

Danish national guideline: Diagnosis and treatment of Irritable Bowel Syndrome

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INTRODUCTION

This guideline concerns diagnosis and treatment of adult patients with irritable bowel syndrome (IBS) in secondary and tertiary care (specialist clinics and hospital outpatient clinics). Approximately 10-16% of adult Danes have symptoms compatible with IBS [1, 2]. IBS is most common between ages 20 to 40 but is seen in children and elderly as well. IBS leads to reduced quality of life and affects social and work life of the sufferer and the condition implies high costs to the society. Fortunately, there is no increased mortality or risk of cancer in IBS. Causes and pathogenesis remain to be clarified but proposed mechanisms include disturbed gut motility and enteric nerve system and dysbiosis of the intestinal microbiota. IBS runs in families but it is unclear whether this is due to a genetic predisposition or to environmental factors. Female gender is a risk factor, and IBS can evolve after an acute gastroenteritis (post-infectious IBS).

DEFINITION OF IBS

IBS is a syndrome characterized by recurrent abdominal pain or discomfort accompanied by a change in the stool pattern. In the current guideline, the Rome III criteria were used [3].

Rome III diagnostic criteria for IBS

Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with *two or more* of the following:

- Improvement with defecation
- Onset associated with a change in the frequency of stool
- Onset associated with a change in the form (appearance) of stool

Symptom start ≥ 6 months prior to diagnosis

Subclassification of IBS by predominant stool pattern:

- IBS with constipation, (IBS-C): hard or lumpy stool* $>25\%$ and loose (mushy) or watery stool** $<25\%$ of bowel movements
- IBS with diarrhea, (IBS-D): loose (mushy) or watery stool $>25\%$ and hard or lumpy stool $<25\%$ of bowel movements
- Mixed IBS, (IBS-M): hard or lumpy stool $>25\%$ and loose (mushy) or watery stool $>25\%$ of bowel movements
- Unsubtyped IBS, (IBS-U): abnormality of stool consistency insufficient to meet criteria for IBS-C, IBS-D or IBS-M

*according to Bristol Stool Form Scale types 1 and 2

** according to Bristol Stool Form Scale types 6 and 7

Symptomatology

IBS patients complain of recurrent or chronic abdominal pain or discomfort associated with changes in the stool pattern, including changes in stool consistency or frequency. Men more frequently complain of diarrhea, while more women suffer from constipation. The patient can present with pain attacks that can be misinterpreted as an acute surgical condition. Bloating is often the dominating symptom. Many patients are troubled by disturbed defecation (urgency, straining or a sensation of incomplete bowel emptying). There is a considerable overlap between IBS, functional dyspepsia and gastro-esophageal reflux disease and with extraintestinal symptoms such as fatigue, urinary tract symptoms and pain; especially headaches, back aches and dyspareunia.

Comorbid anxiety and depression are common and IBS symptoms are often worsened if these conditions are present. IBS is associated to chronic fatigue syndrome and bodily distress syndrome.

of alarm signals, a physical examination and limited diagnostic testing. There is no known biomarker of IBS. In primary care in Denmark, a positive diagnostic strategy is non-inferior to the traditional diagnosis of exclusion including blood tests and a sigmoidoscopy with regard to safety, patient satisfaction and costs [4].

HOW TO DIAGNOSE IBS? (Figure 1 and Table 1)

A positive diagnosis of IBS is based on recognition of the well-described syndrome by means of symptom based criteria and exclusion of organic disease. Organic disease is excluded by evaluation

