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REVIEW

Sex-Gender Differences in the Effectiveness of Treatment of Irritable Bowel Syndrome: A Systematic Review

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Background: In recent years, research on sex-gender differences in health care has increasingly recognized that men and women differ in the way symptoms occur, in risk factors for certain conditions and in the way they respond to the same treatment. A disease that is known to often present differently in women and men is irritable bowel syndrome (IBS). Given the difference in prevalence, predominant symptoms and possible other pathophysiology, it is conceivable that a difference in treatment effectiveness in men and women is a discovery waiting to be found.

Purpose: To determine whether there are differences in treatment effectiveness between men and women with irritable bowel syndrome.

Materials and Methods: We searched on PubMed and EMBASE, selecting randomized controlled trials comparing IBS treatment in men and women over 18 years old. One researcher performed the inclusion process, and two researchers independently performed a quality assessment. A descriptive analysis was conducted.

Results: Twelve studies, randomizing 1847 men and 3562 women, were included in this review. Treatment with serotonin antagonist alosetron, treatment with ibodutant and crofelemer and adding cognitive behavioral therapy to medical treatment found significant differences between men and women in favor of effectiveness towards women in either satisfactory relief of overall IBS symptoms or percentage of pain-free days.

Conclusion: Sex-gender can be a determining factor in the effectiveness of IBS treatment. Due to the limited number of studies per treatment option, no recommendations can be made on the choice of a specific treatment. It is clear, however, that so as not to miss beneficial treatment options for either sex, the inclusion, analysis and description of data on the basis of sex is of the utmost importance.

Keywords: colonic diseases, abdominal pain, randomized controlled trials, male, female, treatment

Introduction

Irritable bowel syndrome (IBS) is a chronic gastrointestinal (GI) disorder, characterized by recurrent abdominal pain and altered bowel movements.[1] The main symptoms are constipation, diarrhea, bloating or pain, which seem to fluctuate in intensity and duration over time.[2] IBS is diagnosed clinically, based on the Rome diagnostic criteria (Appendix 1), physical examination and limited diagnostic tests. IBS is one of the most common GI disorders, accounting for 12% of all primary care visits, and is the most common reason for visiting the gastroenterologist.

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Patients with IBS report that it substantially reduces their quality of life and work productivity.[2,3] IBS affects both men and women, but the prevalence of IBS is higher in women than in men, with an odds ratio of 1.67.[4] Men and women appear to experience different symptoms to be the most bothering and may react differently to treatment. IBS with constipation (IBS-C) is significantly more common in women, whereas IBS with diarrhea (IBS-D) is more common in men.[5]

There are many theories to explain these differences. It can partly be explained by a variety of sex- and gender-related biological and psychosocial factors.[5] Since several studies have shown that there is an effect of sex hormones, especially estrogen and progesterone, on bowel function, gastrointestinal transit time and the processing of pain stimuli in the central nervous system, it is conceivable that this system may be related to the greater prevalence of functional syndromes in women.[6] Whilst recurring pain and discomfort in the pelvic region is quite familiar to women, moreover, it is a rare experience for men. Women, therefore, might be more vigilant toward sensory stimuli from the pelvic area and are also able to discriminate between physiological discomfort and potentially noxious events.[5] In addition, it is becoming evident that the gastrointestinal tract microbiota differ in males and females.[7] Likely causes include differing sex hormone levels in males and females, in part driven by sex differences in systemic sex hormone concentrations but also influenced by microbiota themselves. A different microbiota composition drives sex differences in innate and adaptive immunity, which might lead to sex-dependent susceptibility to IBS. This sexually dysmorphic microbiome has been termed the "microgenderome."[7]

Besides different underlying pathophysiology mechanisms, another reason for male and female patients to require different treatments is a difference in response to drugs. As knowledge of medicinal drug toxicology and pharmacology is expanding, it has become clear that men and women react differently to drug treatments due to physiological differences such as body weight and length, total body water, extra- and intracellular water and surface area, as well as differences in pharmacodynamics and pharmacokinetics.[8] As IBS is a prevalent yet heterogeneous disorder, patient selection for a given treatment can be challenging and, considering the underlying mechanisms indicated above, may be influenced by a patient's sex or gender.[9]

"Sex" is commonly defined as the property or quality by which organisms are classified as female or male on the basis of biological, that is chromosomal and hormonal, characteristics, whereas "gender" is understood in terms of masculinity and femininity, which are largely culturally determined. It is clear that sex and gender, though set apart as two concepts, are strongly intertwined in medicine, and they are used interchangeably in this study.[10]

The above-mentioned differences in pathophysiology might have implications for personalized treatment of IBS. It is of great importance to review what is known about differences in response to treatment in men and women with IBS. The main objective of our study, therefore, is to determine whether there are differences in treatment effectiveness between men and women with irritable bowel syndrome. This way we aim to provide tools for a well-considered personalized treatment of patients with IBS.

Table 1 shows a list of the most commonly used abbreviations in this article.

Materials and Methods

Data Sources and Study Selection

We conducted a broad search on PubMed and EMBASE. With the assistance of a professional librarian, a search strategy was set up with combined MeSH terms and free text terms in order to build a broad discovery net for articles on IBS and these terms: sex, sexism, gender (identity), difference man/women, treatment, disease management, therapy or pharmacology (Table 2). After this search had been executed, studies were loaded in Endnote X9 to delete duplicates. A random sample of ten meta-analyses was examined to determine if they yielded any new RCTs that needed to be considered for inclusion. This was not the case. Studies were screened in title and abstract to ascertain: 1) whether the study was solely about IBS; 2) whether both men and women were included; and 3) whether the study was a randomized controlled trial. Articles were considered eligible for inclusion when they met the following criteria: 1) population included men and women over the age of 18 who were diagnosed with IBS; and 2) study analyzed men and women as two subgroups; and 3) the study was written in English. We have chosen to include only studies that look at the difference between men and women in the effectiveness of treatment. Studies that did not meet the inclusion criteria were excluded.

Table 1 Meaning of Abbreviations from This Systematic Review

Abbreviation	In Full
5-HT	Serotonin
AST	Spherical carbon adsorbent
BS-IBS	Behavior Scale for irritable bowel syndrome
CBT	Cognitive behavioral therapy
EMT	Emotional awareness and medical treatment
FDA	Food and Drug Administration
GI	Gastro-intestinal
GP	General practitioner
HADS	Hospital anxiety and depression scale
IBS	Irritable bowel syndrome
IBS-C	Constipation predominant irritable bowel syndrome
IBS-D	Diarrhea predominant irritable bowel syndrome
IBS-M	Mixed diarrhea and constipation irritable bowel syndrome
LBT	Lactulose breath testing
MT	Medical treatment
RCT	Randomized controlled trial
SIBO	Small intestine bacterial overgrowth
SSS	Symptom severity scale
VAS	Visual analogue scale (for pain measurement)
WASA	Work and social adjustment scale

Quality Assessment

The quality of the eligible studies was assessed by two independent researchers (LK, JW) using the Quality Assessment of Controlled Intervention Studies (QACIS) tool by the National Institute of Health (Appendix 2).[11] The advantage of this tool over other frequently used assessment tools, such as the Cochrane Risk of Bias Tool, is that it consists of specific yes-or-no questions on criteria that a study should meet.[12] As a result, QACIS provides a clear dividing line between whether or not an RCT should be included.

