META-ANALYSIS AND SYSTEMATIC REVIEW

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Searching for a Definition of Refractory Irritable Bowel Syndrome: a Systematic Review and Meta-analysis

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ABSTRACT

Background & Aims: The pathological mechanism of irritable bowel syndrome (IBS) is unclarified, which commonly leads to unresponsiveness to conventional treatments. The diagnostic criteria for refractory IBS are not clearly defined. We performed a systematic review to summarize the key points of the definition of refractory IBS in different studies. We also conducted a meta-analysis to explore whether the diverse definitions for refractory IBS affect the therapeutic effect of gut-directed hypnotherapy (GDH).

Methods: We searched OVID Medline, Embase and Cochrane (until September 2020) for randomized controlled trials (RCTs) recruiting patients with refractory IBS. We evaluated the definition of refractory IBS through the following aspects: duration of symptoms, unresponsive to dietary intervention, lifestyle modification, pharmacology, psychology, severity assessment and adequate explanation. The effect of the different definitions for refractory IBS on the therapeutic effect of gut-directed hypnotherapy (GDH) was checked by a meta-analysis.

Results: Twenty-one RCTs were finally included. Six (28.6%) out of 21 RCTs recruited patients with symptoms lasting for over 12 months; 8 (38.1%) RCTs reported a prior use of dietary intervention; 1 (4.8%) RCT reported the use of lifestyle modification; 11 (52.4%) RCTs recruited patients who were unresponsive to pharmacology; 2 (9.5%) RCTs recruited patients with no response to psychological therapy ; 5 (23.8%) RCTs had symptoms severity assessment; and 8 (38.1%) RCTs recruited patients who were informed adequately. Despite being tested in trials with heterogeneous definition of refractory IBS, GDH had similar effectiveness when compared with supportive treatment [standardized mean difference (SMD)=-0.69, 95%CI: -0.93 to -0.44)] or waiting-list control (SMD=-0.54, 95%CI: -0.98 to -0.10).

Conclusions: Varied definitions in refractory IBS were common phenomena in clinical studies. Resistance to symptom severity assessment and psychological treatments should be more explicitly defined. Gut-directed hypnotherapy was efficacious for refractory IBS and was not affected by the diversity in the definition of refractory IBS among RCTs.

Key words: definition – refractory – irritable bowel syndrome – systematic review – gut-directed hypnotherapy – meta-analysis.

Abbreviations: CI: confidence interval; GDH: gut-directed hypnotherapy; IBS: irritable bowel syndrome; RCT: randomized controlled trial; SMD: standardized mean difference.

INTRODUCTION

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by change of bowel habits, abdominal pain or discomfort, and bloating [1-3]. Irritable bowel syndrome affects 10–25% of individuals in the community samples and 11% of the global population [4, 5]. It has substantial impact on the quality of life and healthcare costs [6, 7]. The pathophysiology of IBS has not been fully elucidated, it was associated with genetic predisposition [8-10], visceral hypersensitivity [11-14], brain-gut axis disorder [15, 16], gastrointestinal inflammation [17], psychosocial disturbance [18], and alteration in intestinal microbiota [19-22].

Owing to the complexity of the pathophysiology of IBS, a large number of treatments have been proposed [1-3, 23], including dietary interventions, life-style education, pharmacological treatments, psychological therapies, and alternative and complementary treatments such as herbal

medicine. The dietary interventions and the pharmacological treatments are usually the conventional treatments. About 25% of IBS patients have persistent symptoms after trying the conventional treatments [24]. In a broad sense, refractory IBS is often defined as persistent symptoms that are unresponsive to conventional treatments and have significant impact on daily lifestyles. The duration of persistent symptoms was defined as over 12 months [1, 25]. But diagnostics of refractory IBS vary in practice. The difference mainly comes from the inadequately evaluation of conventional treatments (pharmacology, dietary intervention, psychological therapies, receiving adequate explanation and reassurance for his/her symptoms). These questions are not well addressed, which might have significant ambiguity on the refractory IBS definition. In 1997, the issue of the use of the term refractory was raised [25]. However, until now an established definition of refractory IBS is still lacking. Most of the papers refer to previous studies [26-29], which have established a definition on their own [30, 31]. As there are no detailed guidelines available for the definition of refractory IBS, there is great uncertainty for clinical practice and inaccuracy for investigational trials.

Therefore, our study primarily aimed to investigate the definition of refractory IBS adopted in randomized controlled trials (RCTs). We also aimed to explore whether the diverse definition affected the therapeutic effect of gut-directed hypnotherapy (GDH) through a meta-analysis.

METHODS

We searched OVID Medline, Embase and Cochrane from inception to September 7, 2020 for RCTs that had recruited patients with refractory IBS. The search was performed without any language restriction. Search strategies in the databases are provided in the Supplementary file (Tables I-III). We also searched in clinicaltrials.gov and Google scholar for any missing RCTs.

These studies were considered eligible: 1) studies with randomized design, including parallel and cross-over design; 2) recruited adult patients (age ≥18 years) with refractory IBS; 3) if they assessed the efficacy of pharmacological (standard medical treatment and guideline recommended medications [32]) or non-pharmacological treatments (hypnotherapy, cognitive-behavioral therapy, biofeedback, symptom monitoring modalities, or natural living products); 4) studies period ≥12 weeks.

Two reviewers (W.Y.P. and K.Y.) independently searched the literature. They screened title, and then conducted full-text screening to obtain potentially eligible articles. Any disagreement in study selection was solved by discussion and arbitrated by a third reviewer (H.Z.).

Two reviewers (W.Y.P. and K.Y.) independently extracted study data from the included RCTs; trials characteristics, participant's baseline characteristics, details for definition of refractory IBS, and outcome parameters were extracted by using a standardized extraction form. The trial characteristics included first author, publication year, participating countries, settings, sample size, study duration, interventions, comparisons, and main outcomes. The participant's baseline characteristics included mean age, proportion of female patients, and disease duration. The detailed inclusion criteria of refractory IBS included diagnostic criteria of IBS, symptom duration, detailed invalid treatments, severity assessment, and diagnostic reference.

Dichotomous data were extracted for the number of participants and events in each arm and the follow-up time points; continuous data were extracted for the number of participants, mean, and standard deviation in each arm and the follow-up time points. Missing values were firstly calculated from other reported statistic parameters (i.e., standard deviations were calculated from 95% confidence intervals (CIs) or standard errors), and secondly acquired by contacting the corresponding authors.

Two reviewers (W.Y.P. and K.Y.) assessed risk of bias of each study respectively, using the Cochrane risk of bias tool, and disagreements were solved by discussion. Included RCTs were evaluated for risk of bias in the following aspects: random sequence generation, allocation concealment, blinding participants, blinding therapist, blinding outcome assessors, unpublished data, selective outcome report, and attrition bias. The methodological quality assessment did not affect the results of eligible studies in terms of main objectives, but only when the meta-analysis of the effect of GDH was considered.