Figure 1. Flowchart – Diagnostic work-up of IBS

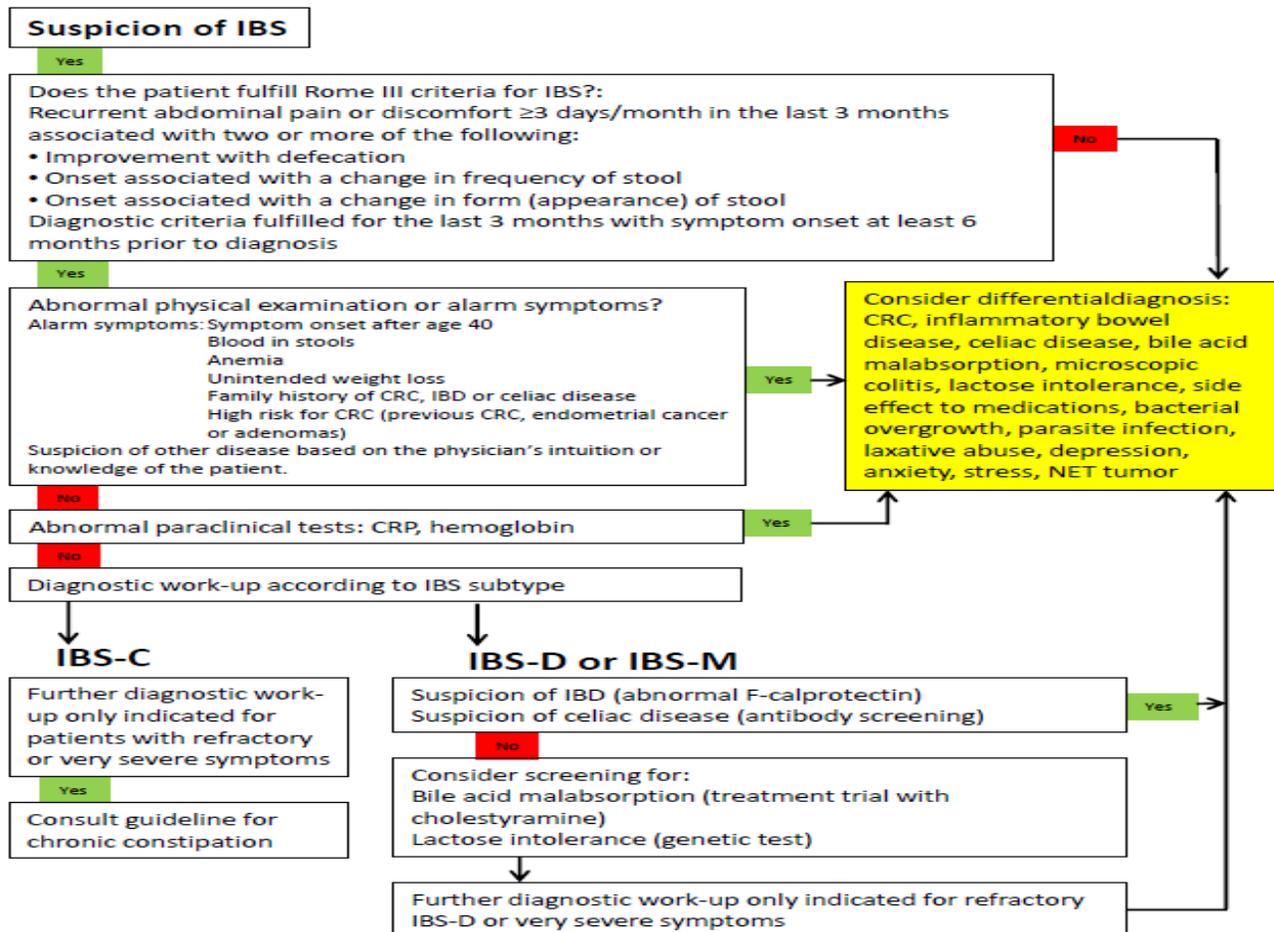


TABLE 1. HOW TO DIAGNOSE IBS?

	Evidence grade
IBS can be a positive diagnosis in patients fulfilling the Rome III criteria for IBS with no alarm signals, a normal physical examination and a normal CRP and hemoglobin	2b
Patients with IBS and diarrhea should be tested for celiac disease	3a
Patients with IBS and diarrhea should not routinely be tested for intestinal parasites	3b
Patients with IBS and diarrhea should not routinely have a breath test for bacterial overgrowth	4
In patients <40 years with IBS symptoms and diarrhea, a normal fecal calprotectin excludes IBD with a high probability	2b
Genetic testing for lactose intolerance may be performed based on clinical suspicion.	1c
Screening for bile acid malabsorption can be attempted with a treatment test of cholestyramine in IBS-D	1c
Lower endoscopy is not routinely recommended in the evaluation of IBS symptoms	4

Symptom-based criteria for IBS. At present, the Rome III criteria are used for IBS. Several systematic reviews and meta-analyses show that the different symptom-based criteria (Manning criteria, Rome I and II) can be used equally [5, 6]. In primary care in Denmark, the sensitivity of the Rome III criteria was estimated at 76%

[7]. In gastroenterological outpatient clinic in Canada, the sensitivity was 69% and specificity 80% [5]. Some patients do not strictly fulfill the symptom-based criteria for IBS; still a diagnosis of IBS can be made based on the typical symptoms if no organic disease is present. IBS symptoms fluctuate and a patient will not

necessarily fulfill the symptom-based criteria of IBS at all times. This should not lead to doubt of the diagnosis and further investigations are only necessary if symptoms change significantly or alarm signals evolve.