Based on the QACIS tool, studies were categorized as POOR, FAIR or GOOD. If a "fatal flaw" was present, studies were instantly rated as POOR. Fatal flaws are high dropout rates, a small sample size and statistical power <80%, no intention-to-treat analysis or other unsuitable statistical analysis. Apart from these fatal flaws, assessment items that were considered to be of special importance to discriminate between studies of good, fair and poor quality were: 1) an adequate description of the randomization method; 2) the blinding of participants and providers; 3) the use of validated outcome measures; 4) the percentage of treatment adherence; and 5) similar baseline characteristics (Appendix 2). To differentiate between POOR, FAIR or GOOD (apart from fatal flaws), a rating scale was constructed, in which the above-mentioned

Table 2 Full Search Strategy

Database	Search Strategy	Results
Pubmed	Intervention: "Colonic Diseases, Functional/therapy"[Mesh] OR Therapeutics [MesH] OR pharmacology [mesh] OR disease management [mesh] OR gastrointestinal agents [mesh] OR "Gastrointestinal Agents" [Pharmacological Action] OR therap* [tiab] OR therapeutic* [tiab] OR treatment* [tiab] OR pharmacolog* OR Disease Management* [tiab] OR gastrointestinal Agent* [tiab] OR gastrointestinal drug* [tiab] OR gastric agent* [tiab] OR digestant* [tiab] AND Population: ("Colonic Diseases, Functional"[Mesh]) OR (continuous abdominal pain[tiab] OR continuous gastrointestinal pain[tiab] OR frequent abdominal pain[tiab] OR frequent gastrointestinal pain[tiab] OR Functional abdominal pain [tiab] OR Functional colon disease*[tiab] OR Functional colonic disease*[tiab] OR Functional colorectal disease*[tiab] OR Functional gastrointestinal pain [tiab] OR Irritable bowel [tiab] OR Irritable Colon[tiab] OR Mucous Coliti*[tiab]) AND Population: "Sexism"[Mesh] OR "Sex Distribution"[Mesh] OR "Sex Factors"[Mesh] OR "Sex"[Mesh] OR "Sex Characteristics"[Mesh] OR "Gender Identity"[Mesh] OR Sex[tiab] OR gender[tiab] OR sexism[tiab] OR (difference* [tiab] AND (man[tiab] OR men[tiab] OR male*[tiab]) AND (woman[tiab] OR women[tiab] OR female*[tiab]))	603
EMBASE	Intervention: Exp therapy/or treatment.mp. or exp pharmacology/or exp "ceiling effect (pharmacology)"/or disease management.mp. or exp disease management Population: Irritable colon.mp. or exp irritable colon/ exp gender identity/or "sex and gender".mp. or exp sex difference/or exp gender/or exp gender bias/or exp sexism/or sex distribution.mp. or exp sex ratio/or exp sex factor/or Sex characteristics.mp. or exp sexual characteristics/	842
		1445
	Full search executed on the 2nd of June, 2020	

assessment items were given 2 points, and the other items were given 1 point each. Cut-off points were discussed and determined, at <11 points as POOR, 11–16 as FAIR and >16 as GOOD. Whenever there was disagreement on certain aspects of the quality assessment of an article, a discussion with the supervising committee was held until consensus was reached.

Data Extraction and Analysis

Data were extracted on population and sample, type of intervention, primary and secondary outcome measures, and outcomes and data on male and female sub-groups, using a standardized extraction form. Whenever results were only presented in a graph, data were manually extracted by enlarging the graph to A3-size and estimating the outcomes. One study mentioned that no differences between men and women were found, but they did not show the subsequent data, so the authors were approached by e-mail to request additional data. Unfortunately, no response was given despite reminders. We performed a descriptive analysis of the included studies.

Results

The search resulted in a sample of 1445 studies (PubMed 603, EMBASE 842) (Figure 1 Prisma Flowchart), of which 1232 studies remained after removing duplicates. Out of these studies, 66 studies were considered potentially eligible after title/abstract screening. Reasons for excluding studies were study type, study population (<18 or only male/female patients included) or no mention of sex- and/or gender differences. Examination of the full text of the remaining studies led to the selection of 17 randomized controlled trials that met the inclusion criteria. After quality assessment, 12 studies, including 1847 men and 3562 women, remained to be included in our systematic review (Table 3). Appendix 3 provides the main characteristics of the studies excluded after quality assessment.

Main Characteristics of Included Studies

Almost all studies were placebo-controlled randomized trials. One study compared *mebeverine* with additional cognitive behavioral therapy to *mebeverine* alone.[13] Most patients were diagnosed according to the current Rome criteria, and one study used GP diagnosis. Of 12 included studies, 4 included only IBS-D patients, and 2 included only IBS-C. The other 8 studies included all types of IBS: constipation dominant, diarrhea dominant or mixed. Studies were published between 1999 and 2019.

Types of Interventions

Intervention types can be divided into pharmaceutical interventions (Table 4), psychological interventions and alternative interventions (Table 5).

Outcome Measures

The primary outcome mostly assessed an adequate reduction of IBS symptoms as indicated by a reduction in the symptom severity scale; reduction in the sum of symptoms; self-reported adequate relief of symptoms; a composite responders score (experiencing a ≥30% reduction of their IBS-symptoms on more than half the days); increased number of pain-free days; improvement in stool consistency; or decreased VAS intensity of pain.

Effects of Interventions

Pharmaceutical Interventions

Table 4 shows the pharmaceutical interventions included in this systematic review, with a brief description of the agent studied. They have been ordered by type of pharmaceutical (either a serotonin antagonist or not), and within these subgroups, they have been ordered by their quality assessment score, starting with the highest scores.

Serotonin Antagonists

George et al studied *renzapride*.[14] No significant differences were observed between male and female participants concerning adequate pain relief of abdominal pain/discomfort, and no significant response was reached in the overall population. The study was rated good (18/20). *Ramosetron* hydrochloride was studied by Matsueda et al.[15] Comparing the differences in response between placebo and *ramosetron*, they found no significant differences between male and female patients. Both men and women showed comparable positive effect. The study was rated good (17/20).

Two studies with *alosetron*, Camilleri et al and Bardhan et al, showed comparable results concerning gender differences in the treatment of IBS.[16,17] First, women reported to experience 12 more pain-free days in the last three weeks of treatment when receiving 2mg of *alosetron* compared to placebo, whereas in males there was no significant benefit with any dose of *alosetron* over placebo. Second, one and a half times as many women experienced an improvement in diarrhea comparing placebo to 2mg *alosetron*. This improvement was barely noticeable in men. Thirdly, almost twice as many women reported