We assessed the definition of refractory IBS characteristics through the following 7 items according to the revised NICE guideline [33] and some reviews [25, 34, 35]: whether IBS symptoms lasted for ≥12 months; whether the participants were unresponsive to dietary intervention; unresponsive to lifestyle modification; whether the participants failed to respond to pharmacological treatments for ≥6 weeks; whether the participants were unresponsive to psychological intervention after trying for at least 6 treatment sessions; whether the IBS symptom severity had been assessed; whether the participants had been received adequate explanation and reassurance for his/her symptoms [25]. If any of the 7 items were not described clearly in the article, we contacted the corresponding authors for more detailed information.

Descriptive statistical analysis was conducted to demonstrate the characteristics of the population with refractory IBS and treatments for the condition, and to analyze the characteristics of the definition of refractory IBS in each included RCT. We therefore summarized baseline age, gender, and disease duration of patients with refractory IBS, described the treatment details, and summarized the features of definitions for refractory IBS by checking whether the following criteria were adopted in each trial: symptoms persisted ≥12 months, unresponsive to dietary intervention, unresponsive to lifestyle modification, pharmacological treatments (≥6 weeks), psychological intervention (≥6 sessions), symptom severity assessment, or adequate explanation and reassurance.

We conducted a further verification test through a meta-analysis to explore whether the diverse definition affects the therapeutic effect of the same intervention. We took GDH intervention as an example because it had the largest number of studies. Standardized mean difference (SMD) was calculated in the comparisons of GDH versus for supportive therapy and GDH versus waiting-list control, and the SMDs were pooled in each comparison by using the inverse variance-weighted average method and their corresponding 95%CIs were estimated.

Table I. Study characteristics

Reference	Country; number of sites	Age (year)	Proportion of female (%)	Disease duration (year)	Sample size	Study duration (weeks)	Treatment details	Main outcome measurements
Whorwell, 1984, [24]	UK; 1	NA	86.7	NA	30	12	Intervention group: hypnotherapy, 7 sessions Control group: placebo pills and 7 sessions of psychotherapy	The overall changes in abdominal pain, bowel habit, abdominal distension, and wellbeing
Harvey, 1989, [27]	UK; 2	38	75	NA	36	19	Intervention group: group hypnotherapy 4 sessions over 7 weeks Control group: individual hypnotherapy 4 sessions over 7 weeks	Improvement of symptoms
Guthrie, 1993, [30]	UK; 1	47	77.1	2 (1-20)	102	72	Intervention group: psychotherapy, 6 sessions over 12 weeks Control group: supportive listening, 4 sessions over 12 weeks	Improvement in gastrointestinal function and psychological symptom scores
Forbes, 2000, [53]	UK; 1	37	71.2	5	52	12	Intervention group: individual hypnotherapy, 6 sessions over 12 weeks Control group: supportive listening, 6 sessions over 12 weeks	Symptom scores
Guthrie, 2003, [49]	UK; 14	40	82	12 (9.3)	107	12	Intervention group: brief psychotherapy, an antidepressant, or treatment as usual 12-week treatment	Subgroups of IBS according to cluster analysis
Tkachuk, 2003, [48]	Canada; 3	39.5	96	NA	28	21	Intervention group: cognitive-behavioral group therapy for 10 sessions over 9 weeks Control group: symptom monitoring with weekly telephone contact for 9 weeks	Improvement in IBS symptoms
Simren, 2004, [38]	Sweden; 1	42	67.9	NA	28	12	Intervention group: gut-directed hypnotherapy 1 hour per week for 12 weeks Control group: supportive therapy (dietary advice, info relaxation, education, general support) for 12 weeks	The sensory and motor component of the gastrocolic response
Davis, 2006, [39]	UK; 2	NA	77.6	5.08	54	12	Intervention group: aloe vera administrated at a dose of 50 ml for 4 times daily for one month Control group: matching placebo	Global symptom score
Roberts*, 2006, [46]	UK; 24	46.1	85.2	NA	81	48	Intervention group: gut-directed hypnotherapy for 5 sessions (approximately once per week) plus treatment as usual Control group: treatment as usual	IBS-specific quality-of-life measure and a full symptom score
Coban, 2012, [40]	Turkey; 3	41.8	73.5	3(1-20)	67	8	Intervention group: vacuum interferential current treatment for 12 sessions over 4 weeks Control group: placebo intervention for 12 sessions over 4 weeks	Global assessment of improvement scale
Lindfors*, 2012a, [41]	Sweden; 1	42	78.9	NA	90	48	Intervention group: gut-directed hypnotherapy for 12 sessions over 12 weeks Control group: supportive therapy with the same treatment frequency	Gastrointestinal symptom severity and quality of life
Lindfors*, 2012b, [41]	Sweden; 1	40.5	81.3	NA	48	48	Intervention group: gut-directed hypnotherapy for 12 sessions over 12 weeks Control group: waiting list control	Gastrointestinal symptom severity and quality of life
Hegade*, 2012, [31]	UK; 1	41.5	85.3	NA	34	64	Intervention group: general hypnotherapy for 4.7 sessions (one session per week) Control group: gut- directed hypnotherapy with similar treatment frequency.	IBS symptom score sheet

Table I (continued).

Dobbin, 2013, [42]	UK; 1	40.4	100	NA	97	24	Intervention group: biofeedback for 3 sessions over 12 weeks Control group: hypnotherapy for 3 sessions over 12 weeks	IBS symptom severity score
Moser*, 2013, [43]	Austria; 1	45.5	78.9	7.2	100	192	Intervention group: gut-directed hypnotherapy plus supportive talks for 10 sessions over 12 weeks Control group: supportive talks with medical treatment for 10 sessions over 12 weeks;	IBS impact scale
Attali, 2013, [28]	France; 1	50	74.2	NA	31	48	Intervention group: osteopathy for 6 sessions Control group: matching placebo	Assessment of IBS symptoms
Lövdahl, 2017, [47]	Sweden; 1	41	73.1	NA	119	12	Intervention group: individual gut-directed hypnotherapy for 8 sessions Control group: group gut-directed hypnotherapy for 8 sessions	IBS severity scoring system
Lackner, 2018, [44]	USA; 2	41.4	80.3	17.1 (14.4)	436	48	Intervention group: standard cognitive behavioral therapy for 10 sessions (once weekly) Control groups: (1) minimal contact cognitive behavioral therapy for 4 sessions; (2) IBS education for 4 sessions and 12 sessions of	Global improvement of IBS symptoms
Berens, 2018, [51]	Germany; 3	37	63.3	6.50 (7.79)	34	12	integrative group therapy (once weekly); (3) wait-listed control for 12weeks	IBS symptom severity scale
Holvoet, 2018, [45]	Belgium; 1	NA	NA	NA	62	12	Intervention group: single-dose fecal microbiota transplantation of donor stools Control group: fecal microbiota transplantation with autologous stools	Improvement of overall IBS symptoms and abdominal bloating
Everitt, 2019, [52]	UK; 77	43	76	7.4 (0.3–64.6)	558	96	Intervention group: telephone-delivered cognitive behavioral therapy for 6 sessions and 2 booster sessions Control groups: (1) web-based cognitive behavioral therapy for 8 sessions and three telephone therapy sessions plus two booster sessions; (2) treatment as usual	IBS symptom severity scale and work and social adjustment scale

IBS: irritable bowel syndrome; *: meta-analysis of hypnotherapy for refractory IBS included this study; NA: not applicable.

