point Likert scale (0=not at all; 4=very much) [b]	2.4 ± 1.0 (reference)	2.7 ± 0.9 (p=0.001 vs IBS-D)	2.5 ± 1.0 (p=0.22 vs IBS-D)
Abdominal pain frequency, 5-point Likert scale (0=never; 4=always) [b]	2.6 ± 0.8 (reference)	2.8 ± 0.8 (p=0.047 vs IBS-D)	2.5 ± 0.8 (p=0.10 vs IBS-D)

National GI Survey using *My GI Health* platform

Shah, Chey et al DDW 2017

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Example 11-Point Pain NRS

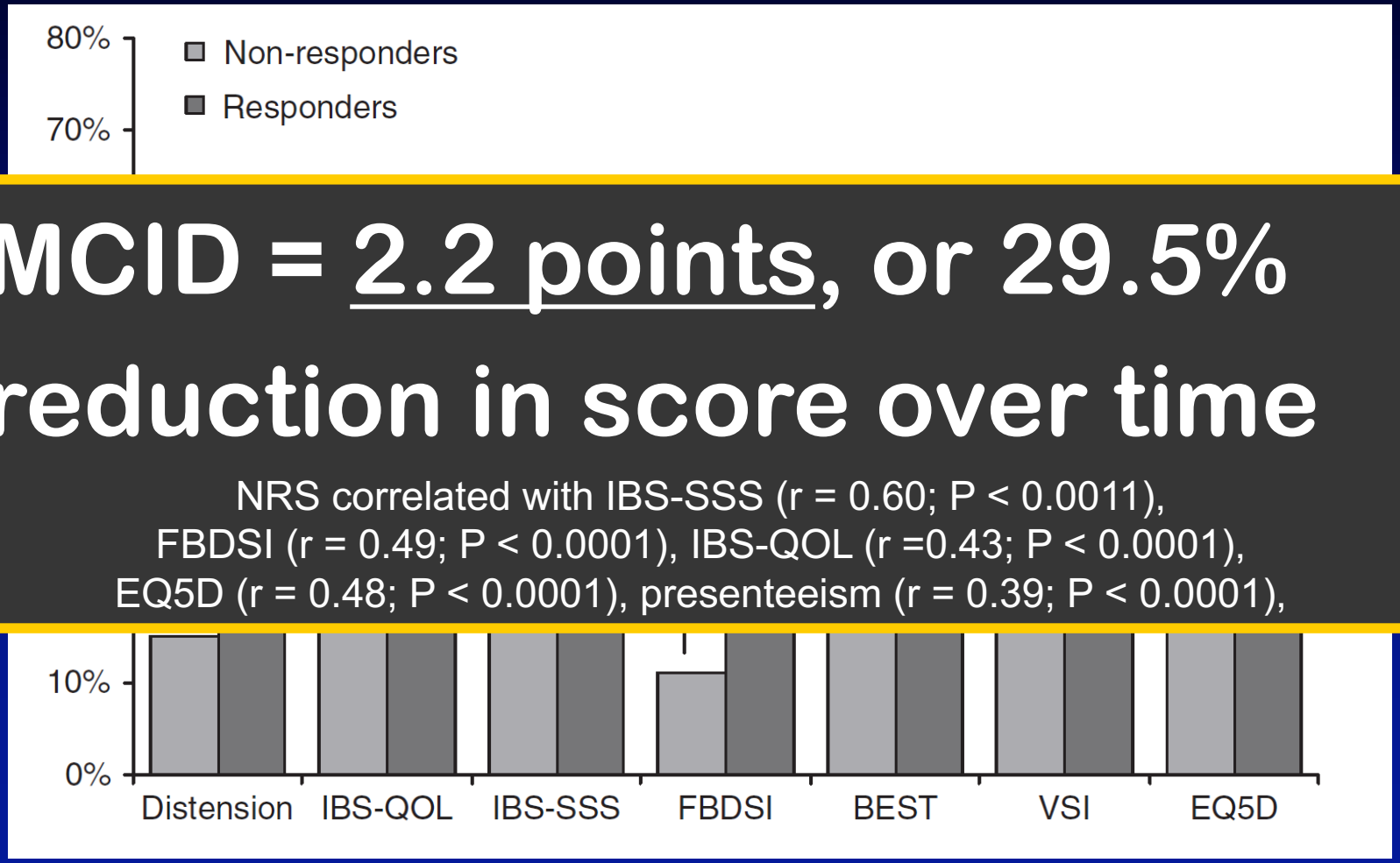
Select the number that best describes your neuropathic pain during the past 24 hours. *(Circle one number only)*