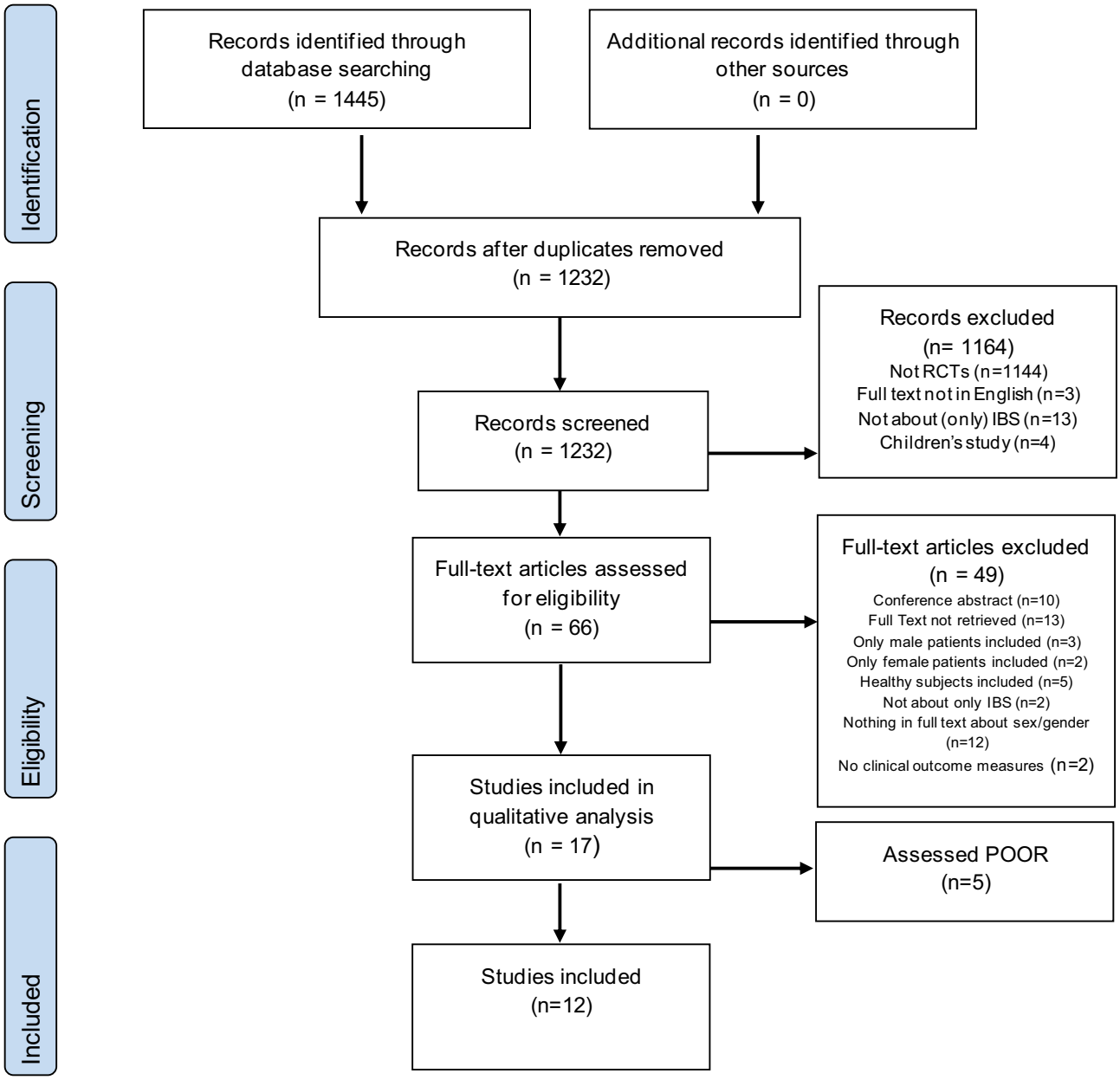

Figure 1 A flowchart of the selection of articles. In the first step of screening, most articles were rejected because they were not RCTs. Other reasons for exclusion were that they were not written in English, were not about (only) IBS or were children's studies. In the next step, where eligibility was considered based on the full text, an additional three-quarters of the articles were dropped for a variety of reasons: not discussing sex-gender differences was the most important (other reasons are mentioned in the figure itself). The remaining articles met all inclusion criteria and were scored for quality. The studies that scored fair/good on this were ultimately included in this review.

adequate relief of their IBS pain and discomfort receiving 1 or 2mg *alosetron*, whereas this barely improved in men. Camilleri et al reported significant improvement in urgency, hardened stool and decreased frequency in women, but not in men. Bardhan et al reported no significant improvement in either male or female patients concerning the improvement of VAS-score and frequency, with no differences between the groups. Stool consistency improved significantly in both males and females, with no significant difference between the groups. Studies were both rated fair (resp. 15/20 and 14/20).

Other Pharmaceutical Interventions

Ibodutant

In the study of Tack et al, *ibodutant* 10mg demonstrated significant superiority over placebo in females.[18] The percentage of satisfactory relief of overall IBS symptoms and abdominal pain doubled in women (24.4% to 46.8%),

Table 3 Characteristics of Included Studies (Ordered by Intervention Type and Quality Assessment)

Study, year, country, quality assessment, care facility, funding	Population and sample	Intervention	Efficacy parameters	Results for primary efficacy parameters Statistically significant difference (⊕/⊖)	Differences between male and female subgroups
George et al, 2008, United Kingdom,[14] Primary care GOOD 18/20 Funded by pharmaceutical industry	Male (54) and female (455) patients diagnosed with IBS-C according to Rome II criteria n=509	Renzapide 1 mg Renzapide 2 mg Renzapide 4 mg Placebo	1. Adequate pain relief of abdominal pain/discomfort 2. Number of stools passed per day 3. Stool consistency	1. Adequate pain relief of abdominal pain/discomfort ⊖ for overall population receiving any dose of renzapide vs placeboThe response was dose dependent, with only the 4 mg dose group showing a consistent improvement vs. placebo, yet not significant 2. Number of stools passed per day ⊕ for overall population receiving 2mg and 4mg renzapide versus placebo Treatment difference vs placebo: weeks 1-4: renzapide 2mg (p=0.0003) and renzapide 4mg (p<0.0001), weeks 5-12: renzapide 2mg (p=0.001) and renzapide 4mg (p<0.0046) 3. Stool consistency ⊕ for overall population receiving 2mg and 4mg renzapide versus placebo in weeks 1-4 and for 4mg in weeks 5-12Treatment difference vs placebo: weeks 1-4: renzapide 2mg (p=0.0154) and renzapide 4mg (p<0.0048), weeks 5-12: renzapide 4mg (p=0.0106)	1. Adequate pain relief of abdominal pain/discomfort Full analysis set (456 of 510), compared to the overall study cohort, a greater average weekly treatment difference vs. placebo was observed in females (8% and 12% respectively)
Matsueda et al, 2008, Japan[15] Multiple centers, primary/ secondary unclear GOOD (17/20) Funded by pharmaceutical industry	Male (n=310) and female (n=91) patients diagnosed with IBS-D according to Rome II criteria n=418	1 µg Ramosetron 5 µg Ramosetron 10 µg Ramosetron Placebo	1. Relief of IBS symptom 2. Relief of abdominal discomfort/pain 3. Improvement of abnormal bowel habits	1. Relief of IBS symptoms ⊕ for overall population receiving 5- or 10µg ramosetron versus placebo Placebo: 26.92%, 1µg ramosetron (p=1.00), 5µg ramosetron 42.57% (p=0.027) and 10µg ramosetron 43.01% (p=0.026). 2. Relief of abdominal discomfort/pain ⊕ for overall population receiving 10µg ramosetron versus placebo at the final pointplacebo: 25.96%, 1µg ramosetron 37.62 (p=0.091), 5µg ramosetron 37.62% (p=0.100) and 10µg ramosetron 48.39% (p=0.002). 3. Improvement of abnormal bowel habits ⊕ for overall population receiving 10µg ramosetron versus placebo at the final point Placebo: 29.81%, 1µg ramosetron (p=0.367), 5µg ramosetron 43.56% (p=0.058) and 10µg ramosetron 45.16% (p=0.038).	Monthly response rate (%)⊖ response rate comparable for males and females Final point: placebo: females 38.10%, males 24.10%, 1µg ramosetron: females 30.00%, males 25.30%, 5µg ramosetron ramosetron: females 53.33%, males 38.03% and 10µg ramosetron: females 50.00%, males 41.10%