The data were primarily analyzed at week 12. We used the forest plot to detect if there were variations in treatment effects among trials (with variations in the definition of refractory IBS) assessing GDH. We also used I2 statistics (a method of detecting heterogeneity in effect sizes of the included trials in meta-analysis) to estimate whether the variations were significant (I2≥50% would be recognized as the evidence of significant variation). Meta-analysis was performed by using Review Manager 5.3.

RESULTS

Studies' Characteristics

A total of 322 articles were identified and 296 of them were excluded. We finally included 21 studies reported in 26 articles. Fig. 1 illustrates the flow of study screening and selection.

The review included 2,194 participants with refractory IBS, 79.2% of the participants being female. The study population had a median age of 41.6 years and a median disease duration of 6.57 years. Ten studies were performed in UK [24, 27, 30, 31, 39, 42, 46, 49, 52, 53], 4 were from Sweden [38, 41, 47], and the remaining 7 experiments came from Canada, Turkey, Austria, France, USA, Germany, and Belgium, respectively [28, 40, 43-45, 48, 51]. Nineteen studies focused on the effectiveness of therapies (1 cross-over included) [24, 27, 28, 30, 31, 39-48, 51-53], 1 mainly studied diagnostic approaches and 1 was about mechanism of hypnotherapy [38]. Two trials had a large sample size: Everitt (n=558) [52] and Lackner (n=436) [52]. They both evaluated the effectiveness of different modes of cognitive behavior therapy for refractory IBS. Table I shows the characteristics of the included studies.

Quality Assessment

The risk of bias in individual RCTs and the overall assessment in each item is detailed in Fig. 2. Fourteen (66.7%) studies were at a low risk of bias in random sequence generation [28, 38-44, 47, 48, 51-53], 10 (47.6%) in allocation concealment [39-42, 44, 47, 48, 52, 53], 2 (9.5%) in blinding of participants and personnel [39, 40], 9 (42.9%) in blinding of outcome assessment [30, 39-41, 44, 45, 48, 52], 11 (52.4%) in incomplete outcome data [27, 28, 38, 41, 43, 44, 47-49, 52], and 3 (14.3%) in selective reporting [43, 44, 52].

Table II. The detailed inclusion criteria of refractory IBS in the included studies

Study	Diagnostic criteria of IBS	Diagnostic criteria of refractory			Diagnostic Reference
		Symptom duration	Detailed invalid treatments	Severity assessment	
Whorwell, 1984, [24]	Others	At least 1 year	Had not responded to any therapy (mean=6 therapies per patient).	NA	NA
Harvey, 1989, [27]	Others	NA	Had not responded to standard medical therapy with various combinations of bulking agents and antispasmodic drugs.	NA	NA
Guthrie, 1993, [30]	Others	Over a year	Had attended the gastroenterology clinic for over six months without any improvement from conventional medical treatment.	NA	NA
Forbes, 2000, [53]	Rome I	At least 6 months	Have failed to respond adequately to the conventional uses of fibre, antispasmodics and dietary manipulation; had previously failed trials of antidepressant medication or any of a variety of "alternative" therapies, either self-administered or prescribed by non-medical practitioners	NA	NA
Guthrie, 2003, [49]	Rome I	At least 6 months	Resistance to medical treatment	Visual analogue scale score>59	NA
Tkachuk, 2003, [48]	Rome II	NA	NA	NA	NA
Simren, 2004, [38]	Rome II	NA	Refractory to standard medical treatment	NA	NA
Davis, 2006, [39]	Rome II	NA	Failed conventional management with antispasmodics, bulking agents and dietary intervention	NA	NA
Roberts*, 2006, [46]	Rome II	NA	NA	NA	NA
Coban, 2012, [40]	Rome III	NA	Unresponsive to diet and lifestyle modifications	NA	NA
Lindfors*, 2012a, [41]	Rome II	NA	Refractory to standard management	NA	NA
Lindfors*, 2012b, [41]	Rome II	NA	Refractory to standard management	NA	NA
Hegade*, 2012, [31]	NA	NA	NA	NA	NA
Dobbin, 2013, [42]	Rome III	NA	No symptomatic improvement eight weeks after the initial clinic visit	NA	NA
Moser*, 2013, [43]	Rome III	NA	Patients with severe and / or incapacitating complaints of IBS symptoms without an adequate response (refractory) to IBS therapies (IBS medication, antidepressants, or psychotherapies)	NA	NA
Attali, 2013, [28]	Rome III	NA	Fail to improve on a variety of drug therapies or have high healthcare utilization despite aggressive treatment of their IBS; unhappy about their care	NA	Olden, 2003
Lövdahl, 2017, [47]	NA	NA	NA	NA	NA
Lackner, 2018, [44]	Rome III	NA	NA	Gastrointestinal symptoms were at least moderately severe (i.e., they occurred at least twice weekly and caused some life interference)	NA
Berens, 2018, [51]	Rome III	NA	Refractory to previous IBS therapies (e.g., communication of the diagnosis or psyllium)	AR = no; SGA ≤ 1; abdominal pain intensity scale ≥3; IBS-C: ≤3 per week) or stool consistency (IBS-D: ≥1 time as type 6 or 7 on the BSF on ≥2 days per week; IBS-M: ≥25% type 6 or 7 and ≥25% type 1 or 2 on BSF	NA

Table II (continued)

Holvoet, 2018, [45]	Rome III	NA	Failed at least 3 conventional therapies for IBS	IBS-D or IBS-M had mean abdominal bloating sub-score of ≥ 3	NA
Everitt, 2019, [52]	Rome III	Over 12 months	Had been offered first-line therapies (eg, antispasmodics, antidepressants or fibre-based medications)	IBS-SSS ≥ 75	NICE,2015

IBS: irritable bowel syndrome; IBS-C: constipation-predominant IBS; IBS-D: diarrhea-predominant IBS; IBS-M: mixed-type IBS; NA: not mentioned; AR: adequate relief. SGA: subject's global assessment; IBS-SSS: IBS Symptom Severity Score; BSF: Bristol Stool Form Scale; NICE: National Institute for Health and Clinical Excellence; *: meta-analysis of hypnotherapy for refractory IBS included this study.