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

PRO Guidance: Need weekly average of *worst* pain to be ≥3 to qualify for clinical trial

Farrar et al. Pain 2001;94:149-58

Pain NRS Works in IBS



MCID = 2.2 points, or 29.5% reduction in score over time

NRS correlated with IBS-SSS (r = 0.60; P < 0.0011),
FBDSI (r = 0.49; P < 0.0001), IBS-QOL (r =0.43; P < 0.0001),
EQ5D (r = 0.48; P < 0.0001), presenteeism (r = 0.39; P < 0.0001),

Spiegel, et al. *APT* 2009;30:1159

Lessons Learned about Pain in IBS

- Pain and discomfort are different – asking about discomfort is nonspecific and should be avoided in future PROs
- IBS pain is multifaceted; some pain dimensions drive illness experience more than others
- Patients with more intense, frequent, constant, and unpredictable pain have higher illness impairment
- The multidimensionality of pain should be born in mind as conceptual frameworks are developed for PROs

Spiegel B et al. *APT* 2010;32:1275

FDA IBS Guidance: Primary Endpoint

- **A single general item asking patients to rate overall change in IBS symptoms as a primary endpoint to support an efficacy claim is not recommended**
- **A primary endpoint that measures treatment effect on abdominal pain & abnormal defecation is recommended**
- **For drugs developed to treat a single IBS symptom**
  - Specific symptom or sign should be the primary endpoint
  - Should be based on drug's mechanism of action
  - Other key efficacy endpoints should be secondary endpoints; show they have not worsened

FDA IBS Guidance 2012

Interim Endpoint: IBS-C Entry Criteria

Proposed Baseline Enrollment Criteria:

- **Pain Severity**
  Weekly average of "worst pain in past 24 hours" score of ≥ 3.0 in a 0 to 10 point scale
- **Stool Frequency**
  < 3 Complete Spontaneous Bowel Movements (CSBM)/week

Efficacy Assessments:

- **Daily symptom diary**
- **Weekly "global assessment"**

Interim Endpoint: IBS-C Responder Definition

Proposed Primary Endpoints:

Patient is a weekly responder in BOTH pain severity AND stool frequency

- **Pain Severity Responder**
  - **Decrease in weekly average of "worst abdominal pain in past 24 hours" score of $\geq$ 30%**
- **Stool Frequency Responder**
  - **An increase of at least 1 complete spontaneous bowel movement (CSBM) per week from baseline**