Camilleri, 1999, United States[16] FAIR (15/20) Funded by the pharmaceutical industry	Male (100) and female (202) patients with IBS-D or IBS-M diagnosed according to Rome criteria n=302	Alosetron 1 mg Alosetron 2 mg Alosetron 4 mg Alosetron 8 mg Placebo	1. Adequate relief (for at least 6 weeks) 2. Improvement of bowel function 3. Urgency	Data for overall population not shown.	1. Adequate relief (for at least 6 weeks) ⊕ for female (not male) patients at 1mg or 2mg of alosetron versus placeboPlacebo: females 33%, males 53%, 1mg alosetron: females 60% (p=0.015), males 20%, 2mg alosetron: females 59% (p=0.023), males 50%, 4mg alosetron females 51%, males 54%, 8mg alosetron females 52%, males 52%. 2. Bloating ⊖ in males or females with any dose of alosetron compared to placebo 3. Bowel related functions: Bloating, hardened stool and decreased stool frequency ⊕ for female (not male) patients at any dose of alosetron versus placebofemales: p<0.05 vs placebo at 1, 2, 3 months for all doses. Males not significant.
Bardhan et al., 2001, United Kingdom,[17] hospital out-patient clinics, primary care practice and private physician clinics FAIR (14/20) Funded by pharmaceutical industry	Male (127) and female (335) patients diagnosed with IBS according to the Rome criteria n=462	Alosetron 0.1 Alosetron 0.5 Alosetron 2 mg Placebo	1. Proportion of pain-free days 2. Proportion of patients with >10% improvement in VAS score 3. Stool consistency 4. Number of actions 5. Improvement in diarrhea	1. Proportion of pain-free days ⊕ for the overall population receiving 2mg alosetron versus placebo in weeks 5-8 and -12. Treatment differences (alosetron versus placebo): 0.1mg alosetron: 9.2 (-1.5-19.8), 0.5 mg alosetron: 1.1 (-9.7 – 12.0), 2mg alosetron: 9.1 (-1.1 – 19.4) (p<0.05) 2. Proportion of patients with >10% improvement in VAS score ⊕ for the overall population receiving 2mg alosetron versus placeboTreatment differences (alosetron versus placebo): 0.1mg alosetron:-3 (-16-10), 0.5 mg alosetron: -5 (-18-9), 2mg alosetron: 12(-1-25) (p<0.05)) 3. Stool consistency ⊕ for overall population receiving 0.5mg or 2mg alosetron versus placebop<0.05 4. Number of actions ⊕ for overall population receiving 0.5mg or 2mg alosetron versus placebop<0.055. improvement in diarrhea ⊕ for overall population receiving 2mg alosetron versus placebo Placebo: 36%, 2mg alosetron 50% (p=0.03)	1. Proportion of pain-free days ⊕ for female (but not male) patients receiving 2mg alosetron versus placebo Treatment differences (alosetron versus placebo): 0.1mg Alosetron: Female: 6.1 (-6.7 – 19.0) and male: 15.4 (-3.9-34.7), 0.5 mg alosetron: female: 0.2 (-12.4 – 12.8) and male: 3.5(-17.9-24.9), 2mg alosetron: female 12.0 (-0.3 – 23.7) (p<0.05) and male: -1.9 (23.1-19.3) 2. Proportion of patients with >10% improvement in VAS score ⊖ for both male and female patients receiving any dose of alosetron versus placebo, no difference between groups Treatment differences (alosetron versus placebo): 0.1mg alosetron: Female -7 (-23-9) and male: 4(-20-27), 0.5 mg alosetron: female: -12(-27-3) and male: 16 (-8-41), 2 mg alosetron: female 9 (-6-24) (p<0.05) and male: 23 (-1-48) (p=<0.05) 3. Stool consistency ⊕ for both female and male patients receiving 0.5mg or 2mg alosetron versus placebo, no difference between groupsweek 12: females: 38% improvement over placebo, males: 50% improvement over placebo (P<0.002) 4. Stool frequency ⊖ for both female and male patients receiving any dose of alosetron versus placebo 5. Improvement in diarrhea ⊕ for female (but not male) patients receiving 2mg alosetron versus placebo Females: placebo: 34%, 2mg alosetron 51% (p=0.033). Males: placebo: 41%, 2mg alosetron 46%

(*Continued*)

Table 3 (Continued).

Study, year, country, quality assessment, care facility, funding	Population and sample	Intervention	Efficacy parameters	Results for primary efficacy parameters Statistically significant difference (⊕/⊖)	Differences between male and female subgroups
Tack et al., 2016, Belgium[18] GOOD (20/20) Funded by the pharmaceutical industry	Male (n=226) and female (n=333) patients with IBS-D according to Rome III criteria. n = 559	Ibodutant 1 mg Ibodutant 3 mg Ibodutant 10 mg Placebo	1. Responders with satisfactory relief of overall IBS symptoms and abdominal pain/discomfort – 75% rule 2. FDA weekly response for stool consistency and abdominal pain 3. FDA weekly response for stool consistency 4. Relief of overall symptoms and abdominal pain – 50% rule 5. Relief of overall symptoms – 75% rule6. Relief of abdominal pain – 75% rule	1. Responders with satisfactory relief of overall IBS symptoms and abdominal pain/discomfort-75% rule ⊖ for overall population receiving any dose of ibodutant versus placeboData not shown, p = 0.032 for ibodutant 10mg. 2. FDA weekly response for stool consistency and abdominal pain ⊕ for overall population receiving 10mg of ibodutant versus placeboPlacebo: 37.4%, 1mg ibodutant 42.5% (p=0.39), 3mg ibodutant 38.4% (p=0.86), 10mg ibodutant 49.3% (p=0.050) 3. FDA weekly response for stool consistency ⊕ for overall population receiving 10mg of ibodutant versus placeboPlacebo: 53.2%, 1mg ibodutant 58.3% (p=0.40), 3mg ibodutant 54.4% (p=0.85), 10mg ibodutant 67.7% (p=0.014) 4. Relief of overall symptoms and abdominal pain – 50% rule ⊕ for overall population receiving 10mg of ibodutant versus placeboPlacebo: 38.7%, 1mg ibodutant 51.4% (p=0.35), 3mg ibodutant 44.2% (p=0.032), 10mg ibodutant 67.7% (p=0.015) 5. Relief of overall symptoms – 75% rule ⊖ for overall population receiving any dose of ibodutant versus placeboPlacebo: 37.3%, 1mg ibodutant 41.4% (p=0.48), 3mg ibodutant 39.1% (p=0.75), 10mg ibodutant 48.2% (p=0.066) 6. Relief of abdominal pain – 75% rule ⊖ for overall population receiving any dose of ibodutant versus placeboPlacebo: 32.4%, 1mg ibodutant 37.9% (p=0.34), 3mg ibodutant 42.0% (p=0.096), 10mg ibodutant 47.5% (p=0.009)	1. Responders with satisfactory relief of overall IBS symptoms and abdominal pain/discomfort-75% rule ⊕ for females (not males) receiving 10mg of ibodutant versus placebo Placebo: 24.4% of females, 31.2% of males, 1 mg ibodutant 36.0% of females, 25.5% of males, 3mg ibodutant 40.2% of females and 21.6% of males, 10mg ibodutant 46.8% of females (p=0.003), 30.0% of males (p=0.881). 2. FDA weekly response for stool consistency and abdominal pain ⊕ for females (not males) receiving 10mg of ibodutant versus placeboPlacebo: 31.2% of females and 45.2% of males, 1mg ibodutant 44.9% of females (p=0.70) and 38.0% of males (p=0.45), 3 mg ibodutant 38.4% of females (p=0.86) and 27.5% of males (p=0.054), 10mg ibodutant 54.4% of females (p=0.003) and 42.4% of males (p=0.76) 3. FDA weekly response for stool consistency ⊕ for females (not males) receiving 10mg of ibodutant versus placeboPlacebo: 49.4% of females, 58.1% of males, 1mg ibodutant 58.4% of females (p=0.24) and 58.0% of males (p=0.99), 3 mg ibodutant 58.9% of females (p=0.18) and 45.1% of males (p=0.17), 10mg ibodutant 74.0% of females (p=0.0017) and 59.3% of males (p=0.025) 4. Relief of overall symptoms and abdominal pain – 50% rule ⊕ for females (not males) receiving 10mg of ibodutant versus placeboPlacebo: 41.0% of females, 35.9% of males, 1mg ibodutant 56.2% of females (p=0.051) and 43.1% of males (p=0.43), 3 mg ibodutant 51.7% of females (p=0.17) and 31.4% of males (p=0.61), 10mg ibodutant 60.8% of females (p=0.0014) and 43.3% of males (p=0.40) 5. Relief of overall symptoms – 75% rule ⊖ for both male and females receiving any dose of ibodutant versus placeboPlacebo: 38.5% of females, 35.9% of males, 1mg ibodutant 44.9% of females (p=0.40) and 35.3% of males (p=0.94), 3 mg ibodutant 46.0% of females (p=0.33) and 27.5% of males (p=0.33), 10mg ibodutant 53.2% of females (p=0.065) and 41.7% of males (p=0.51)6. Relief of abdominal pain – 75% rule ⊕ for females receiving 3mg or 10mg of ibodutant versus placeboPlacebo: 28.2% of females, 37.5% of males, 1mg ibodutant 41.6% of females (p=0.072) and 31.4% of males (p=0.49), 3 mg ibodutant 4.4% of females (p=0.055) and 29.4% of males (p=0.36), 10mg ibodutant 51.9% of females (p=0.0025) and 41.7% of males (p=0.64)