Characteristics of the Definitions of Refractory IBS

The detailed inclusion criteria of refractory IBS are demonstrated in Table II. Table III shows the results of the seven-item rating for summary of the definitions of refractory IBS in the included studies. Two (9.5%) studies used Rome I diagnostic criteria [49, 53], 6 (28.6%) Rome II [38, 39, 41, 46, 48], 8 (38.1%) used Rome III [28, 40, 42-45, 51, 52], 3 (14.3%) used other diagnostic criteria [24, 27, 30], and 2 unmentioned [31, 47]. Two (9.5%) studies provided sufficient information for the 7 items of diagnostic definitions [43, 44]. Six (28.6%) studies recruited patients with refractory IBS who were symptomatic over 12 months [24, 28, 30, 43, 44, 52], two (9.5%) were over 6 months [49, 53], and 13 (66.7%) were unclear. Eight (38.1%) studies recruited participants with previous failure of dietary intervention, and 13 (61.9%) were unclear [27, 31, 38-42, 45-48, 51]. One (4.8%) study recruited participants who failed to change lifestyle [40], and 20 (95.2%) were unclear [24, 27, 28, 30, 31, 38, 39, 41-49, 51-53]. Eleven (52.4%) studies recruited participants unresponsive to pharmacological intervention for ≥ 6 weeks [28, 30, 38, 40, 41, 43, 44, 51-53], and 10 (47.6%) were unclear [24, 27, 31, 39, 42, 45-49]. Two (9.5%) studies recruited participants unresponsive to psychology for ≥ 6 sessions [28, 44], one (4.8%) did not apply this criteria [43], and 18 (85.7%) were unclear [24, 27, 30, 31, 38-42, 45-49, 51-53]. Four (19.0%) studies had IBS symptom severity assessment, and 16 (76.2%) were unclear [24, 27, 28, 30, 31, 38-43, 46-48, 50, 53. Eight (38.1%) studies showed that patients had adequate explanation and reassurance before entering the study [24, 28, 30, 42-44, 46, 52], and 13 (61.9%) were unclear [27, 31, 38-41, 45, 47-49, 51, 53]. Only two (9.5%) RCTs reported diagnostic reference of refractory IBS [48, 52].

Meta-analysis of Gut-directed Hypnotherapy for Refractory IBS

Nineteen out of 21 studies examined the effect of various therapeutics on refractory IBS [24, 27, 28, 30, 31, 39-48, 51-53]; and 5 trials assessed the effectiveness of GDH [41, 43, 46, 51]. Three studies (n=271) compared GDH with supportive

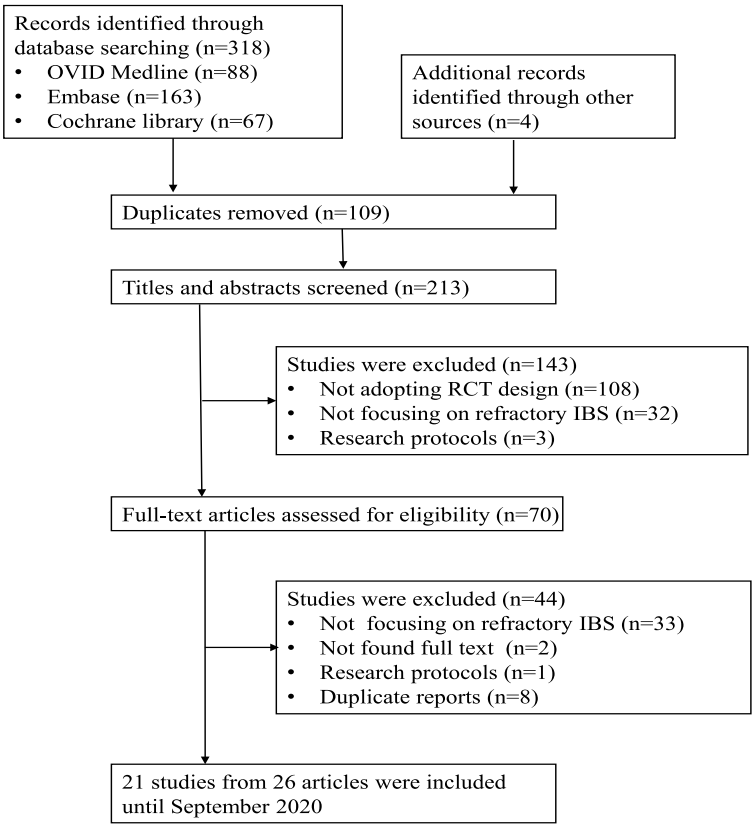

Fig. 1. Search and screening process

Table III. Characteristics of definition of refractory IBS in the included studies

Study	Symptoms ≥12months	Dietary intervention	Lifestyle modification	Pharmacological treatments ≥6weeks	Psychological treatments ≥6 sessions	Severity assessment	Adequate explanation and assurance
Whorwell, 1984, [24]	🟢	🟡	🟡	🟡	🟡	🟡	🟢
Harvey, 1989, [27]	🟡	🟡	🟡	🟡	🟡	🟡	🟡
Guthrie, 1993, [30]	🟢	🟡	🟡	🟢	🟡	🟡	🟢
Forbes, 2000, [53]	🔴	🟢	🟡	🟢	🟡	🟡	🟡
Guthrie, 2003, [49]	🔴	🟡	🟡	🟡	🟡	🟢	🟡
Tkachuk,2003, [48]	🟡	🟡	🟡	🟡	🟡	🟡	🟡
Simren, 2004, [38]	🟡	🟡	🟡	🟢	🟡	🟡	🟡
Davis, 2006, [39]	🟡	🟢	🟡	🟡	🟡	🟡	🟡
Roberts*, 2006 [46]	🟡	🟡	🟡	🟡	🟡	🟡	🟢
Coban, 2012, [40]	🟡	🟢	🟢	🟢	🟡	🟡	🟡
Lindfors*, 2012a, [41]	🟡	🟢	🟡	🟢	🟡	🟡	🟡
Lindfors*, 2012b, [41]	🟡	🟢	🟡	🟢	🟡	🟡	🟡
Hegade*, 2012, [31]	🟡	🟡	🟡	🟡	🟡	🟡	🟡
Dobbin, 2013, [42]	🟡	🟡	🟡	🟡	🟡	🟡	🟢
Moser* 2013, [43]	🟢	🟢	🟡	🟢	🔴	🟡	🟢
Attali, 2013, [28]	🟢	🟢	🟡	🟢	🟢	🟡	🟢
Lövdahl, 2017, [47]	🟡	🟡	🟡	🟡	🟡	🟡	🟡
Lackner, 2018, [44]	🟢	🟡	🟡	🟢	🟢	🟢	🟢
Berens, 2018, [51]	🟡	🟡	🟡	🟢	🟡	🟢	🟡
Holvoet, 2018, [45]	🟡	🟡	🟡	🟡	🟡	🟢	🟡
Everitt, 2019, [52]	🟢	🟢	🟡	🟢	🟡	🟢	🟢