Alarm signals. Alarm signals, indicating further investigations, include a family history of colorectal cancer (CRC) or inflammatory bowel disease (IBD), weight loss, rectal bleeding, anemia or abnormal findings on physical examination. All patients presenting after age 40 and patients in high risk of CRC of all ages (previous CRC, adenomas or endometrial cancer, IBD or a family history of hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis) should undergo investigations according to national guidelines on CRC (http://www.dccg.dk/03_Publikation/01_ret.html). According to the Danish national guideline on celiac disease (CD) (<http://www.dsgh.dk/home/guidelines>) patients with a first degree relative with CD should be offered testing for this disease.

Physical examination and diagnostic testing. A proper physical examination of the patient and a minor paraclinical examination program (hemoglobin and CRP) serves the purpose to exclude organic diseases. There is an international consensus concerning offering patients >45 years of age (Denmark: >40 years) a lower GI-tract endoscopy due to the higher risk of CRC. Further investigations should be targeted according to IBS subtype. There is no evidence for routinely analyzing sedimentation rate, thyroid status or performing ultrasound examination of the abdomen [8]. There are no studies regarding the value of MRI scanning of the small intestines, small-bowel follow-through or capsule enteroscopy in patients with symptoms suggesting IBS.

Further investigations in IBS-D and IBS-M. The most important differential diagnoses to IBS, where diarrhea is dominating, are celiac disease, IBD, microscopic colitis, bile acid malabsorption, bacterial overgrowth, giardiasis, lactose intolerance and CRC. In secondary care, the probability of organic disease in patients fulfilling symptom-based criteria for IBS with no alarm signals is below 15% [5, 9]

Celiac disease. Testing for celiac disease (CD) is cost effective in populations with a prevalence of CD >1% [10, 11]. At present, it is not known whether the prevalence in Danish patients with symptoms of IBS with no alarm signals is higher than the 0.5-1% seen in the background population. Since serologic tests for CD are available and cheap, the test should be offered to patients presenting with diarrhea (IBS-D and IBS-M).

Fecal calprotectin. Fecal calprotectin (F-Cal) can be used for screening for IBD instead of CRP. Both sensitivity and specificity are higher for F-Cal compared to CRP and F-Cal has been shown to differentiate between IBS and IBD with a high negative predictive value in populations with a prevalence of IBD <25% [12, 13]. An F-Cal value <50 µg/g, which is the most commonly used cut-off in Denmark, reduces the probability of IBD to 1.3%. Patients with a test value <50 µg/g should not routinely have a sigmoidoscopy or colonoscopy performed. For patients with a higher test value, evaluation for IBD should be considered recognizing that there is an overlap between IBS and IBD, especially for test results between 50 - 200 µg/g. Furthermore, F-Cal can be elevated in other

inflammatory conditions of the intestinal tract. The cost effectiveness in secondary care is not known, but in primary care in the UK the test has been shown to reduce the number of lower endoscopies in patients suspected of IBS [14]. If lower endoscopy is planned, F-Cal is redundant.

Fecal testing for intestinal parasites. There is no evidence to suggest that intestinal parasites are more common in subjects with IBS compared to healthy subjects; on the contrary, a Danish study showed that parasites were significantly less common in IBS [15]. Therefore, routine testing for intestinal parasites is not recommended.

Breath test for bacterial overgrowth. Studies on the prevalence of bacterial overgrowth in patients fulfilling symptom-based criteria for IBS show heterogeneity [16]. Therefore, routine breath testing is not recommended.

Lactose intolerance. Lactose malabsorption verified by a breath test is not more prevalent in IBS patients than in the general population [17]. Nevertheless, IBS patients report more symptoms when ingesting lactose products compared to controls with verified lactose malabsorption [17, 18]. English and Swedish guidelines recommend an exclusion and re-introduction of dairy products if lactose intolerance is suspected, as opposed to testing for lactase insufficiency. In Denmark, the genetic test for primary lactase insufficiency is still used if the suspicion is reinforced.