Pimentel et al., 2003, United States,[19] Recruited via newspaper GOOD (19/20) Funded by private foundation	Male (50) and female (61) patients with diagnosed IBS according to Rome I criterian=111	Neomycin 500mg Placebo	1. Composite score (CS) calculated from the three main IBS symptoms (abdominal pain, diarrhea, and constipation) 2. Overall percent bowel normalization 3. True clinical response (>50% reduction of CS)	1. Composite score (CS) reduction ⊕ for overall population receiving 500mg neomycin versus placebo Placebo: 11.4±9.3% reduction, neomycin 35.0±5.0% reduction (p<0.05) 2. Overall percent bowel normalization ⊕ for overall population receiving 500mg neomycin versus placebo Placebo: 15.1±3.6% normalization, neomycin 40.1±5.3% normalization (p=0.001) 3. True clinical response (>50% reduction of CS) ⊕ for overall population receiving 500mg neomycin versus placebo Placebo: 23%, neomycin 45% (OR: 4.3, CI: 1.05-6.3, p=0.05	2. Overall percent bowel normalization ⊖ between male and female patients in any responsePlacebo: female 10.9% and male 18.8%, neomycin 500mg: female 43.6% (p<0.05) and male 37.6% (p<0.01). No significant difference between the groups was observed in any response.
Mangel & Chaturvedi, 2008, United States,[20] Private or university based practices GOOD (18/20) Funded by the pharmaceutical industry	Male (25%) and female (75%) patients diagnosed with IBS-D according to Rome II criteria n=245	Crofelemer 125 mg Crofelemer 250mg Crofelemer 500 mg Placebo	1. Stool consistency responders 2. Stool frequency 3. Urgency 4. Adequate relief 5. Pain score 6. Pain-free days	1. Stool consistency responders (%) ⊖ for overall population receiving any dose of crofelemer versus placeboPlacebo: 48%, 125mg crofelemer: 49% (p=0.9), 250mg crofelemer: 40% (p=0.39) 500mg crofelemer: 46% (p=0.88) 2. Stool frequency improvement ⊖ for overall population receiving any dose of crofelemer versus placeboPlacebo: -0.98 ± 1.646, 125mg crofelemer: -1.05 ± 1.333 (p=0.84), 250mg crofelemer: -0.58±0.937 (p=0.89), 500mg crofelemer: -0.43±1.86 (p=0.03) 3. Urgency ⊖ for overall population receiving any dose of crofelemer versus placeboPlacebo: 30.8±34.8, 125mg crofelemer: 30.8±31.2 (p=0.99), 250mg crofelemer: -99 22.2±32.3 (0.41), 500mg crofelemer: 23.1±32.7 (0.46)4. Adequate relief (%) ⊖ for overall population receiving any dose of crofelemer versus placeboPlacebo: 53%, 125mg crofelemer: 57% (p=0.74), 250mg crofelemer: 40% (p=0.19), 500mg crofelemer: 54% (p=0.89)5. Pain score ⊖ for overall population receiving any dose of crofelemer versus placeboPlacebo: -0.73±0.92, 125mg crofelemer: -0.82±0.88 (p=0.38), 250mg crofelemer: -0.62.2±0.70 (0.94), 500mg crofelemer: -0.83±0.85 (0.26) 6. Pain-free days ⊕ for overall population receiving 500mg crofelemer versus placebo after 3 months Placebo: 13.1%, 125mg crofelemer: 19.4% (p=0.23), 250mg crofelemer: 13.2% (p= 0.99), 500mg crofelemer: 24.3% (p=0.03)	6. Pain-free days ⊕ ITT significance was driven by female population Females: placebo 10.6%, 125mg crofelemer 20.5% (p=0.078), 250mg crofelemer: 13.3% (p=0.62), 500mg crofelemer: 26.1% (p=0.0076)

(*Continued*)

Table 3 (Continued).

Study, year, country, quality assessment, care facility, funding	Population and sample	Intervention	Efficacy parameters	Results for primary efficacy parameters Statistically significant difference (⊕/⊖)	Differences between male and female subgroups
Lacy et al., 2019, United States,[21] Health centers GOOD (17/20) Funded by the pharmaceutical industry	Male (n = 821) and female (n = 1602) patients with IBS-D according to Rome III criteria. Two trails included (IBS-3001 and IBS-3002) n = 2423	Eluxadoline 75 mg Eluxadoline 100mg Placebo	1. Composite responders (i.e., patients who recorded a reduction of ≥30% from their average baseline score for their worst abdominal pain on ≥50% of the days and a stool-consistency score of <5 on the same days)2. Abdominal pain (improvement >30%)3. Stool consistency (meets stool consistency criterion >50% of days)	1. Composite responders ⊕ for both doses of eluxadoline 75mg and eluxadoline100mg versus placebo Pooled data: eluxadoline 75 mg: 26.2%, eluxadoline 100 mg: 27.0% and as compared with placebo 16.7%, P<0.001 2. Abdominal Pain ⊖ for both doses of eluxadoline 75mg and eluxadoline 100mg versus placebo in both IBS-3001 and IBS-3002 trials IBS-3001: placebo 39.6%; eluxadoline 75mg: 42.4% (p=0.40); eluxadoline 100mg: 43.2% (p=0.28).IBS-3002: placebo 45.3%; eluxadoline 75mg: 48.0% (p=0.45), eluxadoline 100mg: 51.0% (p=0.11). 3. Stool consistency ⊕ for both doses of eluxadoline 75mg and eluxadoline 100mg versus placebo in both IBS-3001 and IBS-3002 trialsIBS-3001: placebo 22.0%; eluxadoline 75mg: 30.0% (p=0.008), eluxadoline 100mg: 34.3% (p<0.001).IBS-3002: placebo 20.9%; eluxadoline 75mg: 37.0% (p<0.001), eluxadoline 100mg: 35.6% (p<0.001).	1. Composite responders ⊖ between males and females receiving 100mg of eluxadolinePlacebo: 17.5% of females and 15.2% of males, 100mg eluxadoline: 27.5% of females, 26.1% of males. 2. Abdominal pain response ⊖ between males and females receiving both doses of eluxadoline or placeboPlacebo: 45.0% of females and 42.2% of males, 75mg eluxadoline: 46.9% of females and 45.0% of males, 100mg eluxadoline: 48.0% of females, 48.9%. 3. Stool consistency responders ⊖ between males and females receiving both doses of eluxadoline or placeboPlacebo: 24.1% of females and 23.4% of males, 75mg eluxadoline 30.5% of females and 32.1% of males, 100mg eluxadoline 36.4% of females and 37.7% of men.

