
2020 VIRTUAL
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Functional Bowel Disease: IBS Updates

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Disclosures

- None

Background: Irritable Bowel Syndrome

- 10% of population
- Disorder of gut-brain interaction
- Abdominal pain associated with a change in stool frequency and/or form
- Multifactorial pathophysiology: disturbed GI motility, visceral hypersensitivity, altered CNS processing

Overview

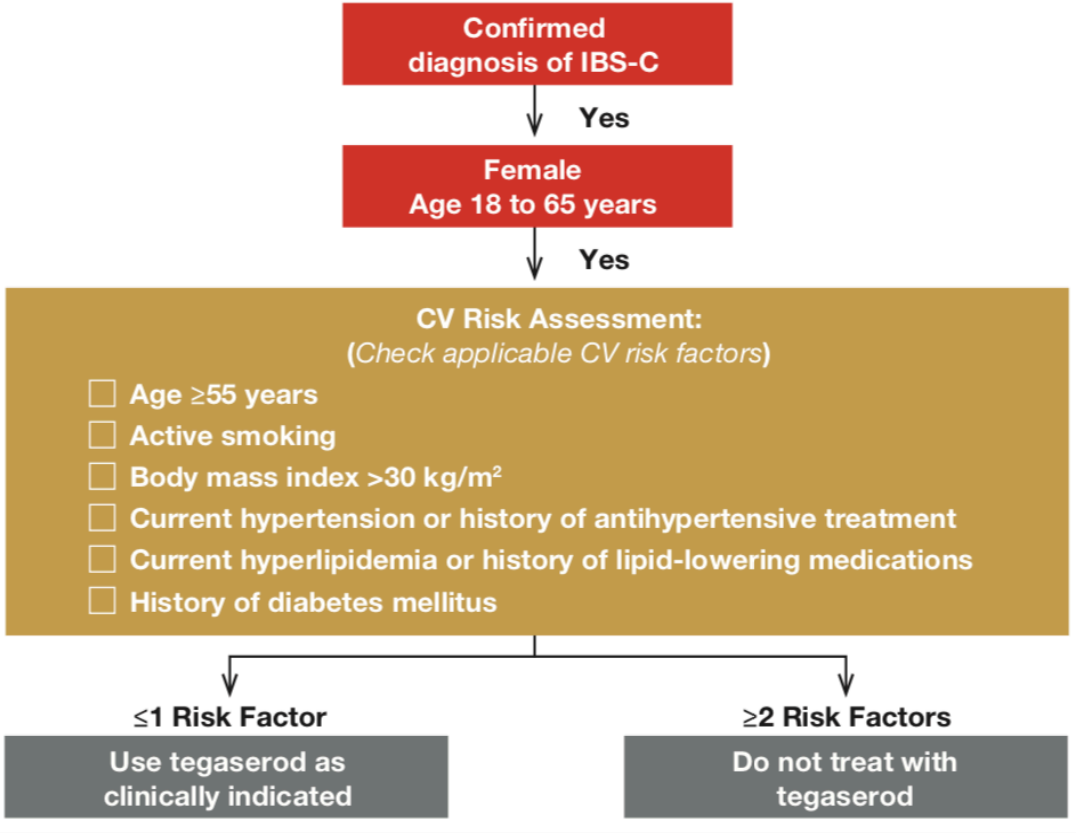
- Tegaserod in IBS-C
- Multidisciplinary care versus standard gastroenterologist care for functional GI disorders
- Efficacy of psychological therapies for IBS

Everything Old Is New Again

- Tegaserod is a 5-HT4 receptor agonist, stimulating GI motility
- The only 5-HT4 receptor agonist approved for IBS-C
- 2002 - Approved by US FDA for women with IBS-C
- 2004 – Indication expanded to CIC in men and women
- 2007 – Withdrawn from market due to concern for increased cardiovascular events
- 2019 – Reintroduced to US market after new application to FDA and two independent reviews of safety data didn't consistently show an increased risk for CV events with tegaserod
  - All tegaserod patients with reported CV ischemic events had ≥1 CV risk factor and majority had ≥2 CV risk factors

Reevaluation of the Cardiovascular Safety Profile of Tegaserod: A Review of the Clinical Data

- Tegaserod is safe in female patients <65 years old with:
  - no history of CV ischemic disease (TIA, stroke, angina, MI)
  - ≤1 CV risk factor



Lacy et al. DDW Abstract #Mo1548

Efficacy of Tegaserod 6mg BID for Treating IBS-C in Women <65 Years of Age Without Cardiovascular Risk Factors: A Pooled Analysis of 4 Clinical Trials

Shah et al. ACG Abstract #P1131 (S0494)

Tegaserod 6mg BID for Treating Abdominal Pain and Bloating in Women with IBS-C but Without Cardiovascular Risk Factors: A Pooled Analysis of 4 Clinical Trials

Shah et al. ACG Abstract #P1129 (S0492)

The Safety Profile of Tegaserod 6mg BID in IBS-C in Women <65 Years of Age Without Cardiovascular Disease History

Shah et al. ACG Abstract #P1132 (S0495)