🟢 Yes; 🟡 Unclear; 🔴 No. Annotations: The characteristics of definition were examined in 7 aspects: duration of symptoms lasting for at least 12 months, unresponsive to dietary intervention, unresponsive to lifestyle modification, pharmacological treatments, psychological treatments, severity assessment or adequate explanation and assurance. *: the meta-analysis of hypnotherapy for refractory IBS included this study.

treatments [41, 43, 46]. Two studies used Rome I diagnostic criteria [41, 46], and 1 used Rome III [43]. One study recruited patients with refractory IBS symptoms over 12 months and did not adopt unresponsive to psychology therapy for ≥ 6 sessions [43], and two were unclear [41, 46]. Two studies recruited participants with previous failure of dietary intervention, unresponsive to pharmacological intervention for ≥ 6 weeks, and adequate explanation and reassurance [41, 43], and one was unclear [46]. Three studies were unclear about lifestyle modification and symptom severity assessment [41, 43, 46]. Two studies (n=82) compared GDH with waiting-list control [41, 51]. The studies may have had different definitions in the above seven criteria except unresponsiveness to pharmacological intervention. Compared with supportive treatments, the SMDs of GDH ranged from -0.56 to -0.87, and the pooled result was -0.69 (95%CI -0.93 to -0.44; I^2=0%; Fig. 3A), indicating the results were consistent among the three studies. Compared with the waiting-list control, the SMDs of GDH ranged from -0.54 to -0.55, and the pooled result was -0.54 (95% CI -0.98 to -0.10; I^2=0%; Fig. 3B), also indicating a consistent result in the two studies.

DISCUSSION

We performed a systematic review to summarize the key points of the definition of refractory IBS in published RCTs and further to explore the impact of variations in the definition on therapeutic effect of GDH. We found that the definition of refractory IBS was obscure in most published trials. Persistent symptoms ≥ 12 months and unresponsiveness to adequate explanation and reassurance were the most confirmed statements in defining refractory IBS. Our meta-analysis showed that GDH was efficacious for refractory IBS and variations in the definition of refractory IBS had no impact on the effect size estimation of GDH.

Rome criteria were used widely in the diagnosis of IBS [36, 37], but the diagnostic criteria of refractory IBS were not clearly defined, although the question and the solution had been proposed in 1997 [25]. There is still no clear definition for refractory IBS in subsequently conducted clinical trials. The term "refractory" was used to express "intractable", "resistant", or "failed". In our systematic review, 14 studies reported that their definitions of refractory IBS were developed based on a consensus from gastroenterologists or research investigators [31, 24, 38-48], 5 studies referred to the previous trials directly [28, 30, 49-51], and only 2 studies reported clearly diagnostic reference [28, 52]. In addition, "refractory", in these studies, was defined as "not responded to any therapy" [24], or "standard medical treatment" [28, 50], or "no response to standard medical therapy" [39, 50], or "conventional treatment" [30, 39, 49], or "refractory to their former treatment" [43, 51], or

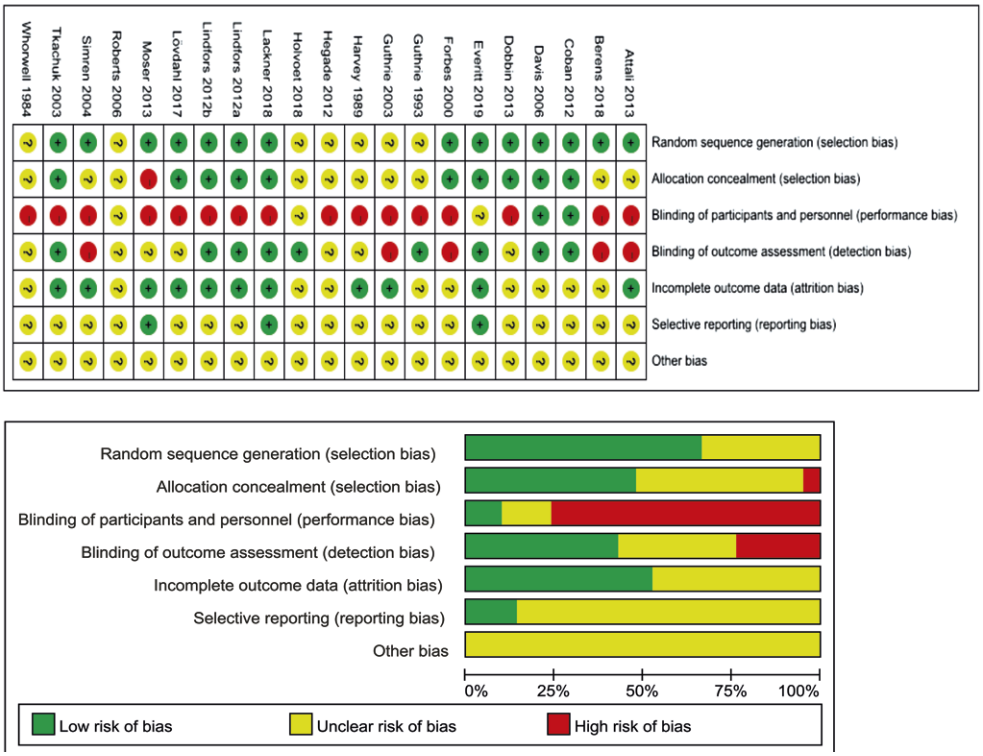

Fig. 2. The risk of bias assessment.

"not responded to first-line therapies" [52], or "unresponsive to diet and lifestyle modifications or/and medical therapy"[40, 41, 53], or "no symptomatic improvement after the initial clinic visit" [42], and 5 studies had no specific description [31, 45-48]. These facts showed an inconsistent recognition in how to define a refractory condition in the IBS population, which might have significant impact on future meta-analyses aiming to study the efficacy of target therapeutics in patients with refractory IBS and might confuse clinicians in which population they should apply the evidence. Therefore, our review demonstrated an urgent need to develop consensus and guidance to define the refractory IBS population, since the proportion of patients refractory to conventional pharmacological treatments is substantial.