Kennedy et al., 2006, United Kingdom,[13] Primary care GOOD (16/20)	Male (43) and female (192) patients diagnoses with IBS according to their GPn=235	Mebeverine 270mg Mebeverine 270mg + 6 sessions of CBT No therapy	1. SSS[a] 2. HADS[a] 3. WASA[a] 4. BS-IBS[a] 5. CS-FBD[a]	1.SSS[a] ⊕ time by treatment interaction for overall population receiving CBT+meb vs meb only at 1.5 and 3 monthsDifference in means meb+CBT vs meb only: 1.5 months: -68 (-104 to -32), 3 months: -71 (-109 to -32), 6 months: -14 (-51 to 23), 12 months: 3 (-35 to 40). Significant treatment by time interaction p<0.0001. 2. HADS[a] ⊖ time by treatment interaction for overall population receiving CBT+meb vs meb only.There was no significant treatment by time interaction (p = 0.12). 3. WASA[a] ⊕ time by treatment interaction for overall population receiving CBT+meb vs meb only. Difference in means meb+CBT vs meb only: 1.5 months: -4.1 (-6.4 to -1.8), 3 months: -5.0 (-7.5 to -2.6), 6 months: -1.7 (-4.1 to 0.7), 12 months: -2.8 (-5.2 to 0.4). There was a significant time by treatment interaction (p = 0.03). 4. BS-IBS ⊕ time by treatment interaction for overall population receiving CBT+meb vs meb only.Difference in means meb+CBT vs meb only: 1.5 months: -32.0 (-43.7 to -0.4), 3 months: -26.6 (-35.4 to -7.9), 6 months: -16.0 (-23.4 to -8.6), 12 months: 5.4 (-14.6 to 25.3). There was a significant treatment by time interaction (p = 0.01). 5. CS-FBD[a] ⊕ time by treatment interaction for overall population receiving CBT+meb vs meb only.Difference in means meb+CBT vs meb only: 1.5 months: -16 (-25 to -7), 3 months: - 21 (-31 to -12), 6 months: -6 (-15 to 4), 12 months: -8 (-17 to 2). There was a significant treatment by time interaction (p = 0.001).	Linear regression with the mean (of values at 3, 6 and 12 months) outcome on the WASAMale gender was a significant predictor of a negative outcome: β coefficient (95% CI): 3.49 (0.46-6.52) (p=0.025)
Farnham et al., 2014, Iran,[22] Out-patient clinic FAIR (15/20)	Male (n=36) and female (n=34) patients with IBS diagnosed according to Rome III criteria n=70	Medical treatment (MT) Medical treatment + emotional awareness (EMT)	1. VAS intensity of pain 2. Frequency of pain	1. VAS intensity of pain ⊕ for overall population receiving EMT versus MT only MT: 61.36± 23.52 mm pre-treatment to 41.67 ± 31.20 mm posttreatment, EMT: 66.87 ± 23.45 mm pre-treatment to 26.10 ± 25.93 mm at posttreatment. Significant group x time interaction (F =8.99; p = 0.004) 2. Frequency of pain ⊖ for overall population receiving EMT versus MT onlyMT: 5.41 ± 1.91 per week pre-treatment to 3.65 ± 2.55 post-treatment, EMT: 4.93 ± 2.12 pre-treatment to 1.88 ± 2.48 post-treatment (effect 0.7), not significant.	Gender had no effect on the outcome of pain severity (p = 0.317) or pain frequency (p = 0.438).

(*Continued*)

Table 3 (Continued).

Study, year, country, quality assessment, care facility, funding	Population and sample	Intervention	Efficacy parameters	Results for primary efficacy parameters Statistically significant difference (⊕/⊖)	Differences between male and female subgroups
Tack et al., 2011, United States[23] GOOD (19/20)	Male (42) and female (73) patients with IBS-C diagnosed according to Rome III criteria n=115	AST-120 2g tds Placebo	1. Pain-free days (50% reduction) 2. Pain severity 3. Bloating 4. Proportion of subjects with global relief, HADS[a], IBS-QOL[a], BSFS[a]	1. Pain-free days (50% reduction) ⊕ for overall population receiving AST-120 versus placebo at week 4, ⊖ at week 8. Week 4: placebo 10.2%, AST-120: 26.8% (p=0.029), week 8: placebo 25.4%, AST-120: 32.1% (not significant) 2. Pain severity ⊖ for overall population receiving AST-120 versus placebo 3. Bloating ⊕ for overall population receiving AST-120 versus placebo at week 2 and week 4placebo: 2.2mm, AST-120: 11.9mm (p=0.007) 4. Proportion of subjects with global relief, HADS, IBS-QOL, BSFS ⊖ for overall population receiving AST-120 versus placebo	The likelihood of response was not gender-dependent (data not shown). [b]
Hong et al., 2011, Korea,[24] Secondary care GOOD (18/20)	Male (n=22) and female (n=51) patients diagnosed with IBS according to Rome III criteria n=73	Probiotic Yoghurt Milk (Lactobacillus sp, Bifidobacterium longus, and Lactobacillus Brevis)Placebo	1. Sum of symptom scores (abdominal pain, bloating and defecation discomfort) 2. Abdominal pain 3. Bloating 4. Defecation discomfort 5. Stool frequency 6. Stool consistency 7. ^{1}H NMR[a] metabolic profiling of serum and fecal samples	1. Sum of symptom scores ⊕ for overall population receiving probiotics versus placebo after 8 weeks4 weeks: placebo -53.5, probiotics -78.9 (p=0.1142); 8 weeks: placebo -51.9, probiotics -85.6 (p=0.0217) 2. Abdominal pain ⊖ for overall population receiving probiotics versus placebo after 4 and 8 weeks 4 weeks: placebo: -22.0, probiotics -26.0 (p=0.55); 8 weeks: placebo -19.8, probiotics -29.5 (p=0.15) 3. Bloating ⊖ for overall population receiving probiotics versus placebo after 4 and 8 weeks 4 weeks: placebo: -14.3, probiotics -24.9 (p=0.12); 8 weeks: placebo -15.9, probiotics -26.1 (p=0.12) 4. Defecation discomfort ⊕ for overall population receiving probiotics versus placebo after 8 weeks 4 weeks: placebo: -17.3, probiotics -27.9 (p=0.14); 8 weeks: placebo -16.3, probiotics -30.1 (p=0.0314) 5. Stool frequency ⊕ for overall population receiving probiotics versus placebo after 8 weeks8 weeks: placebo 0.5, probiotics -1.5 (p=0.0410) 6. Stool consistency ⊖ for overall population receiving probiotics versus placebo after 8 weeks 8 weeks: placebo 0.23, probiotics 0.14 (p=0.2224) 7. ^{1} H NMR metabolic profiling Visual inspection of human serum 1H NMR spectra showed marked increases in lactate levels and decreases in glucose levels after probiotics administration.	^{1}H NMR metabolic profiling ⊕ significant differentiation in females, not in malesfemales: The OPLS-DA scoreplot shows significant differentiation of female sera before and after probiotics administration (R2X=0.856, R2Y=0.393, Q2=0.279) Males: OPLS-DA models were unable to discriminate probiotic-administered and placebo-administered male sera from controls, resulting in poor predictabilities (Q2 values -0.263 and -0.364)

Notes: [a]^{1}H NMR, proton nuclear magnetic resonance; AST, spherical carbon adsorbent; BSFS, Bristol Stool Form Scale; BS-IBS, Behavior Scale for irritable bowel syndrome; CBT, cognitive behavioural therapy; CSFBD, Cognitive Scale for Functional Bowel Disorders; EMT, medical treatment + emotional awareness protocol; HADS, Hospital Anxiety and Depression Scale; IBS-SSS, IBS Symptom Severity Scale; MT, medical treatment; QOL, quality of life; SSS, symptom severity score; VAS, Visual Analogue Scale; WASA, Work and Social Adjustment Score. [b]Authors were approached for data on this likelihood of response; unfortunately, no response was given despite reminders.