Study Aim

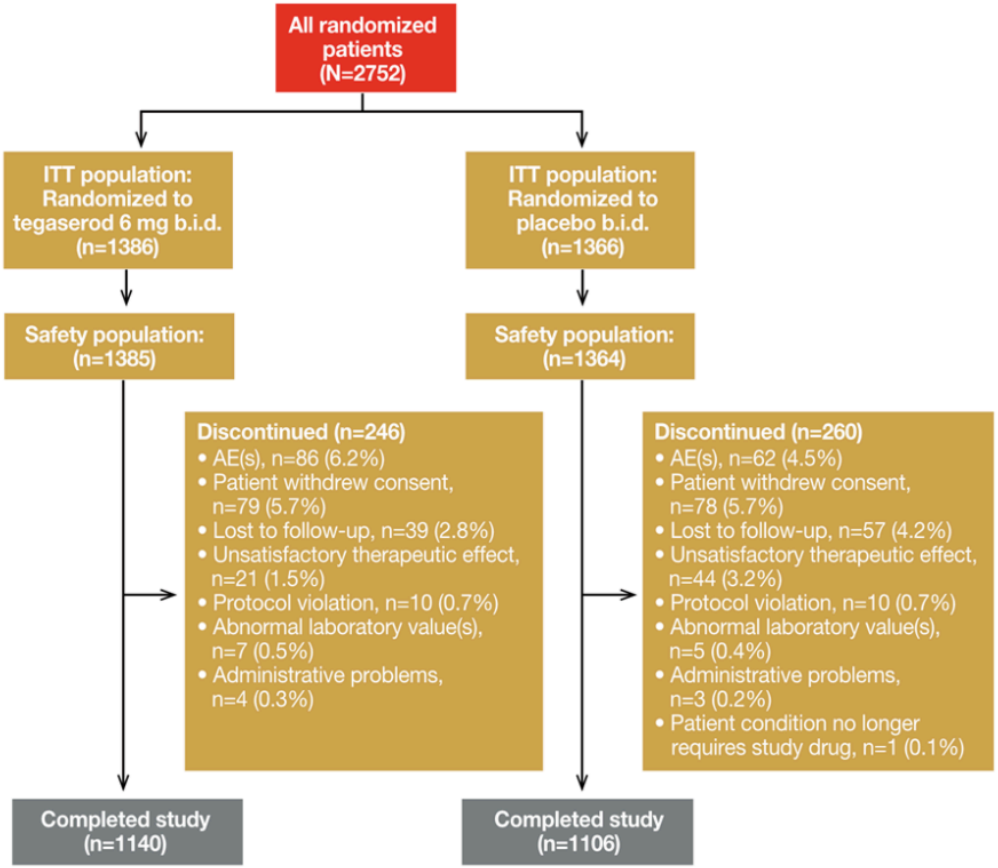
- To assess the effectiveness of tegaserod 6mg bid on primary and key secondary outcomes in women with IBS-C <65 years old with no history of CV ischemic events.

Methods

- Four 12-week randomized, placebo-controlled trials enrolling IBS-C patients with ≥3 month symptom histories
- Only data from women <65 years old with no known history of CV ischemic events who received tegaserod 6mg bid or placebo were included
- **Primary efficacy endpoints:** subjective global assessment (SGA) of relief of IBS-C symptoms.
  - Responders were defined as rating themselves ”considerably” or “completely” relieved ≥50% of the time or at least “somewhat relieved” 100% of the time over the first month and last 4 weeks of the 12-week studies (50%/100% SGA Responder)
- **Secondary endpoints:**
  - ≥30% reduction in composite weekly abdominal pain intensity and ≥50% increase in stool frequency (≥1/week) for at least 6 of 12 weeks

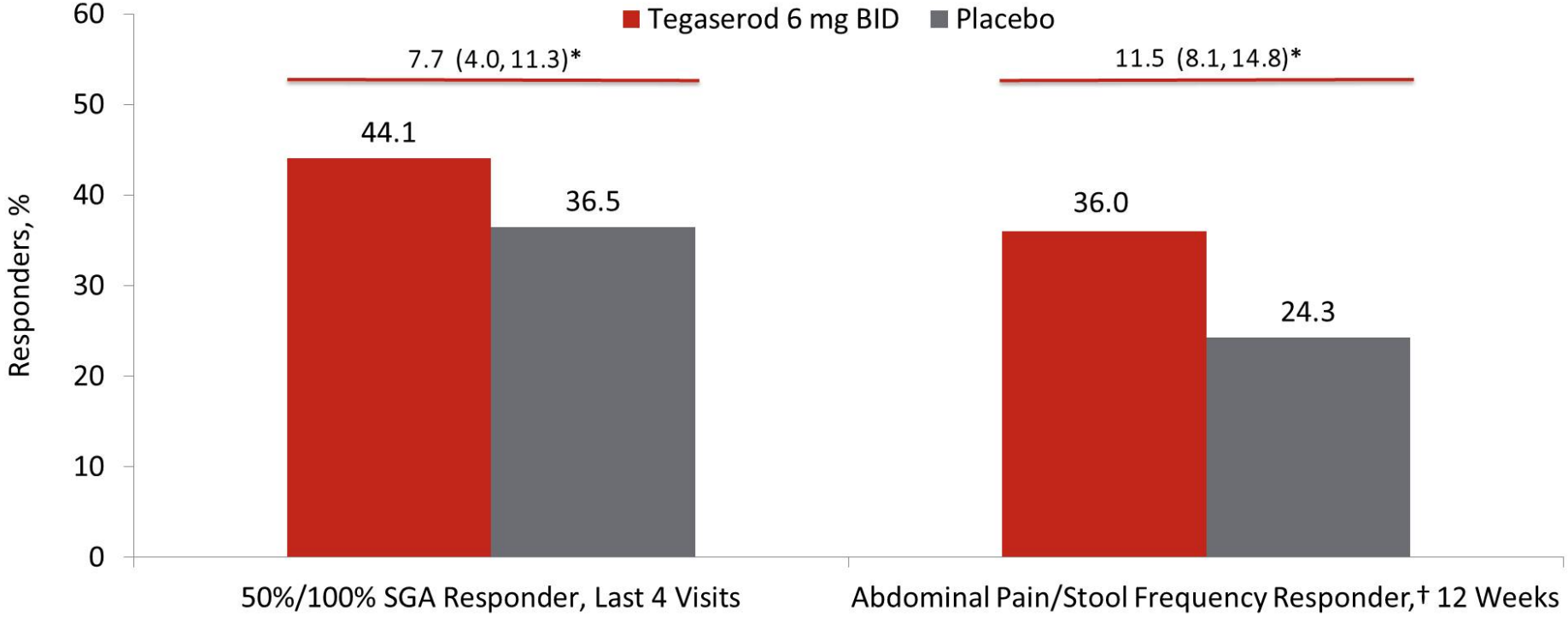
Results: Study Flow

- Baseline demographics were similar between both groups:
  - Age
  - Race
  - Duration of IBS Symptoms



Shah et al. ACG Abstract #P1131 (S0494)