The diversity in the diagnostic criteria of refractory IBS was reflected in the following aspects. First, the symptom

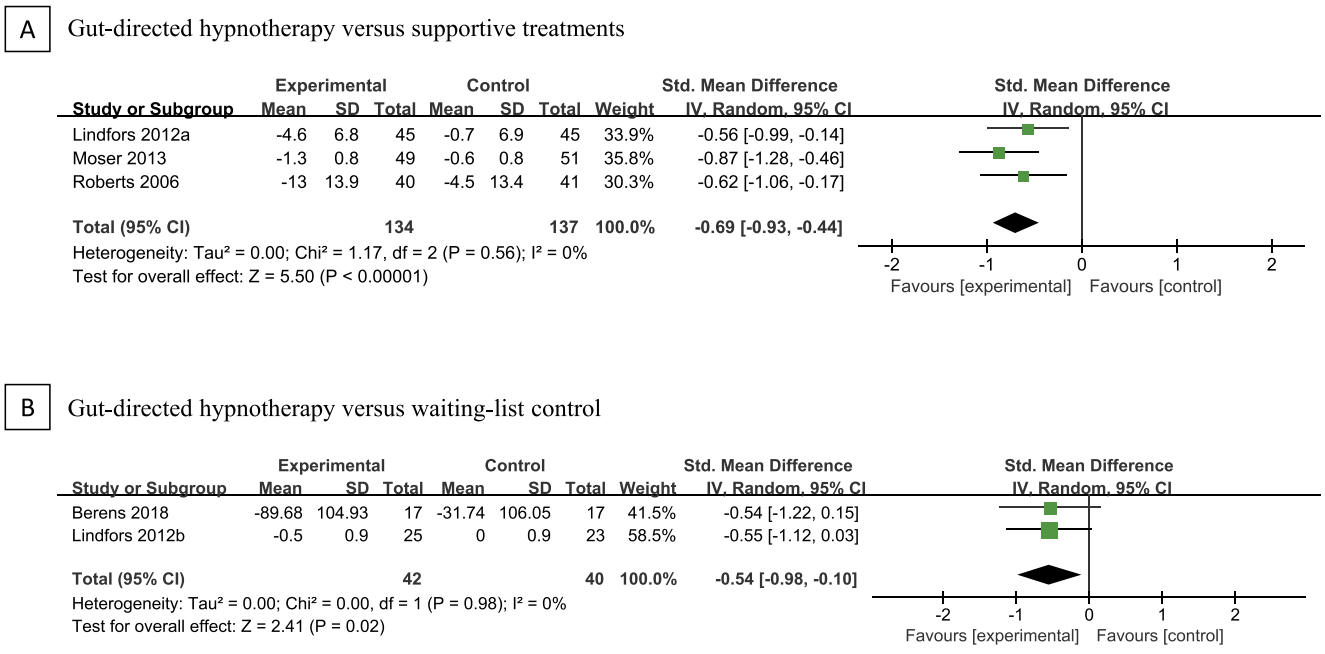

Fig. 3. Meta-analysis of gut-directed hypnotherapy for refractory IBS. Annotations: The aim of the meta-analysis was to examine the impact of varied definitions on the effect size estimation of gut-directed hypnotherapy. The results showed that the effect size was consistent in the comparison of gut-directed hypnotherapy versus supportive treatments and gut-directed hypnotherapy versus waiting-list control.

duration of refractory IBS was inconsistent among trials. Six RCTs reported the eligible participants with refractory IBS had ongoing symptoms over a year [24, 28, 30, 43, 44, 54], but two RCTs had ongoing symptoms at least 6 months [49, 53]. The NICE guideline [33], and Rajagopalan [25] indicated that patients with "true" refractory IBS had persistent symptoms more than 12 months despite dietary intervention, lifestyle changes and pharmacological treatment. Although the duration for a refractory IBS seems to be clearly defined, only six of the included studies adopted the criterion. Secondly, although resistant to pharmacological treatments was a consensus in defining refractory IBS, the types of drugs and the total duration of drug administration were ambiguously described in most of the studies. We defined unresponsiveness to pharmacological treatments for at least 6 weeks in the review, which was fulfilled by only four studies; the types of drugs were not mentioned. Types and dosages of drugs are essential in defining refractory IBS, since resistant to antispasmodics is different to resistant to 5-HT3 antagonists - the latter has more convincing evidence. Additionally, differentiation in the subtypes of IBS leads to a different choice of pharmacological treatments (loperamide is the recommended drug for diarrhea-predominant IBS, but it is not recommended for overall IBS symptoms [32]), so future studies should at least provide information for whether the participants use guideline-recommended treatments or treatments with convincing evidence. Thirdly, the dietary interventions and lifestyle modifications should be met. In most of the published guidelines and reviews [1, 34, 55, 56] the two interventions were the first choices for relieving IBS symptoms; the studies suggested that low fermentable oligosaccharides, disaccharides, and monosaccharides and polyols (FODMAPs) diet, gluten-free diet, probiotic supplements and moderate to high levels of physical activity are beneficial for the patients, although the evidence is limited to low quality. Our review showed that most of the studies did not report the history of dietary interventions and lifestyle modifications, which may cause bias, as some patients might have symptoms relieved through an improvement in diet. And the two items link to the 7th item, whether the participants had been adequately educated or reassured for their symptoms. Fourth, the severity of symptoms seemed to play a role in defining refractory IBS. In our study, 5 trials reported the clinically significant symptoms assessed by scales, but 16 trials did not mention this issue.

Finally, resistance to psychological treatments should be considered as one of the criteria. Ford et al. [34] believed that psychological disorders were a common in patients with refractory IBS, Simrén et al. [38] shared the same perspective. However, many included studies tested the effectiveness of psychological treatments for refractory IBS (ie, cognitive behavioral therapy and hypnotherapy), meaning that we should not limit the psychological interventions to pharmacological therapy, such as antidepressants. Our review found that the criteria "a history of failure to psychological therapy" used in the definition of the refractory IBS was not specified in 3 studies [28, 43, 44], two adopted the criteria [28,45], and one denied it [43]. In future trials, failure to antidepressants should at least be considered in the definition of refractory IBS.

In our meta-analysis, we found that GDH had a consistent beneficial effect, although the included studies had different definitions for refractory IBS. The results could not be simply viewed as varied definition for refractory IBS had no impact on the results. On the contrary, it may reflect that the included population might not be the refractory IBS; the included participants might just be unresponsive to one or some of the pharmacological treatments for gastrointestinal symptoms, but not to treatments for psychological symptoms. In addition, the analysis was limited by the small number of included studies and by the lack of participant-level data.

The strength of our review was the discovery of variations in the diagnostic criteria of refractory IBS in published RCTs, and we found it a widespread problem through a systematic review. Moreover, we also conducted a verification test through a meta-analysis of the effect estimates of GDH. Our study provided evidence for future trials and diagnoses of refractory IBS for researchers and clinicians.