Table 4 Descriptions of Studied Pharmaceutical Interventions

Pharmaceutical Agent	Description	Used in Article
Ibodutant	A selective neurokinin-2 (NK2) receptor antagonist.	Tack et al[18]
Neomycin	An aminoglycoside antibiotic.	Pimentel et al[19]
Crofelemer	Inhibits cAMP-mediated chloride ion secretion in Caco-2 and T84 cells, and therefore has antisecretory activity.	Mangel et al[20]
Eluxadoline	A mixed μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist, that acts locally in the enteric nervous system, possibly decreasing adverse effects on the central nervous system.	Lacy et al[21]
Renzapide	A benzamide derivative with not only 5-HT4 receptor full agonist properties, but also 5-HT3 receptor antagonist properties.	George et al[14]
Ramosetron hydrochloride	A potent and selective synthetic 5-HT 3 receptor antagonist.	Matsueda et al[15]
Alosetron	A potent, highly selective 5-HT3 receptor antagonist.	Bardhan et al.[17] Camilleri et al.[16]

Table 5 Descriptions of Studied Psychological and Alternative Interventions

Psychological Intervention	Description	Used in Article
CGT	Cognitive behavioral therapy: a talking therapy that can help you manage your problems by changing the way you think and behave.	Kennedy et al.[13]
EMT	Emotional awareness training in addition to medical treatment: a method of increasing the level of conscious awareness of emotions in patients with IBS.	Farnam et al.[22]
Alternative Interventions		
AST-120	Spherical carbon adsorbent is a non-absorbed, carbon-based adsorbent with adsorbing capability for histamine, serotonin and other substances implicated in IBS pathogenesis.	Tack et al.[23]
Probiotic Yoghurt Milk	Fermented milk containing $4x10^9$ colony forming units of Lactobacillus sp. HY7801, Bifidobacterium longum HY8004, and Lactobacillus brevis HY7401.	Hong et al.[24]

while no improvement occurred in men. There was also a significant improvement of stool consistency, relief of overall symptoms and relief of abdominal pain in female participants. All of these outcomes did not reach significance in male participants. If we look at the entire population (ie, all men and women together), no significant difference in effectiveness of *ibodutant* compared to placebo is seen. The study was rated good (20/20).

Neomycin

Pimentel et al studied whether a significant reduction of IBS symptoms is observed in patients receiving *neomycin*.[19] Both male and female *neomycin*-treated patients had a significant improvement of their IBS-symptoms versus placebo, with no significant difference in improvement between the sexes. The study was rated good (19/20).

Crofelemer

Mangel et al concluded that female IBS-D patients receiving 500mg *crofelemer* reported an improvement of 16% increase in pain- and discomfort-free days over that seen in placebo.[20] No benefit was seen in male IBS-D patients. The study was rated good (18/20).

Eluxadoline

The study by Lacy et al demonstrated that the total group of patients, male and female, receiving *eluxadoline* instead of placebo, had 10% more composite responders (ie, patients who recorded a reduction of

≥30% from their average baseline score for their worst abdominal pain on ≥50% of the days and a stool-consistency score of <5 on the same days), which was a significant improvement.[21] Male and female patients did not differ in outcomes, nor did *eluxadoline* influence stool consistency significantly in either sex. The study was rated as good (16/20).

Psychological Interventions

Table 5 displays the non-pharmaceutical interventions, sub-grouped into psychological and alternative interventions and ordered by their quality assessment score.

Cognitive Behavioral Therapy (CBT)

In the study by Kennedy et al, groups received either *mebeverine* and six sessions of CBT, or *mebeverine* alone. Men reported to feel more disabled in their work and social life because of their IBS symptoms. On other outcomes, no sex-gender impact was mentioned. The overall population showed significant improvement of their symptoms, the longer they had received CBT.[13] The study was rated good in quality assessment (17/20).

Emotional Awareness Protocol

In the study by Farnam et al, regular medical IBS treatment was compared to medical treatment with additional emotional awareness training. Gender did not have an impact on the outcome of pain severity or pain frequency. Pain severity decreased significantly the longer patients received additional emotional awareness training; for pain frequency, no significant improvement was seen in the intention-to-treat analysis.[22] The study was rated fair (15/20).

Alternative Interventions

Spherical Carbon Adsorbent −120 (AST-120)

The study by Tack et al reported that the significant reduction of pain-free days (50% reduction) for the overall study population receiving *AST-120* versus placebo was not gender-dependent.[23] The study was rated good (20/20).

Probiotic Yoghurt Milk

Hong et al reported no gender differences in IBS symptoms before or after administration of probiotics. Sum of scores on abdominal pain, bloating and defecation discomfort showed significant improvement in the overall population after 8 weeks.[24] The study was rated good (18/20).

Discussion

Gender Differences in Effect of Intervention

As five out of 12 RCTs found a significant difference between men and women in at least one of their measured outcomes, gender clearly matters in the effectiveness of IBS treatment. Of the investigated pharmaceutical interventions, *ibodutant* and *crofelemer* have a better effect in women with IBS-D symptoms than in men. Of the serotonin antagonists, *alosetron* has a positive effect on women with IBS-M or IBS-D but demonstrates no effect in men. Men show significantly worse outcomes when cognitive behavioral therapy is added to medical treatment. All of the other RCTs but one show an equal positive effect in men and women. The administration of probiotics has no significant effect whatsoever.

Finally, our study demonstrates the importance of sex-disaggregated data collection (separated for women and men) because the positive influence of treatments for either men or women would otherwise be missed. This does not only apply to IBS but to many – if not all – other diseases. If we take a look at the current COVID-19 pandemic, for example, mortality and morbidity data show that women are faring better than men in terms of severity of disease course, likelihood of hospitalization and risk of death.[25] Ultimately, the hope is that this segregated data analysis could also lead to other therapeutic choices for IBS between men and women. Today, surveys already show a difference in lifestyle changes and dietary suggestions. They were more frequently prescribed in males than in females.[26] Currently, *alosetron* is only registered for women and *ramosetron* only for men with severe IBS-D. Based on this review, we can support that *alosetron* is only effective in women, but *ramosetron* appears to have equally positive effects in women based on the studies we reviewed. This highlights the importance of continuing to investigate and report differences between men and women in the effectiveness of a treatment. In this way, doctors can make the most considered possible decision for a tailor-made treatment.