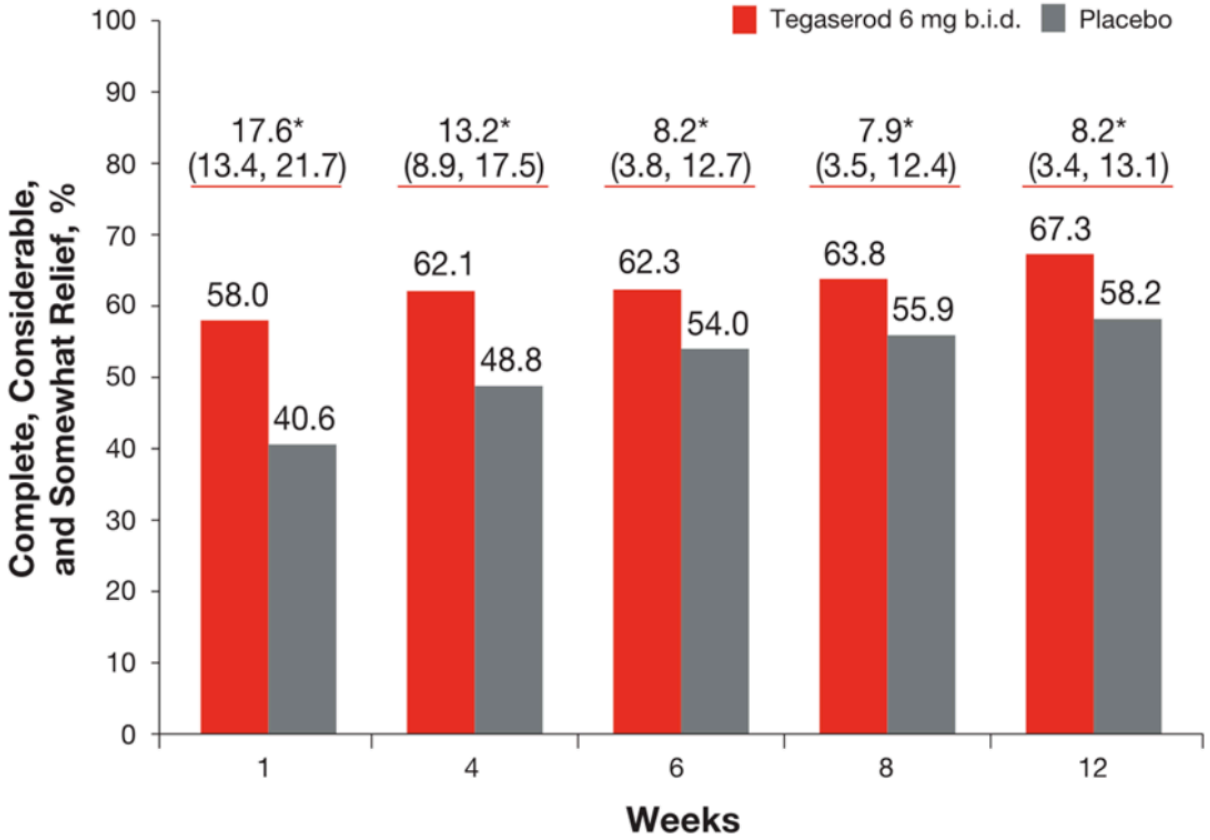
Results: Primary and Secondary Endpoints



*Difference (95% CI); P<.001.
†Abdominal pain intensity weekly responder (≥30% reduction) and stool frequency increase (≥1/week) ≥50% response.
CI, confidence interval; SGA, subject global assessment.

Shah et al. ACG Abstract #P1131 (S0494)

Results: IBS-C Symptom Relief



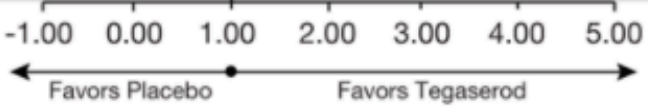
*P<0.001

Shah et al. ACG Abstract #P1129 (S0492)

Results: Secondary Endpoint

- Significant improvement in bloating at 12 weeks

Study	Tegaserod n/N (%)	Placebo n/N (%)	OR (95% CI), *P*-value
301	13/160 (8.1)	8/159 (5.0)	1.66 (0.66–4.17), .282
307	13/164 (7.9)	11/162 (6.8)	1.22 (0.53–2.83), .647
351	12/175 (6.9)	8/166 (4.8)	1.45 (0.58–3.65), .426
358	202/604 (33.4)	138/571 (24.2)	1.57 (1.22–2.02), <.001
Pooled	240/1103 (21.8)	165/1058 (15.6)	1.54 (1.23–1.93), <.001



CCI, confidence interval; OR, odds ratio.
Bloating response defined as a ≥2-point improvement on a 7-point Likert scale.

Shah et al. ACG Abstract #P1129 (S0492)

Results: Adverse Events

Preferred Term, n (%)	Tegaserod 6 mg b.i.d. (n=1385)	Placebo (n=1364)
Headache	197 (14.2)	165 (12.1)
Abdominal pain	170 (12.3)	149 (10.9)
Nausea	111 (8.0)	93 (6.8)
Diarrhea	119 (8.6)	53 (3.9)
Flatulence	93 (6.7)	73 (5.4)
Dyspepsia	65 (4.7)	46 (3.4)
Influenza-like illness	52 (3.8)	49 (3.6)
Dizziness	52 (3.8)	47 (3.4)

Shah et al. ACG Abstract #P1132 (S0495)

Conclusions

- In women <65 years old without history of CV ischemic events (TIA, stroke, MI, angina), tegaserod 6mg twice daily reduced symptoms of IBS-C compared to placebo
- Tegaserod improved subjective global IBS symptom relief. Effects were seen as early as week 1 and were maintained throughout the 12 week study period
- Tegaserod improved abdominal pain/discomfort, stool frequency, and bloating
- Serious adverse event rates were similar between the tegaserod and placebo groups

Randomised Trial of Multi-Disciplinary Versus Standard Gastroenterologist Care for Functional Gastrointestinal Disorders (MANTRA)