Bile acid malabsorption. The prevalence of comorbid bile acid malabsorption is high (~25%) within patients with IBS-D symptoms in secondary care settings. The effect of colestyramin is limited to treating diarrhea. Hence, colestyramin has no effect on other IBS symptoms [21]. If bile acid malabsorption is suspected, a treatment period with colestyramin can be performed followed by a SeCHAT scan if efficacious.

Endoscopy. Colonoscopy can be performed in patients with symptoms compatible with IBS-D to exclude CRC and IBD. There is no evidence to support routine colonoscopy amongst IBS-D or IBS-M patients <40 years without any alarm symptoms [22, 23].

Further investigations in IBS-C. There is no evidence for further examination of the patient with IBS-C without alarm symptoms, unless the patient is refractory to treatment or suffers from severe symptoms. In these cases refer to the Danish national guideline for chronic constipation (www.dsgh.dk/home/guidelines).

HOW TO TREAT IBS?

In general, the therapeutic gain is small and most likely overestimated in older studies. On the other hand, side effects are usually mild and - owing to high placebo responses - the potential symptomatic benefit is relatively large, which may justify empirical treatment. The choice of therapy based on IBS subtyping is pragmatic and rests mainly on clinical experience and there are only few treatment trials as guidance. Importantly, the significance of previous failure with another treatment modality is unclear. There is a lack of long-term treatment trials. The generalizability of the trials is poor, mainly due to selection bias (See Figures 2 and 3 and Table 2).

Figure 2. Flowchart – Treatment of IBS

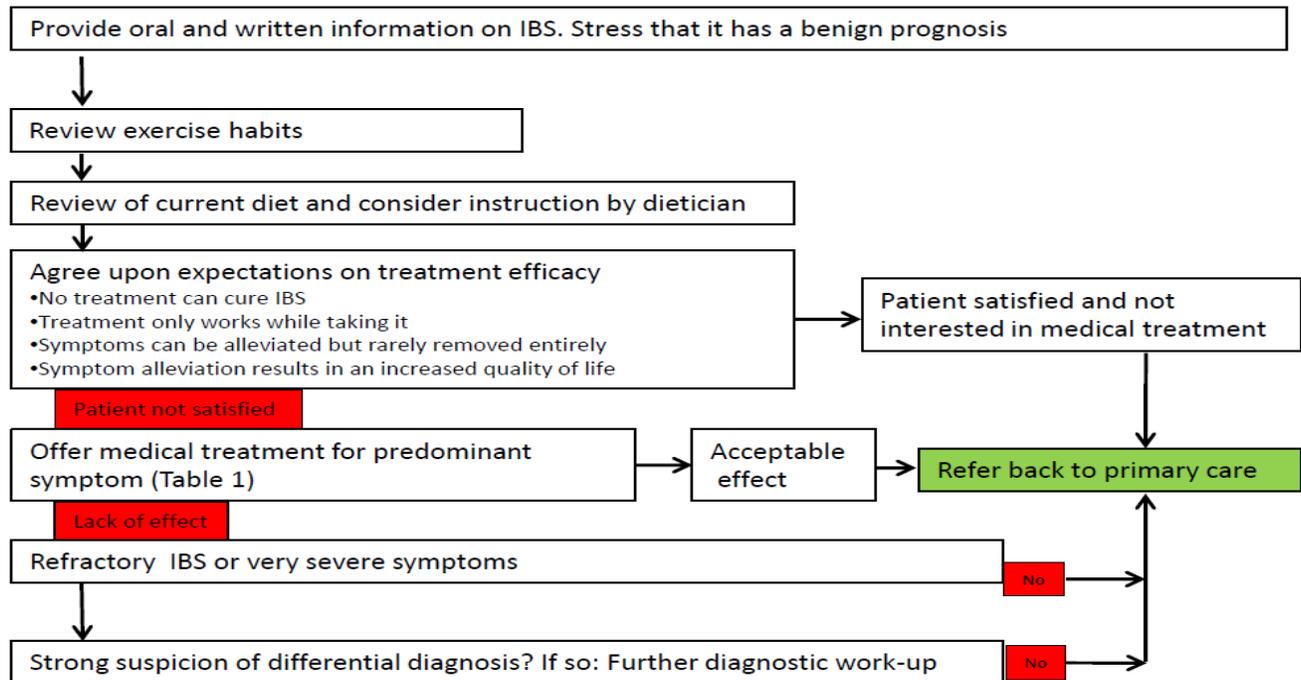


Figure 3. Treatment of predominant IBS symptom

Start from the top of the table and move down stepwise if treatment fails. Steps can be skipped based on physician or patient preferences. See guideline text for details.