Interpretation

To explain the demonstrated differences between men and women in the effectiveness of IBS treatment, we have to

consider several components that could be affected by sex and gender. First, there is a physiological sex-related component. Studies have shown differences between men and women in the effects of sex hormones, most importantly estrogen and progesterone, on bowel function, gastrointestinal transit time, the processing of pain stimuli in the central nervous system and visceral sensitivity of the gut, as well as differences in pharmacodynamics and pharmacokinetics.[6,8] Second, sex-gender differences related to bowel function or pain processing may also play a role, such as stress processing and the neuroendocrine or autonomic nervous system. However, the specific link between gut motility or sensitivity and these factors has not yet been clarified. Third, gender differences in psychological factors can also play a role, such as anxiety and depression, a history of (sexual) abuse or the tendency to somatization.[6]

Pharmaceutical Interventions

In the pharmaceutical group, there are three drugs that demonstrate a more positive effect on women than on men. The greater effect of *ibodutant* could indicate differences between men and women in the pathophysiology of IBS-D, or differences between men and women in neurokinin-2 receptor expression and sensitivity. No difference in plasma levels or volume of distribution was found in previous pharmacokinetic studies with colon models.[27] Faster breakdown by men, therefore, does not explain the difference, and a higher dose would not solve this lack of effect. The effect of *crofelemer* on IBS has hardly been investigated. In the only other study investigating *crofelemer*, only women with IBS-D were included and *crofelemer* did not significantly improve abdominal pain over placebo, nor did it improve the number of pain-free days.[28] Further research, therefore, needs to be done to determine any effect of *crofelemer* on IBS. As regards IBS treatment with *neomycin*, our study shows significant improvement of IBS symptoms in both male and female patients. As the female gender is associated with Small Intestine Bacterial Overgrowth (SIBO), which in turn is thought to cause IBS symptoms, it seems plausible that women would find greater benefit in treatment targeting SIBO, such as antibiotics.[29] However, it is difficult to correctly diagnose SIBO. Therefore, caution must be exercised when drawing conclusions about SIBO, and further research must be conducted.

With regard to serotonin antagonists, *alosetron* is the only approved 5HT-3 receptor antagonist and is it approved only for severe IBS-D in females as the effect has not been confirmed in males. Reasons to explain these observations include sex-related differences in 5HT-3 receptor expression, lower *alosetron* clearance in women and/or greater 5HT synthesis under the influence of *alosetron* in certain brain regions in male compared with female IBS patients.[30] Chang and Heitkemper suggest that possible factors that influence sex-gender differences are biobehavioral responses to stress, the menstrual and hormonal cycle and different roles and emotions between men and women, resulting in a variety of physiological and clinical responses.[6] How these factors influence the response to the 5HT-3 receptor antagonist in men and women is not yet clear. Furthermore, *ramosetron* only works on peripheral tissues, whereas *alosetron* is reported to be transferred to the brain. It can be suggested that this difference in the site of action between *alosetron* and *ramosetron* contributes to the gender-related differences in responses to 5HT-3 receptor antagonists. However, further study is needed to ascertain the possibility that sex-gender differences such as site of action, menstrual and hormonal cycle and different roles and emotions between men and women are crucial factors in the response to (pharmaceutical) treatment.

Psychological Interventions

As IBS is considered a functional syndrome, somatization is an essential factor. Somatization can be described as the tendency to express psychological problems in somatic biological rather than emotional ways. A personality trait more commonly seen in somatizing patients is alexithymia, which is expressed as difficulty experiencing, expressing and describing emotional responses, and which is more common in men than women.[31,32] By training emotional awareness, an attempt is made to create awareness, to reduce internalization of emotions and to deal with psychological stress in a different way. As alexithymia is more prevalent in men than in women, the effect of emotional awareness training would be expected to be greater in men. That this is not the case in the study by Farnam et al may be due to the fact that the personality trait of alexithymia is more common in patients with IBS anyway.[32] Another explanation is that men do not necessarily have more difficulty with the recognition and awareness of emotions, but rather with their expression.[33] As emotional awareness training does not cover this, it will not have the expected impact.

The only described difference between men and women after CBT treatment was the score for work and

social adjustment, expressing how disabling IBS symptoms are in work and private activities. Male gender is a significant predictor of a poor outcome on this score, meaning men feel more disabled in their work and social life because of their IBS symptoms. One of the reasons for this might be that men experience diarrhea more often as their main symptom,[5] which may be more bothersome in a work environment than constipation. The fact that no other differences are found between men and women receiving CBT is noteworthy as previous studies into the effect of CBT have shown women to report higher commitment to and stronger belief in the helpfulness of therapy.[34]

Alternative Interventions

The response to *AST-120* was reported not to be gender-dependent. This is noteworthy because *AST-120* absorbs mast cell-derived mediators and thus prevents sensitization of nociceptors in the intestinal mucosa, reducing abdominal pain and discomfort.[35] As an increased level of mast cells is observed in female patients with IBS, it would seem rational to expect *AST-120* to have a more positive effect in women than in men.[36] It would be interesting for future research, therefore, to focus on why this more positive effect for women is not found. In a probiotics study, only differences in ^{1}H NMR metabolic profiling of serum and fecal samples were analyzed separately for men and women, without elaborating on gender differences in IBS symptoms. It would be interesting, though, to examine whether this is the case, since, as we said before, the female gender is associated with SIBO and might experience a more positive effect from probiotics targeting this overgrowth. Recent studies into probiotics with different Lactobacillus species show that female subjects, particularly of the IBS-D subtype, have good response in terms of stool frequency and consistency, and show improvement of symptoms and quality of life.[37]

Strengths and Limitations

In this article, we have chosen to only look at articles that have included both men and women. We have therefore not discussed any articles that found a (beneficial) effect in one of the sexes, but did not look at the effect in the other sex. We also excluded studies in which both men and women were included, but in which the data were not analyzed in a segregated manner. This rules out many studies (RCTs), which immediately reveals part of the problem for which this article aims to raise awareness: often insufficient attention is paid to gender as an influencing factor on the effectiveness of treatment.

In general, most studies included a small sample size of male IBS patients. Although the total sample size had enough power as required by the quality assessment criterion, some studies report that the male subgroup is too small to draw conclusions about the effect on men. Due to this lack of power for the male subgroups, chances of finding significant differences between the intervention and the placebo are small, leaving a blind spot, therefore, in the treatment effectiveness in men with IBS. This warrants a cautious interpretation of the observed results. The risk of publication bias and incomplete literature retrieval cannot be completely ruled out. We have sought to mitigate this risk with a broad search strategy. We have decided not to include separate terms in our search strategy for the different subtypes of IBS. We do not expect to have missed any studies, because these will also fall under the umbrella term, but of this, we cannot be completely certain. It is also important to note that most studies were subsidized and executed by the pharmaceutical company that also produces the drug.[15,16,18,20,21,23] Research shows that studies sponsored by pharmaceutical companies are more likely to find outcomes that benefit the sponsor than studies that are not and that there is a significant publication bias for such studies.[38] Such pharmaceutical funding should be kept in mind when interpreting the observed results.

In addition, we searched meta-analyses for randomized controlled trials we might have missed. The strengths of this study are its inclusion of randomized controlled trials only and its rigorous quality assessment procedure, ensuring the best possible quality of the included trials.

In the case of IBS, future research can be conducted to explore possible gender differences in pro- or antibiotics, and head-to-head trials comparing different types of 5HT-3 antagonists should be conducted to assess possible differences in effectiveness and tolerability and the underlying mechanism of mast cells and possible therapeutic options.

Conclusion

The main conclusion of our study is to emphasize that the sex-gender factor can be a determining one in the effectiveness of IBS treatment. Our study shows that differences in responsiveness can be so great that, while the entire population shows no significant improvement, a subgroup of male or female patients does. Future research into IBS treatments should not only segregate on the basis of sex, but also on the basis of IBS subtype within sex, so that no bias can arise.

This way firmer recommendations can be made concerning treatment. Due to the limited number of studies per treatment option, and because some studies included all types of IBS, no strong recommendations can be made on the choice of treatment in this review. The fact that only a limited number of studies remained, due to the limited number of studies looking at gender differences per drug, immediately reveals part of the problem for which this article aims to raise awareness: often insufficient attention is paid to gender as an influencing, maybe even determining factor, on the effectiveness of treatment.

Drawing a broader conclusion, we propose that an adequate number of men and women should always be included in future research. In order to ensure the reliability and assess the potential health benefits and risks for both men and women regarding risk factors, disease management, treatment and side effects, patients should be included in studies and data should be analyzed and described on the basis of sex.

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