Basnayake, C et al. DDW Abstract #409

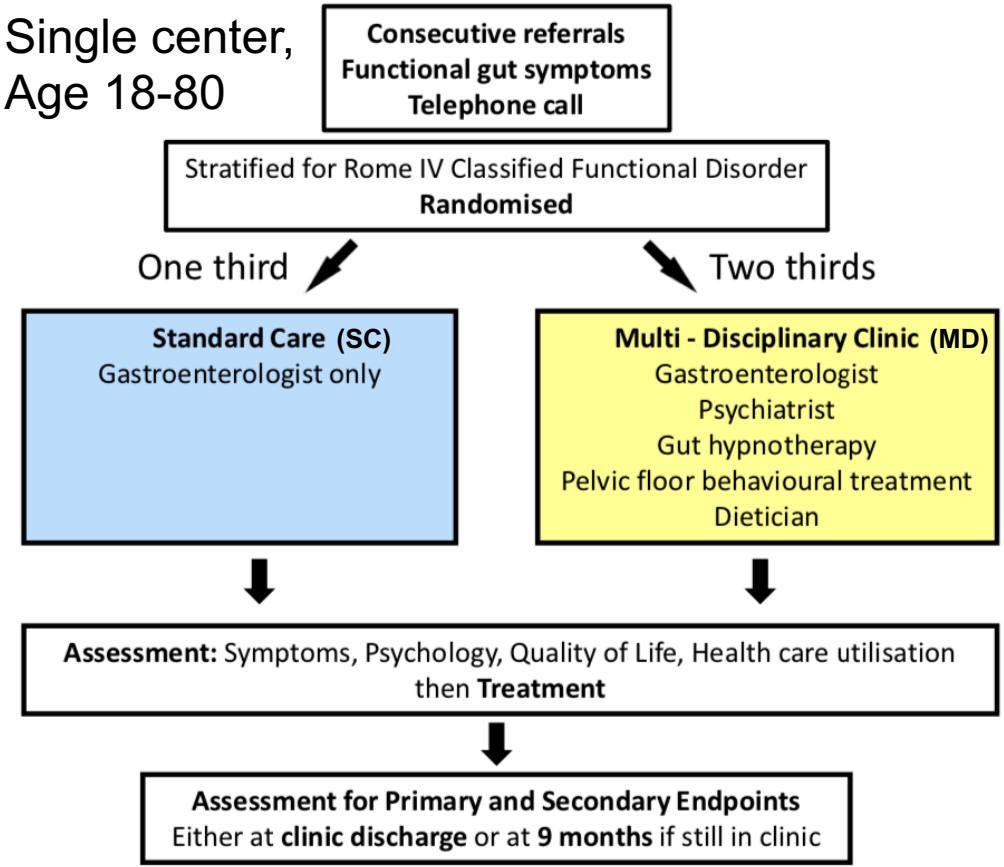
The Lancet Gastroenterology & Hepatology 2020; 5(10): 890-899.

Hypothesis

- Multi-disciplinary frontline care for functional GI disorders is superior to standard gastrointestinal outpatient care with respect to symptoms, psychological well-being, quality of life, and cost of care

Methods

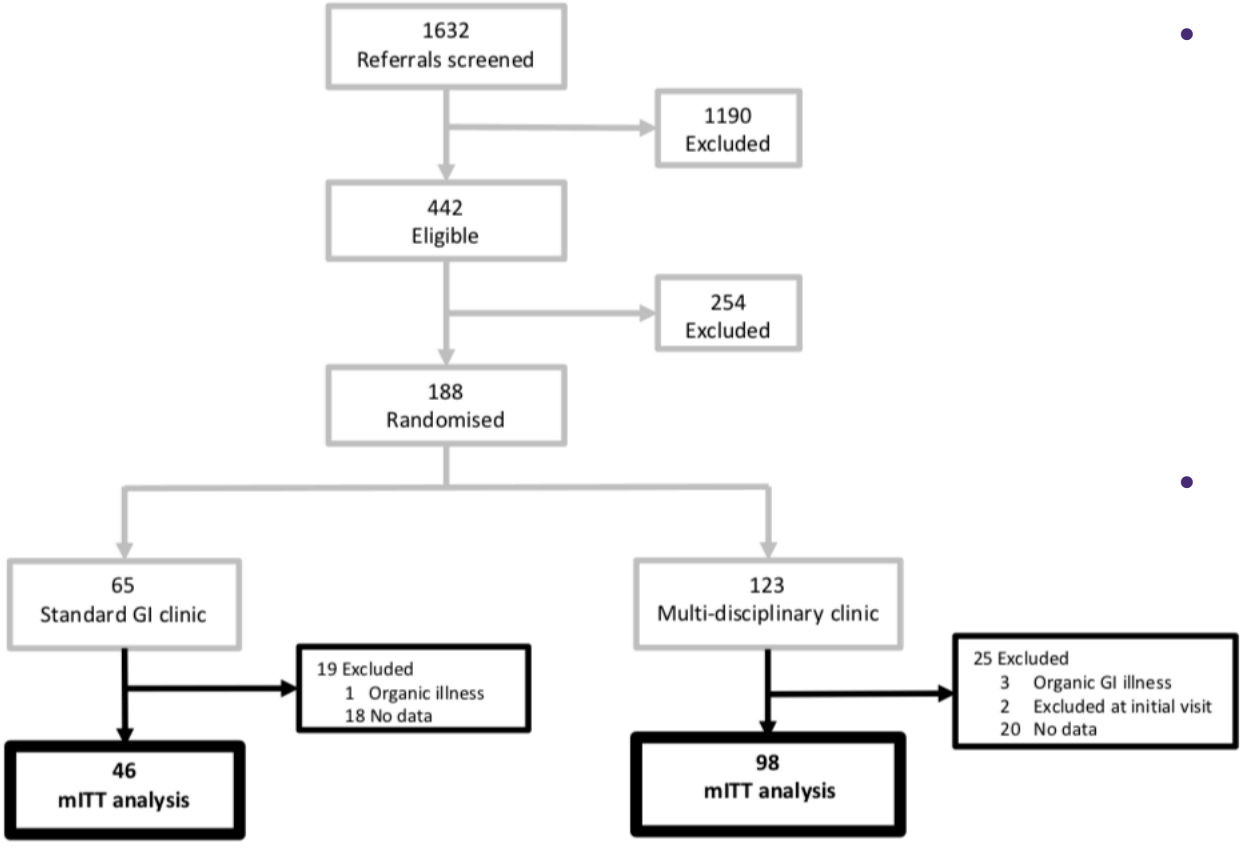
Single center,
Age 18-80



Exclusion criteria: Organic GI disorders, non-gut severe organ disorder, opioid use, active eating disorder, major psychiatric disorder, substance abuse, previous GI surgery

Primary outcome: global symptom improvement (5-point Likert scale)
Secondary outcomes: gut symptoms (GISSI, IBS-SSS, NDI), psychological well-being (HADS), quality of life (Euro-QOL, EQ-5D), and cost