Green: recommended: 1) Good evidence; 2) Potentially effective with few/mild side effects; 3) Acceptable efficacy and cheap with few/mild side effects
Yellow: Can be used: 1) Evidence less good, but potentially effective; 2) Evidence acceptable, but expensive compared to efficacy
Red: Not recommended: 1) No effect proven or poor evidence; 2) Expensive and poor efficacy; 3) Poor efficacy and severe side effects

Diarrhea	Constipation	Pain	Bloating
Psyllium NNT unknown 1 measure (5 g) × 2-3/day	Psyllium NNT 11 1 measure (5 g) × 2-3/day	Peppermint oil (capsules) NNT 3 0,2-0,4ml × 3/day	Psyllium NNT unknown 1 measure (5 g) × 2-3/day
Loperamide NNT 1-2 4 mg × 1-2/day or 4 mg × 1/day + 2 mg p.n. up to 16 mg/day	Osmotic laxatives NNT 3 Magnesiumoxide 1 g × 1-2/day or Macrogol (PEG) 1-4 sachets/day	Antispasmodics NNT 3-4 Hyoscinebutylbromid 10-20 mg × 3-5/day	Simethicone/dimethicone NNT unknown 240 mg × 3/day
Ondansetron NNT 2-3 4 mg × 1-3/day	Ad stimulant laxative NNT 3 (without osmotics) (oral use at night or rectal use in the morning): Bisacodyl 5-10 mg × 1/day or sodium picosulfate 5-20 dr. daily	Low dose tricyclic antidepressants (TCA) NNT 4 Imipramine or amitriptyline 10-25 (100) mg/day (side effect: constipation)	Rifaximine NNT 10 550 mg × 2-3/day for 14 days
Colon cleansing (bowel preparation) if overflow diarrhea is suspected	Linaclotide NNT 6 290 mikrogram × 1/day	Selective serotonin reuptake inhibitors (SSRI) NNT 4 Citalopram, paroxetine or fluoxetine 20-40 mg × 1/day (side effect: diarrhea)	
	Prucalopride NNT 6 1-2 mg × 1/day	Linaclotide NNT 14 Only in IBS-C	
Treatment of comorbid depression, anxiety or stress			
TCA (side effect: constipation) SSRI (side effect: diarrhea) Serotonin-norepinephrine reuptake inhibitors (SNRI)	SSRI (side effect: diarrhea) TCA (side effect: constipation) SNRI	SSRI or TCA SNRI	TCA or SSRI SNRI

Non-pharmacological therapy (Table 2)

TABLE 2. HOW TO TREAT IBS?

	Evidence grade
Exercise 3 times weekly of moderate intensity can reduce symptoms and increase quality of life (QOL) in motivated patients	1b
Low FODMAP diet can be tried in motivated patients supervised by a dietician. In short term studies in selected patients the diet may reduce bloating and pain and increase QOL.	1b
Traditional dietary advice can reduce symptoms to the same extent as the low FODMAP diet	1c
Gluten free diet. There is no clinical relevant effect of a gluten free diet on IBS symptoms	1b
Probiotics do not have a significant effect on symptoms of IBS	1a
Psyllium may reduce symptoms of IBS (global effect)	1a
Acupuncture is not better in reducing symptoms in IBS patients compared to placebo-acupuncture	1b
Loperamide can reduce stool frequency in patients with IBS-D	1c
Ondansetron can reduce urgency, bloating and stool frequency in patients with IBS-D (limited data)	1b
Cholestyramine is not efficacious in IBS-D patients without bile acid malabsorption	4
Osmotic laxatives (but not lactulose) and stimulant laxatives can be used for IBS-C	5
Linaclotide has a positive effect on constipation and pain in IBS-C	1b
Prucalopride can be used for IBS-C	5
Peppermint oil may reduce abdominal pain in IBS	1b
Antispasmodics (hyoscine) may have a slight effect on abdominal pain	1a
Low-dose TCA may reduce abdominal pain in IBS	1a
SSRI drugs may reduce IBS symptoms (global effect)	1a
Rifaximin is not recommended for bloating in patients with IBS due to a limited and short lasting effect	1b
Simethicone/dimethicone is not recommended (never tested in IBS patients)	5

Exercise. Exercise as treatment for IBS has been tested in two RCTs with a total of 150 patients [24, 25]. Both trials showed that exercise decreased symptoms and increased quality of life, but were flawed by a substantial dropout rate and possible selection bias.