Thresholds for clinical meaningfulness based on anchor-based methods

Post-hoc analysis from Linaclotide Phase III Trials

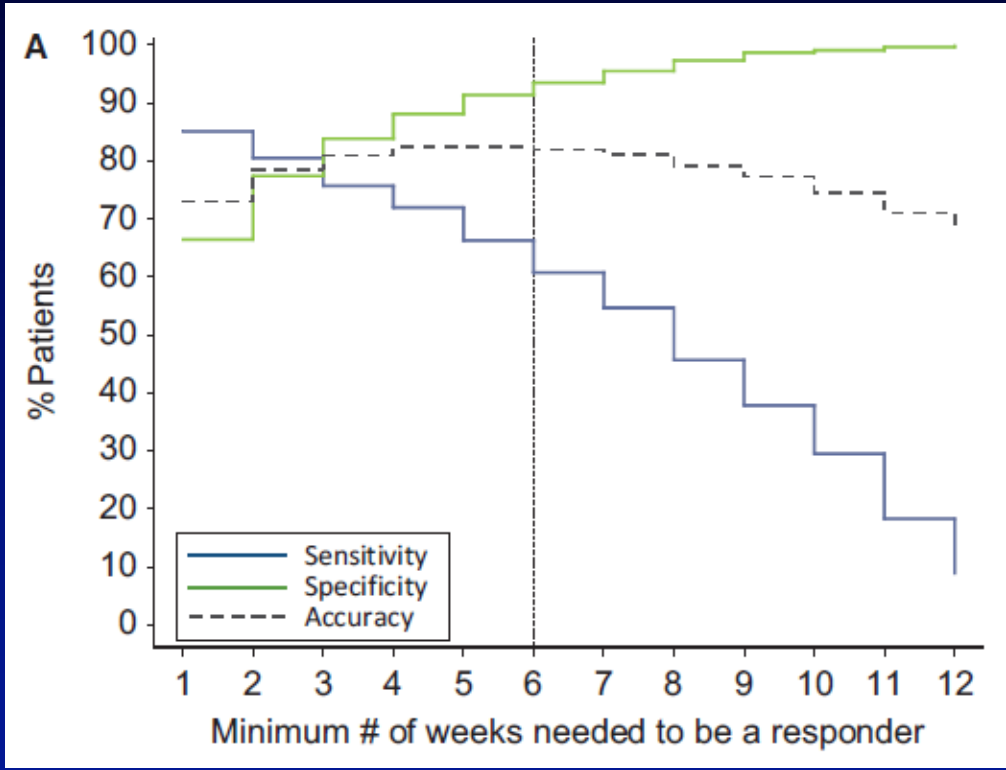
	Anchors			
	PRCQs		Current severity questions	
	Symptom-specific patient rating of change†	Degree relief of IBS symptoms	IBS symptom severity	Constipation symptom severity
Improvement in Abdominal Pain (%)*	25.8 (24.1, 27.5)	27.6 (26.0, 29.1)	30.4 (28.7, 32.0)	28.4 (26.7, 30.1)
Increase in weekly CSBM frequency*				
Mean	1.4 (1.2, 1.5)	1.4 (1.3, 1.5)	1.5 (1.3, 1.6)	1.3 (1.2, 1.4)
Median	[1.0 (0.6,1.0)]‡	[0.5 (0.5,0.6)]‡	[0.5 (0.0, 0.5)]‡	[0.5 (0.0, 0.5)]‡

*CMC estimates and 95% confidence intervals.
†PRCQ Abdominal Pain Relief was the anchor for the percent improvement in Abdominal Pain; PRCQ CSBM Frequency Improvement was the anchor for increase in weekly CSBM Frequency.
‡Median-based CMC estimates and 95% CIs; as the CSBM change from baseline distribution is non-Gaussian, both median- and mean-based CMC estimates are presented.