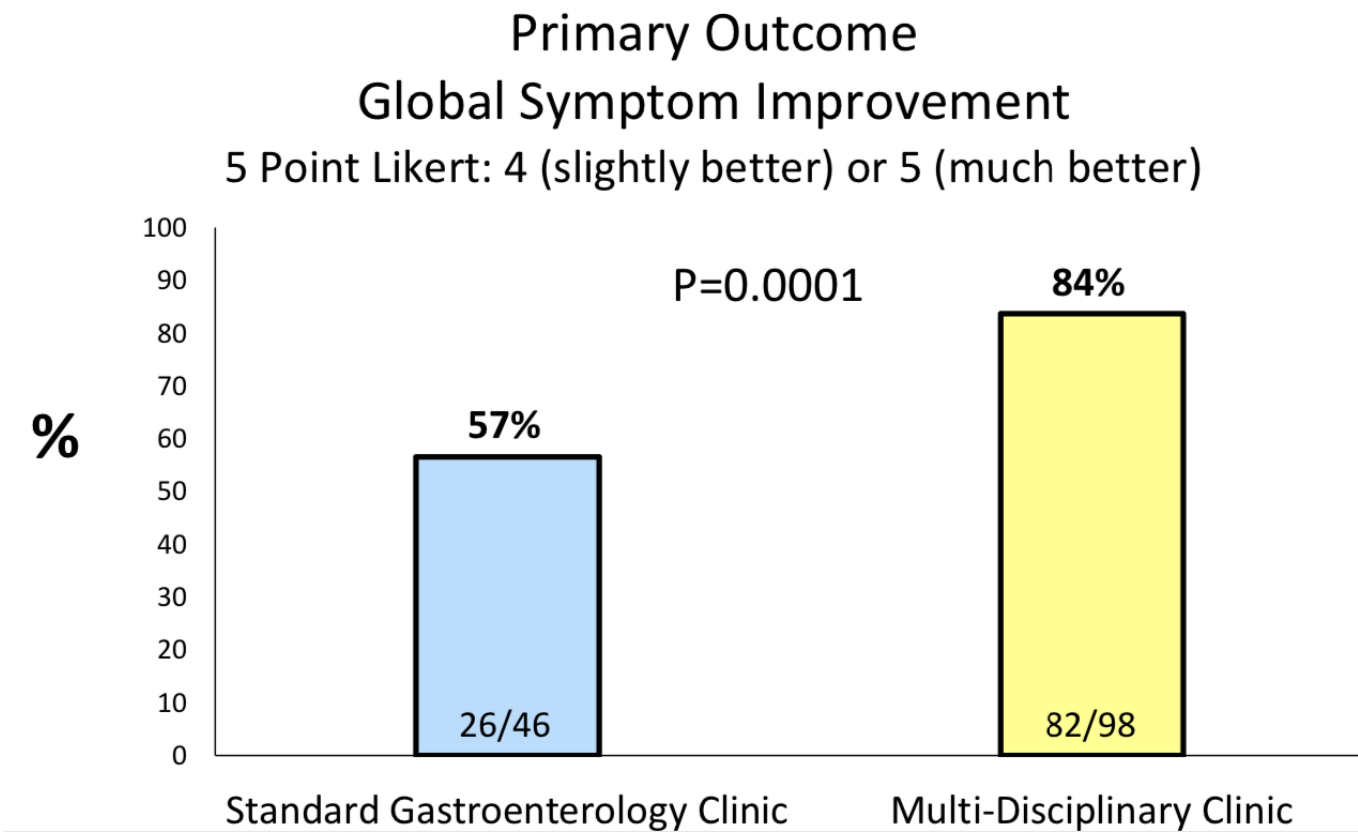
Study Flow



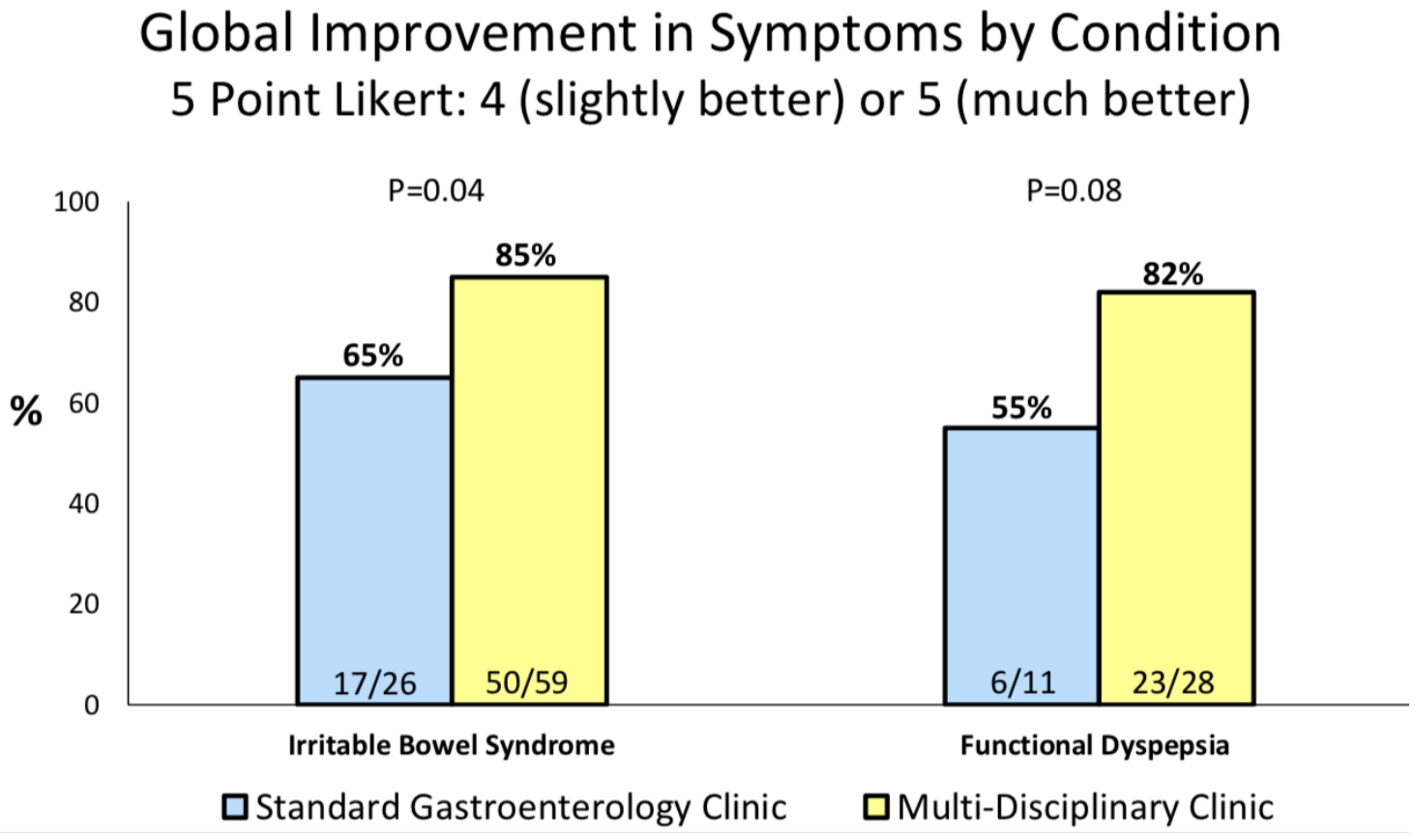
- Baseline demographics were similar between both groups
  - Sex
  - IBS, functional dyspepsia, other
  - Self-rated severity (majority were moderate)
- Slightly older age in SC vs MD (38 vs 33 years old)