Probiotics. More than 50 RCTs have tested the symptomatic effects of different mixtures and doses of probiotics. Differences in design and in the interventions complicate evaluations by meta-analyses. The majority of the 27 studies that evaluated mixtures of probiotics showed no effects. Studies in Danish patients have all been negative. Most studies with lactobacilli and saccharomyces were also negative, whereas 4/6 RCTs with bifidobacteria showed positive results (global effect). Overall, there is very limited evidence for a symptomatic effect of probiotics for IBS [26].

Low FODMAP diet (LFD). The LFD has not been sufficiently tested for a possible effect to be estimated. [27]. There are six RCTs with durations between two days and four weeks, only two were double blinded. In 5/6 trials a symptom reduction was reported, how-

ever, there were no effects in objective measures (stool frequency/consistency). There are no long term RCTs (>4 weeks) or studies of the recommended reintroduction period. LFD may reduce IBS symptoms with approximately 20% and yield approximately 50% responders (50 point reduction on the IBS-SSS questionnaire), including the placebo effect.

Traditional dietary advice. A so-called Swedish IBS diet is less invasive and can reduce symptoms as effectively as LFD (LFD: 22% symptom reduction and 50% responders vs. 24% symptom reduction and 46% responders). There was no placebo group in the trial, which had a duration of four weeks [28].

Gluten free diet. Gluten free diet is not efficacious in IBS patients. Patients on LFD got the same increase in symptoms when informed that they are receiving either a blinded gluten containing test meal or placebo. The symptoms increased to an equal extent regardless if the meal contained a high amount of gluten, a lower amount or no gluten [29]. A randomized trial of gluten free diet in IBS-D patients showed a clinically insignificant effect on number of stools (0.25 lower stool frequency per day) [30].

Psyllium. A meta-analysis based on six trials showed heterogeneity and more symptom-free patients in the actively treated group (therapeutic gain of 12%). This effect was no longer statistically significant if a low quality study was omitted from the analysis [31]. It has never been tested whether addition of calcium to the psyllium has any effect on diarrhea in IBS patients.

Acupuncture works only via the placebo effect. Acupuncture has been tested in several well designed RCTs with placebo acupuncture [32]. The largest trial randomized 230 patients [33]. Acupuncture and placebo acupuncture reduced symptoms to a comparable degree.

Pharmacological treatment of diarrhea (Figure 3 and Table 2)

Loperamide. Loperamide has been tested in several old studies of low quality and a single good quality RCT with 90 patients [34]. Loperamide reduces stool frequency in IBS-D patients. The therapeutic gain (reduction in stool frequency) was 30% (40% in the loperamide group vs. 10% in the placebo group). There was no significant effect on pain or bloating.

Ondansetron has been tested in a placebo controlled cross-over trial with 120 IBS-D patients [35]. Ondansetron showed efficacy on reducing stool frequency, urgency and bloating, but not on reducing pain.

Cholestyramine. The drug can be used as a diagnostic test, when bile acid malabsorption is suspected before a Se-HCAT scan is performed (see above). In selected patients from secondary care as many as 10 - 33% of IBS-D patients have bile acid malabsorption as measured by a pathological se-HCAT (<5% retention) [36]. These patients benefit from cholestyramine. IBS-D patients with a normal se-HCAT or mild bile acid malabsorption (10-15% retention) report no effect from cholestyramine. The effects of cholestyramine on patients with IBS-D without co-morbid bile acid malabsorption have not been studied in RCTs yet [23].

Pharmacological treatment of constipation (Figure 3 and Table 2)

Laxatives. The effects of polyethylenglycol (PEG) have been tested in an RCT with 139 patients. PEG was efficacious in treating constipation but had no effect on pain [37]. There is a lack of RCTs testing the other traditional laxatives in patients with IBS-C. Chronic constipation and IBS-C overlap. For chronic constipation experts usually recommend to start with osmotic laxatives (magnesia or PEG) and add laxatives that stimulate peristalsis and this strategy is also recommended for IBS-C. Lactulose is effective against constipation, but has more side-effects; therefore this drug is not recommended.