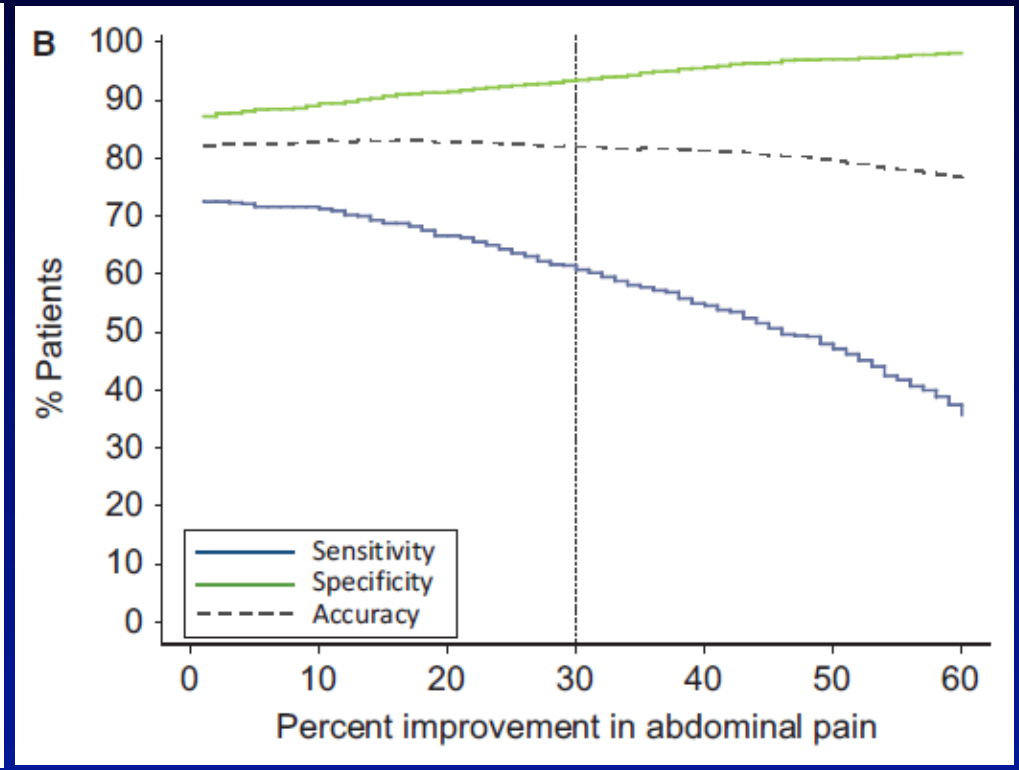
McDougall J et al. Neurogastroenterol Motil (2013) 25, 481

Variations on the FDA Responder Endpoint

Post-hoc Analysis from Linaclotide Phase III Trials



Varying the number of weeks needed to meet the Responder Endpoint. Note: FDA Responder Endpoint criterion is > 6/12 weeks



Varying the percent improvement (weekly average) in Abdominal Pain threshold

McDougall J et al. Neurogastroenterol Motil (2013) 25, 481

Interim Endpoint: IBS-D Entry Criteria

Proposed Baseline Enrollment Criteria:

- **Pain Severity**
  Weekly average of "worst pain in past 24 hours" score of ≥ 3.0 in a 0 to 10 point scale
- **Stool Form**
  At least 2 days/wk with a BM of type 6 or 7 by Bristol Stool Form Scale

Efficacy Assessments:

- **Daily symptom diary**
- **Weekly "global assessment"**

Interim Endpoint: IBS-D Responder Definition

Proposed Primary Endpoints:

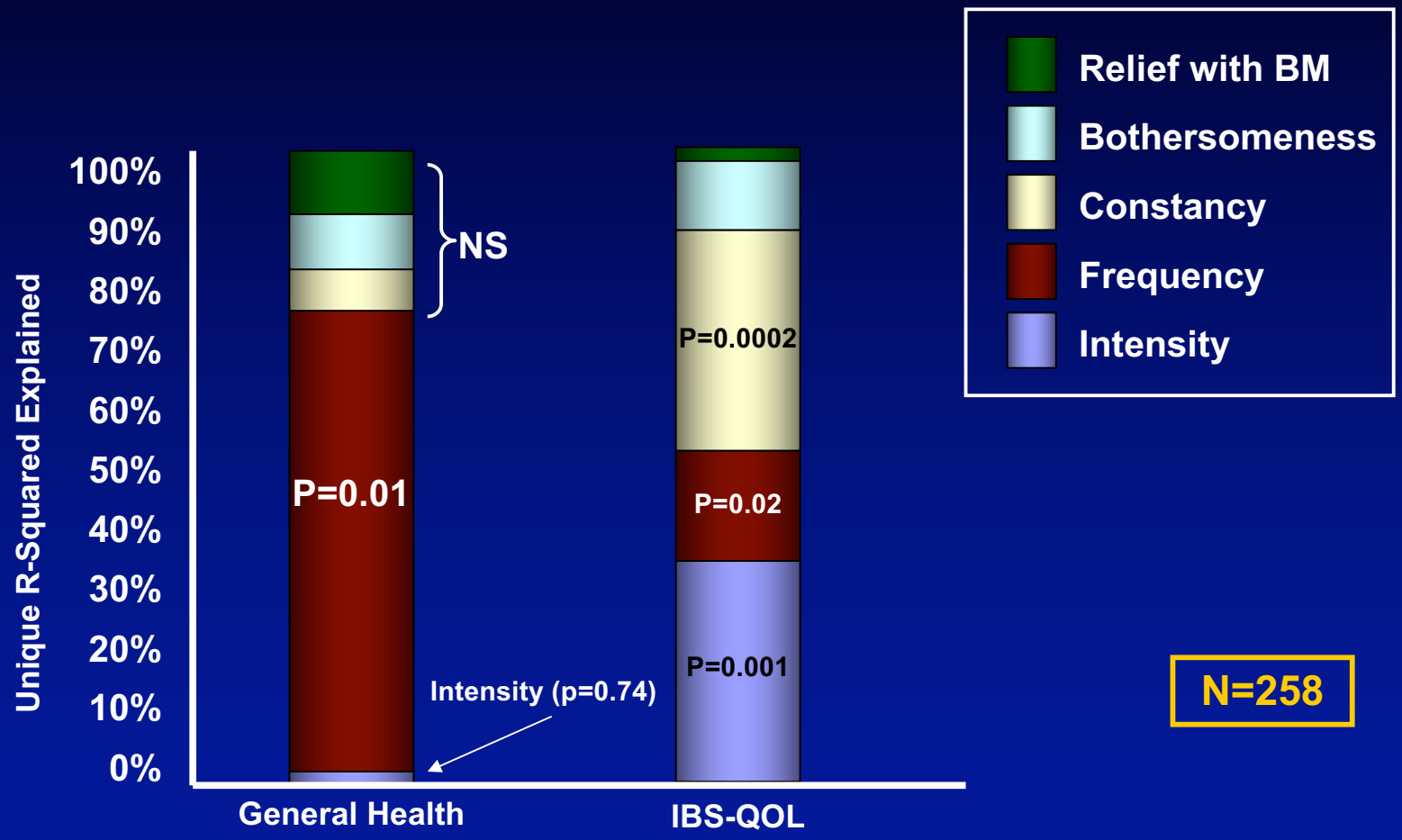
Patient is a weekly responder in BOTH pain AND stool form

- **Pain Severity Responder**
  - **Decrease in weekly average of "worst abdominal pain in past 24 hours" score of $\geq$ 30%**
- **Stool Frequency Responder**
  - **At least 50% reduction in number of days with a BM with stool form of type 6 or 7 by Bristol Stool Form Scale**

Summary

- IBS is a symptom-based disorder without a reliable biomarker
- It is a multi-symptom heterogenous condition
- Symptoms are largely measured using patient-reported outcomes
- Pain measurement in IBS focuses on severity
- A >30% reduction in abdominal pain severity has been determined to be clinically meaningful and is the recommended threshold for pain response according to the FDA

Independent Contributions of Various Pain Dimensions



N=258

Spiegel B et al. *APT* 2010;32:1192

Interim Endpoint: Abdominal Pain Responder Definition (FDA 2012)

- **Abdominal Pain Responder (Both IBS-C & IBS-D)**
  - Decrease in weekly average of "worst abdominal pain in past 24 hours" score of $\geq$ 30%
- **Stool Frequency Responder (IBS-C)**
  - Stool Frequency is unchanged or improved compared with baseline
- **Stool Consistency Responder (IBS-D)**
  - **Weekly:** # days/week with ≥ 1 BM of Type 6 or 7 is same as baseline or decreased and # BMs of Type 6 or 7 on those days remains unchanged or decreased
  - **Daily:** Stool consistencies are < 5 for all BMs or no BM