Results

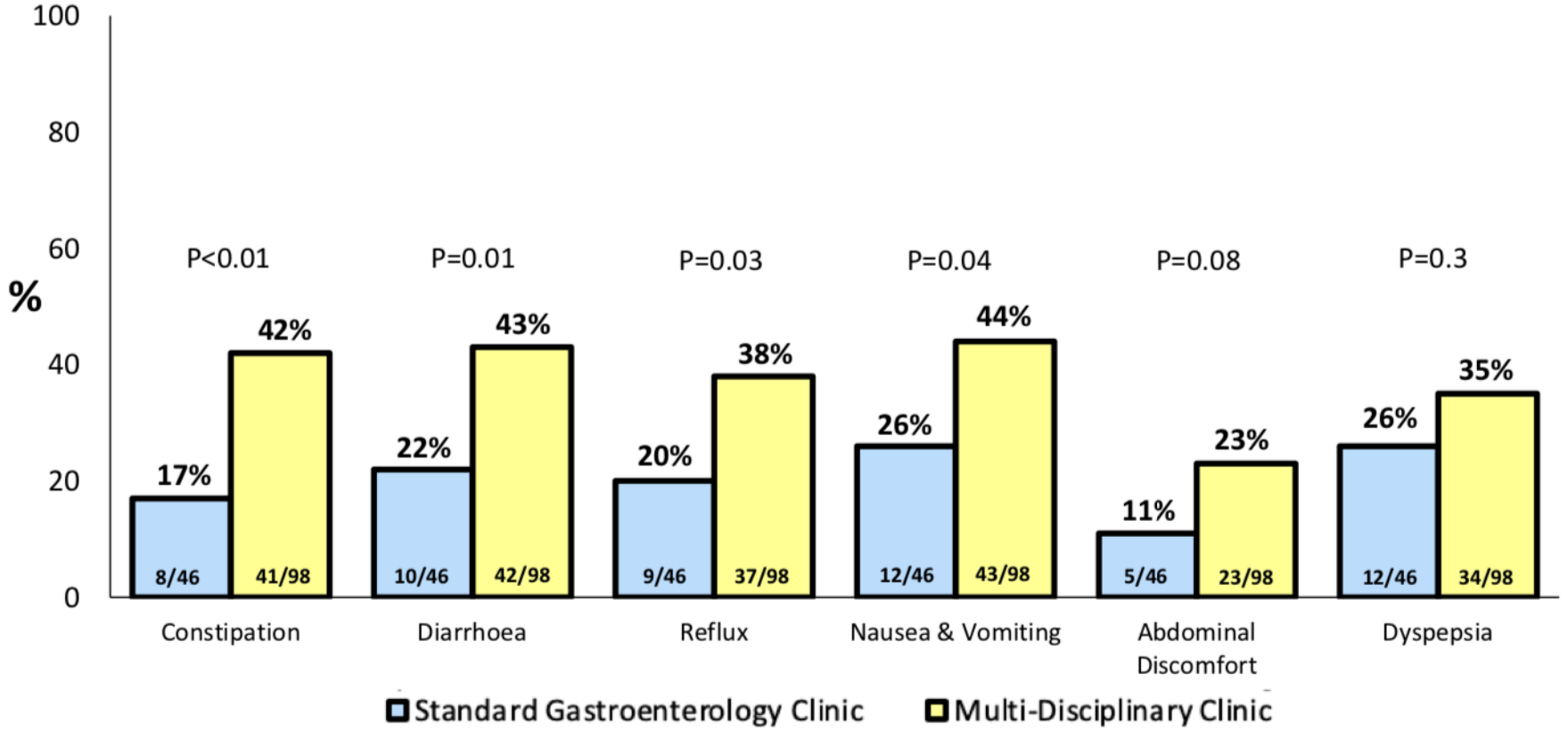
- 144 patients included in MITT analysis (59% IBS, 27% functional dyspepsia)
- 62% of MD patients saw allied clinicians



Result


Global Improvement in Symptoms by Condition
5 Point Likert: 4 (slightly better) or 5 (much better)
P=0.04
P=0.08
100
80
60
40
20
0
%
65%
85%
55%
82%
17/26
50/59
6/11
23/28
Irritable Bowel Syndrome
Functional Dyspepsia
Standard Gastroenterology Clinic
Multi-Disciplinary Clinic

Results: GI Symptom Severity Index (GISSI)
>50% Reduction in Sub-Scores at Discharge



Results: Other Secondary Outcomes

- Significantly more improvement in MD
  - Median HADS (hospital anxiety and depression scale) score
  - EQ-5D
- Estimated incremental cost of MD care was $2909 per QALY gained

Conclusions

- Multi-disciplinary care was significantly superior to standard gastroenterologist-only care in relation to global symptoms, specific GI symptom improvement, psychological state, quality of life, and cost
- Consideration should be given to providing routine multi-disciplinary care for FGIDs

Efficacy of Psychological Therapies for Irritable Bowel Syndrome: Systematic Review and Network Meta-Analysis

Black CJ, Thakur ER, Houghton LA, Quigley EM, Moayyed P, Ford A.

Gut 2020; 69: 1441-1451.