Several limitations of this study are as follows. First, the quality of the included trials was poor, but it was considered only in the meta-analysis. Second, the definition of refractory IBS was neither detailed, nor available in most of the included studies.

CONCLUSIONS

Our review found that varied definitions in refractory IBS were common phenomena in clinical studies. Resistance to symptom severity assessment and psychological treatments should be more explicitly defined. GDH was efficacious for refractory IBS and was not affected by the diversity in the definition of refractory IBS among RCTs.

Conflicts of interest: None to declare.

Authors' contribution: H.Z. and M.C. designed the study. W.Y.P., K.Y., D.Q., and T.C.T. acquired the study data. H.Z and M.C. analyzed the data. W.Y.P drafted the manuscript. M.C. and H.Z. checked the correctness and completeness of the study data. All the authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. They also revised the manuscript and approved it for publication.

REFERENCES

1. National Collaborating Centre for Nursing and Supportive Care (UK). Irritable Bowel Syndrome in Adults: Diagnosis and Management of Irritable Bowel Syndrome in Primary Care [Internet]. London: Royal College of Nursing (UK); 2008. [Cited 2020 Jun 21]. (National Institute for Health and Clinical Excellence: Guidance). Available from: http://www.ncbi.nlm.nih.gov/books/NBK51953/
2. Spiller R, Aziz Q, Creed F, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut 2007;56:1770–1798. doi:10.1136/gut.2007.119446
3. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. JAMA 2015;313:949–958. doi:10.1001/jama.2015.0954
4. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol 2014;6:71-80. doi:10.2147/CLEP.S40245

5. Lovell RM, Ford AC. Global Prevalence of and Risk Factors for Irritable Bowel Syndrome: A Meta-analysis. Clin Gastroenterol Hepatol 2012;10:712-721.e4. doi:10.1016/j.cgh.2012.02.029
6. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. Health Qual Life Outcomes 2017;15:35. doi:10.1186/s12955-017-0611-2
7. Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. Aliment Pharmacol Ther 2014;40:1023–1034. doi:10.1111/apt.12938
8. Ek WE, Reznichenko A, Ripke S, et al. Exploring the genetics of irritable bowel syndrome: a GWA study in the general population and replication in multinational case-control cohorts. Gut 2015;64:1774–1782. doi:10.1136/gutjnl-2014-307997
9. Kalantar JS, Locke GR 3rd, Zinsmeister AR, Beighley CM, Talley NJ. Familial aggregation of irritable bowel syndrome: a prospective study. Gut 2003;52:1703–1707. doi:10.1136/gut.52.12.1703
10. Makker J, Chilimuri S, Bella JN. Genetic epidemiology of irritable bowel syndrome. World J Gastroenterol 2015;21:11353-11361. doi:10.3748/wjg.v21.i40.11353
11. Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. Gut 1973;14:125–132. doi:10.1136/gut.14.2.125
12. Trimble KC, Farouk R, Pryde A, Douglas S, Heading RC. Heightened visceral sensation in functional gastrointestinal disease is not site-specific: Evidence for a generalized disorder of gut sensitivity. Dig Dis Sci 1995;40:1607–1613. doi:10.1007/BF02212678
13. Zhou Q, Zhang B, Verne NG. Intestinal membrane permeability and hypersensitivity in the irritable bowel syndrome. Pain 2009;146:41–46. doi:10.1016/j.pain.2009.06.017
14. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: A technical review for practice guideline development. Gastroenterology 1997;112:2120–2137. doi:10.1053/gast.1997.v112.agast972120
15. Blomhoff S, Spetalen S, Jacobsen MB, Malt UF. Phobic Anxiety Changes the Function of Brain-Gut Axis in Irritable Bowel Syndrome. Psychosom Med 2001;63:959–965. doi:10.1097/00006842-200111000-00015
16. Mayer EA, Tillisch K. The Brain-Gut Axis in Abdominal Pain Syndromes. Annu Rev Med 2011;62:381–396. doi:10.1146/annurev-med-012309-103958
17. Ford AC, Talley NJ. Mucosal inflammation as a potential etiological factor in irritable bowel syndrome: a systematic review. J Gastroenterol 2011;46:421–431. doi:10.1007/s00535-011-0379-9
18. Surdea-Blaga T, Băban A, Dumitrascu DL. Psychosocial determinants of irritable bowel syndrome. World J Gastroenterol 2012;18:616-626. doi:10.3748/wjg.v18.i7.616
19. Simrén M, Barbara G, Flint HJ, et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut 2013;62:159–176. doi:10.1136/gutjnl-2012-302167
20. DuPont HL. Review article: evidence for the role of gut microbiota in irritable bowel syndrome and its potential influence on therapeutic targets. Aliment Pharmacol Ther 2014;39:1033-1042. doi:10.1111/apt.12728
21. Bhattarai Y, Muniz Pedrogo DA, Kashyap PC. Irritable bowel syndrome: a gut microbiota-related disorder? Am J Physiol Gastrointest Liver Physiol 2017;312:G52–G62. doi:10.1152/ajpgi.00338.2016
22. Pimentel M, Lembo A. Microbiome and Its Role in Irritable Bowel Syndrome. Dig Dis Sci 2020;65:829–839. doi:10.1007/s10620-020-06109-5
23. Camilleri M. Management Options for Irritable Bowel Syndrome. Mayo Clin Proc 2018;93:1858–1872. doi:10.1016/j.mayocp.2018.04.032
24. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. Lancet 1984;2:1232-1234. doi:10.1016/s0140-6736(84)92793-4
25. Rajagopalan M. Defining treatment resistance in the irritable bowel syndrome. Gut 1997;41:723. doi:10.1136/gut.41.5.723
26. Guthrie E. Brief Psychotherapy with Patients with Refractory Irritable Bowel Syndrome. Br J Psychother 1991;8:175–188. doi:10.1111/j.1752-0118.1991.tb01174.x
27. Harvey RF, Hinton RA, Gunary RM, Barry RE. Individual and group hypnotherapy in treatment of refractory irritable bowel syndrome. Lancet 1989;333:424–425. doi:10.1016/s0140-6736(89)90013-5
28. Attali TV, Bouchoucha M, Benamouzig R. Treatment of refractory irritable bowel syndrome with visceral osteopathy: Short-term and long-term results of a randomized trial. J Dig Dis 2013;14:654–661. doi:10.1111/1751-2980.12098
29. Sibelli A, Chalder T, Everitt H, Workman P, Bishop FL, Moss-Morris R. The role of high expectations of self and social desirability in emotional processing in individuals with irritable bowel syndrome: A qualitative study. Br J Health Psychol 2017;22:737–762. doi:10.1111/bjhp.12264
30. Guthrie E, Creed F, Dawson D, Tomenson B. A randomised controlled trial of psychotherapy in patients with refractory irritable bowel syndrome. Br J Psychiatry 1993;163:315–321. doi:10.1192/bjp.163.3.315
31. Hegade VS, Mohammed N, Barnett A, Denyer M. PWE-063 Effectiveness of general hypnotherapy and gut-directed hypnotherapy in refractory irritable bowel syndrome. Gut 2012;61(Suppl 2):A323. doi:10.1136/gutjnl-2012-302514d.63
32. Moayyedi P, Andrews CN, MacQueen G, et al. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome (IBS). J Can Assoc Gastroenterol 2019;2:6–29. doi:10.1093/jcag/gwy071
33. National Institute for Health and Care Excellence (UK). Addendum to NICE guideline CG61, Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care. London: National Institute for Health and Care Excellence (UK); 2015 Feb. (NICE guideline, No. CG61.1.). Available from: http://www.ncbi.nlm.nih.gov/books/NBK550725/
34. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. Longo DL, editor. N Engl J Med 2017;376:2566-2578. doi:10.1056/NEJMra1607547
35. Olden KW. Approach to the Patient with Severe, Refractory Irritable Bowel Syndrome. Curr Treat Options Gastroenterol 2003;6:311–317. doi:10.1007/s11938-003-0023-8
36. Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. J Clin Med 2017;6:99. doi:10.3390/jcm6110099
37. Schmulson MJ, Drossman DA. What Is New in Rome IV. J Neurogastroenterol Motil 2017;23:151–163. doi:10.5056/jnm16214
38. Simrén M, Ringström G, Björnsson ES, Abrahamsson H. Treatment with hypnotherapy reduces the sensory and motor component of the gastrocolonic response in irritable bowel syndrome. Psychosom Med 2004;66:233–238. doi:10.1097/01.psy.0000116964.76529.6e
39. Davis K, Philpott S, Kumar D, Mendall M. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. Int J Clin Pract 2006;60:1080–1086. doi:10.1111/j.1742-1241.2006.00980.x
40. Coban Ş, Akbal E, Köklü S, et al. Clinical trial: transcutaneous interferential electrical stimulation in individuals with irritable bowel syndrome - a prospective double-blind randomized study. Digestion 2012;86:86–93. doi:10.1159/000338301