Linacotide. Two American RCTs with >1600 patients showed effects on the number of defecations, pain and bloating. The laxative effect starts within a few weeks, whereas the effects on pain and bloating are delayed (weeks – months). The therapeutic gain against placebo (composite end point) is in the order of 12-15% [38].

Prucalopride. Has been approved for chronic constipation, but can be tried in IBS-C as well.

Pharmacological treatment of abdominal pain (Figure 3 and Table 2).

Peppermint oil. The few RCTs are old and with a low number of participants. However, meta-analyses agree on a therapeutic gain [39, 40]. Side effects are rare and the most frequent (heartburn), can be avoided if the oil is ingested in a capsule.

Antispasmodics. A recent Cochrane review of 13 RCTs ($\Sigma N=1392$), including 10 subgroups of antispasmodics, showed a combined therapeutic effect of 12% compared to placebo (58% vs. 46%) [40]. Another systematic review investigated the therapeutic effect of 12 different antispasmodics [31]. Of these, only mebeverine (Duspatalin®) and hyoscine (Buscopan®) are available in Denmark. The study found no therapeutic gain of mebeverine (1 RCT, 80 patients), while there was a therapeutic effect of 17% using hyoscine (3 RCTs, 426 patients). However, the review found signs of heterogeneity and a risk of publication bias.

Antidepressants. A meta-analysis from 2014 including seven RCTs ($\Sigma N=384$) concluded a relative risk of persisting abdominal pain of 0.62 (95% CI: 0.43-0.88). The authors subdivided the studies and found a considerable heterogeneity among the studies testing selective serotonin reuptake inhibitors (SSRI) but not within the tricyclic antidepressant (TCA) studies [41]. Recently, a Cochrane review found SSRI and TCA drugs comparable for IBS, because SSRI drugs show a significant global symptomatic effect despite no effect on pain [40]. The choice of drug should be guided by the IBS subtype. TCA drugs may cause constipation, while SSRI drugs can cause diarrhea. To reduce any side-effects it is recommended to use a low dose of TCA and the lowest dose of SSRI [23] (see Table 1).

Pharmacological treatment of bloating (Figure 3 and Table 2)

Rifaximine has been tested in two large RCTs (>1200 patients) with IBS-D or IBS-M. Rifaximine is not recommended since the therapeutic gain, when treating bloating, was at best 10% and repeated treatment often was necessary for effect (therapeutic gain for re-treatments: <8%) [42, 43].

Simethicone. The possible effects of simethicone (activated dimethicone) is difficult to evaluate as the drug has only been tested in combination with other drugs for IBS.

Psychological treatment (Table 2)

If the treatment options mentioned above are not satisfactory, the next step could be psychotherapy, cognitive behavioral therapy, meditation or hypnosis. According to several meta-analyses, these treatments are effective despite the fact that the included patients in the trials were more severely affected by IBS [41, 44, 45]. In general, the trials were small, with a short follow-up time and of varying quality and unblinded. In Denmark, reimbursement for these therapies is not offered. Furthermore, no secondary care centers in Denmark offer these modalities and patients are thus forced to seek the therapy in primary care themselves.

Summary

National Danish guidelines for the diagnosis and treatment of irritable bowel syndrome (IBS) in adult patients in secondary and tertiary care have been approved by the Danish Society for Gastroenterology and Hepatology. IBS can be a positive diagnosis in patients fulfilling the Rome III criteria for IBS with no alarm signals, a normal physical examination and a normal CRP and hemoglobin. In patients <40 years with IBS and diarrhea, a normal fecal calprotectin excludes inflammatory bowel disease with a high probability. Patients with IBS and diarrhea should be tested for celiac disease. Endoscopy is not routinely recommended. The therapeutic gain of various treatment modalities is small and most likely overestimated in older studies. However, side effects are usually mild which may justify empirical treatment. The choice of therapy based on IBS subtyping is pragmatic and there are only few trials as guidance. The significance of previous failure with another treatment modality is unclear. There is a lack of long-term treatment trials. The generalizability of the trials is poor, mainly due to selection bias.

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