Methods

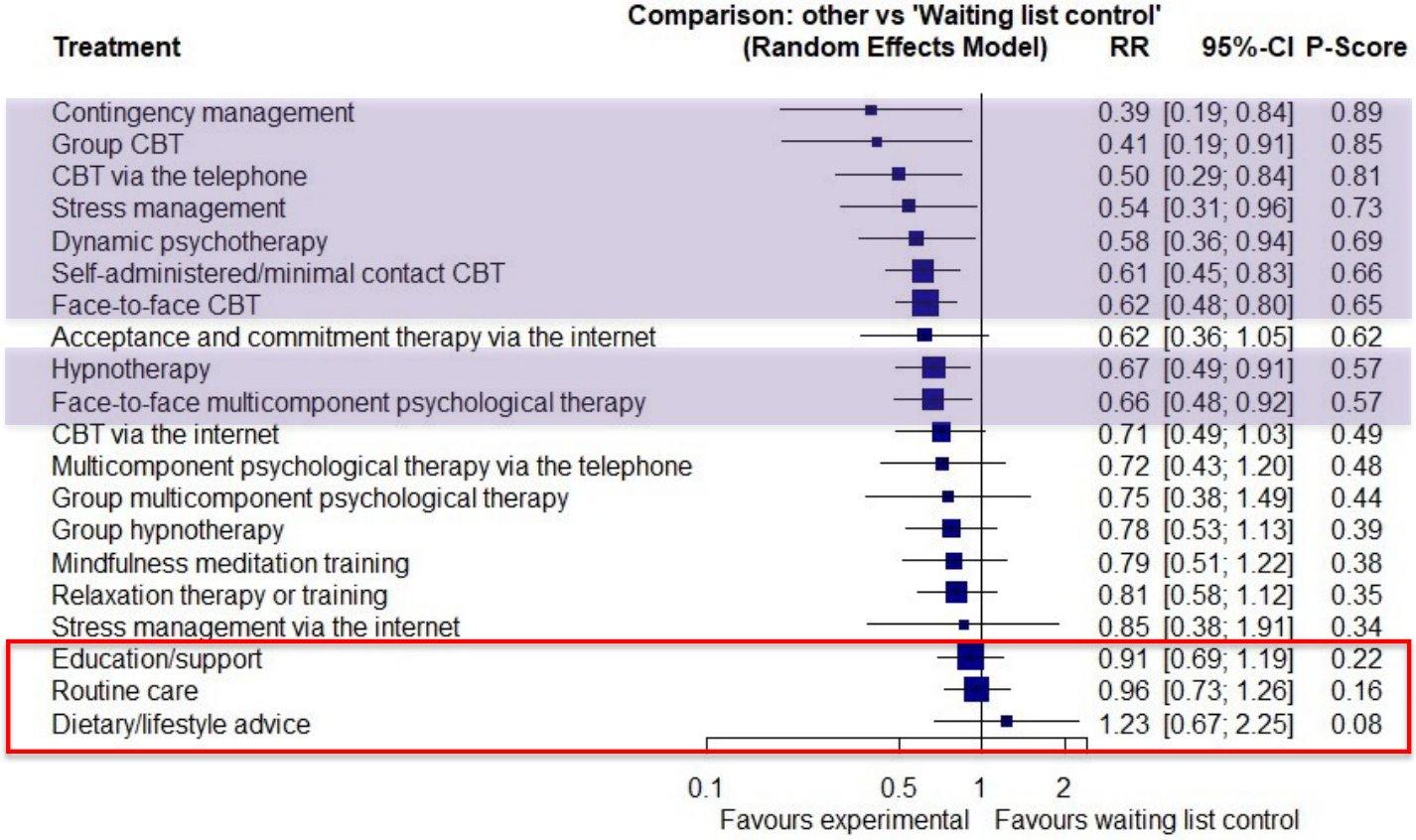
- Searched MEDLINE, EMBASE, PsycINFO, Cochrane, major GI conferences in U.S., Europe, Asia
- Randomized controlled trials examining the efficacy of psychological therapies for IBS in adults ≥18 years old
- Control intervention could consist of being on a waiting list (where patients were left on a waiting list to receive the active intervention after the trial had ended), education and/or support, dietary and/or lifestyle advice, or routine care.
- Duration of therapy ≥ 4 weeks
- **Primary outcome:** Efficacy of all psychological therapies and control interventions in IBS, in terms of effect on global IBS symptoms or abdominal pain after completion of therapy
- **Secondary outcome:** Adverse events

Results

- 41 separate randomized controlled trials, comprising 4072 participants (2616 received a psychological therapy, 1456 received a control intervention)
- Adverse events were not reported in sufficient detail in the majority of trials to allow meaningful pooling of data

Results: Failure to Achieve an Improvement in IBS Symptoms

- Many psychological therapies were more efficacious than control interventions
- No psychological therapy was significantly more efficacious than any of the other active therapies