41. Lindfors P, Unge P, Arvidsson P, et al. Effects of gut-directed hypnotherapy on ibs in different clinical settings—results from two randomized, controlled trials. Am J Gastroenterol 2012;107:276-285. doi:10.1038/ajg.2011.340
42. Dobbin A, Dobbin J, Ross C, Graham C, Ford MJ. Randomised controlled trial of brief intervention with biofeedback and hypnotherapy in patients. J R Coll Physicians Edinb 2013;43:15-23. doi:10.4997/JRCPE.2013.104
43. Moser G, Trägner S, Gajowniczek EE, et al. Long-Term Success of GUT-Directed Group Hypnosis for Patients With Refractory Irritable Bowel Syndrome: A Randomized Controlled Trial. Am J Gastroenterol 2013;108:602-609. doi:10.1038/ajg.2013.19
44. Lackner JM, Jaccard J, Keefer L, et al. Improvement in Gastrointestinal Symptoms After Cognitive Behavior Therapy for Refractory Irritable Bowel Syndrome. Gastroenterology 2018;155:47–57. doi:10.1053/j.gastro.2018.03.063
45. Holvoet T, Joossens M, Jerina B, et al. 617 - Fecal Microbiota Transplantation in Irritable Bowel Syndrome with Predominant Abdominal Bloating: Results from a Double Blind, Placebo-Controlled Clinical Trial. Gastroenterology 2018;154 Suppl 1:S-130. doi:10.1016/S0016-5085(18)30860-6
46. Roberts L, Wilson S, Singh S, Roalfe A, Greenfield S. Gut-directed hypnotherapy for irritable bowel syndrome: piloting a primary care-based randomised controlled trial. Br J Gen Pract 2006;56:115–121.
47. Lövdahl J, Palsson OS, Ringström G, Törnblom H, Simrén M. OP282 Individual versus group hypnotherapy for IBS: A randomized controlled trial. United Eur Gastroenterol J 2017;5(5_suppl):A120–121. doi:10.1177/2050640617725668
48. Tkachuk GA, Graff LA, Martin GL, Bernstein CN. Randomized controlled trial of cognitive-behavioral group therapy for irritable bowel syndrome in a medical setting. J Clin Psychol Med Settings 2003;10:57–69. doi:10.1023/A:1022809914863
49. Guthrie E, Creed F, Fernandes L, et al. Cluster analysis of symptoms and health seeking behaviour differentiates subgroups of patients with severe irritable bowel syndrome. Gut 2003;52:1616-1622. doi:10.1136/gut.52.11.1616
50. Harvey RF, Hinton RA, Gunary RM, Barry RE. Individual and group hypnotherapy in treatment of refractory irritable bowel syndrome. Lancet 1989;1:424–425. doi:10.1016/s0140-6736(89)90013-5
51. Berens S, Stroe-Kunold E, Kraus F, et al. Pilot-RCT of an integrative group therapy for patients with refractory irritable bowel syndrome (ISRCTN02977330). J Psychosom Res 2018;105:72–79. doi:10.1016/j.jpsychores.2017.12.002
52. Everitt HA, Landau S, O'Reilly G, et al. Assessing telephone-delivered cognitive–behavioural therapy (CBT) and web-delivered CBT versus treatment as usual in irritable bowel syndrome (ACTIB): a multicentre randomised trial. Gut 2019;68:1613-1623. doi:10.1136/gutjnl-2018-317805
53. Forbes A, MacAuley S, Chiotakakou-Faliakou E. Hypnotherapy and therapeutic audiotape: effective in previously unsuccessfully treated irritable bowel syndrome? Int J Colorectal Dis 2000;15:328-334. doi:10.1007/s003840000248
54. Everitt HA, Landau S, O'Reilly G, et al. Cognitive behavioural therapy for irritable bowel syndrome: 24-month follow-up of participants in the ACTIB randomised trial. Lancet Gastroenterol Hepatol 2019;4:863-872. doi:10.1016/S2468-1253(19)30243-2
55. Simrén M, Törnblom H, Palsson OS, Whitehead WE. Management of the multiple symptoms of irritable bowel syndrome. Lancet Gastroenterol Hepatol 2017;2:112-122. doi:10.1016/S2468-1253(16)30116-9
56. Moayyedi P, Ford AC. Symptom-Based Diagnostic Criteria for Irritable Bowel Syndrome: the More Things Change, the More They Stay the Same. Gastroenterol Clin North Am 2011;40:87-103. doi:10.1016/j.gtc.2010.12.007