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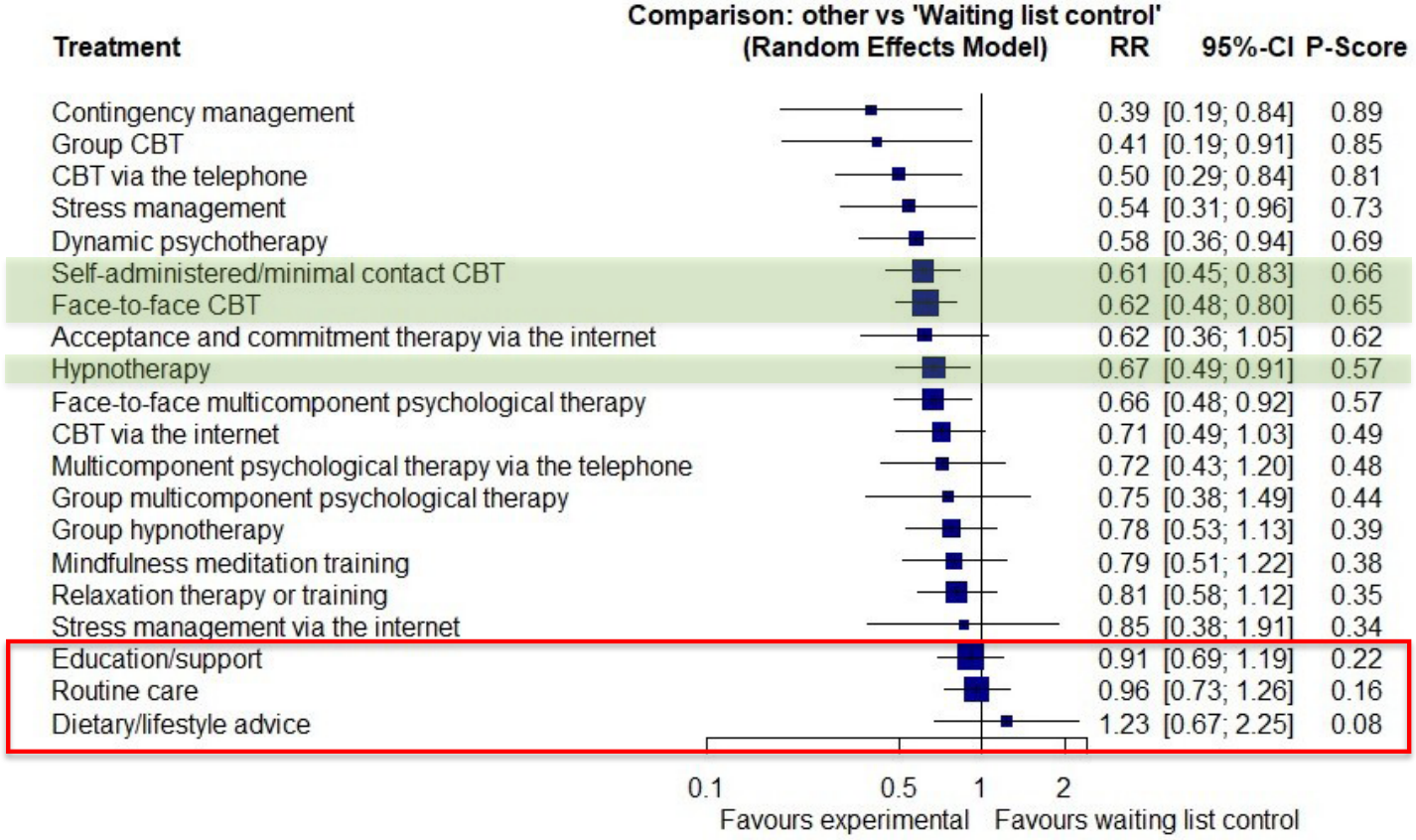
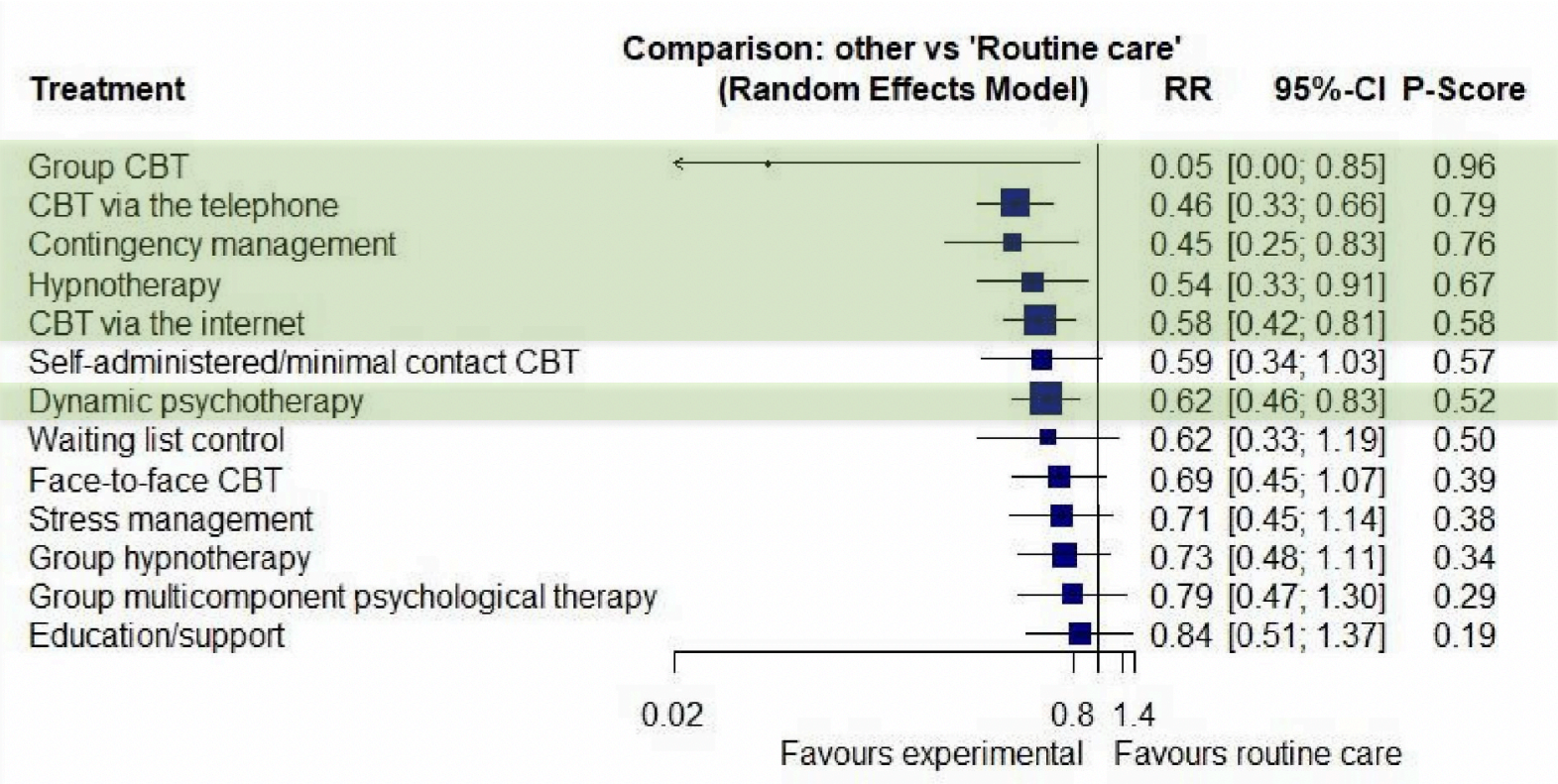


Results: Failure to Achieve an Improvement in IBS Symptoms in Refractory Patients



Conclusions

- Overall, psychological therapies were more efficacious for IBS symptoms than a control intervention (education/support, routine care, diet/lifestyle advice), even in more refractory patients
  - CBT (group, face-to-face, telephone, self-administered/minimal contact)
  - Gut directed hypnotherapy
  - Contingency management
  - Stress management
  - Dynamic psychotherapy
- Weaknesses include moderate study heterogeneity, difficulty with blinding, lack of screening for presence of psychological comorbidities