

Systematic review on the management of irritable bowel syndrome in the European Union

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2.1 Methods

2.1.1 Introduction

This evidence-based monograph utilizes:

- A transparent link between the evidence and recommendations in the executive summary
- Explicit study selection criteria for studies that support evidence-based recommendations
- Comprehensive searching of the literature for relevant studies
- A standardized and explicit system for grading the methodologic quality of relevant studies
- A standardized and explicit system for grading evidence-based recommendations

f Recommendations that reflect the magnitude of treatment benefit, the adverse events associated with the treatment, and individual patient preferences which may guide the application of these recommendations [1–3]

In order to fulfill these requirements, several different techniques have been applied. Each section of the systematic review has been numbered to provide a link between the evidence and the recommendations. Standard techniques for literature searching and study selection were utilized for each section of this document [4,5]. Advisory board members also relied upon several systematic reviews that were recently completed [6–8].

Information from these systematic reviews regarding study methodology and outcome was assessed, thereby, ensuring that the methodologic rigor of individual studies was defined and the magnitude of treatment effect quantified. A commonly used system for grading recommendations in evidence-based guidelines [9] was adapted for this document to ensure that an explicit and transparent process formed the basis for the development of all recommendations. Adverse events and individual patient preferences may affect the application of these recommendations. Therefore, adverse events have been assessed, relative contraindications to specific treatments have been described, and advisory board members contributed their advice about the effect of individual patient preferences on these recommendations.

This approach reflects the process utilized to produce a similar evidence-based monograph, the American College of Gastroenterology's 'Evidence based approach to the management of irritable bowel syndrome in North America' [6], and parts of the ACG monograph were adapted for this evidence-based monograph with permission from the authors of the ACG document. A medical education and research company (EBMed, LLC, Anaheim Hills, California) assisted the advisory board with literature searches, application of study selection criteria, data extraction and analysis, and assessment of methodologic quality of individual trials.

2.1.2 Literature search

In order to identify relevant treatment trials, the ACG evidence-based monograph [6] employed separate PUBMED, MEDLINE and EMBASE searches of English language articles from 1980 to 2001 with different combinations of the following search terms: 'antispasmodics', 'antimuscarinics', 'dicyclomine', 'hyoscyamine', 'constipation', 'fibre', 'polycarbophil', 'bulking agents', 'laxatives', 'antidepressants', 'tricyclic antidepressants', 'tegaserod', 'irritable bowel syndrome', 'clinical trial', and 'randomized (pt)'. The bibliographies of IBS therapy trials, selected review articles and selected meta-analyses were manually searched. Similar search strategies were also performed for the additional systematic reviews [7,8], although the timeline for publication of studies was extended to 2004 and included anti-spasmodic agents available in the EU.

In order to identify relevant trials about the *Epidemiology of IBS* in the EU, the following literature search techniques were employed. Separate MEDLINE and EMBASE searches of English language articles were performed with different combinations of the following search terms: 'colonic diseases, functional' was exploded with key words 'incidence', 'prevalence', 'prognosis', and 'natural history'. Similar combinations were exploded using 'irritable colon'. Bibliographies from potentially relevant articles were manually searched.

2.1.3 Study selection criteria

Since an EU perspective was used, only treatments available in the EU were examined and only epidemiologic studies from EU populations were reviewed. For this monograph, the selection criteria for *IBS therapy trials* were: (a) randomized controlled trial; (b) population of adult patients with IBS; (c) comparison of IBS therapy vs. placebo or control therapy; (d) evaluation of relief of IBS symptoms; and (e) published in English in full manuscript form (or adequate data available after written communication with investigators). Similar study selection criteria were used for the ACG evidence-based monograph and the two systematic reviews [6–8] that formed the basis for this monograph. For *Epidemiology of IBS* studies, the selection criteria were: (a) studies of population-based samples of IBS patients in the EU; (b) use of Manning, Rome I, or Rome II criteria to identify IBS patients; (c) population of adult patients; (d) results reported on prevalence, incidence, natural history of IBS, quality of life, or healthcare utilization by IBS patients; (e) results published in full manuscript form; and (f) English language only.

2.1.4 Data extraction and analysis

For *IBS therapy trials*, data from the ACG monograph [6] and the systematic reviews [7,8] about treatments available in the EU were utilized. Using these reports, data about study design and study results was extracted. In this monograph, improvement in global IBS symptoms was considered the primary outcome of interest (see Section 2.5). The Task Force agrees with the recommendations of the Rome Committee [10]: 'the primary outcome measure should ... integrate the key symptoms of [IBS] ... allowing the patient to integrate the contribution of a disparate group of symptoms [abdominal pain, bloating, and altered bowel function] into a single global clinical rating.' This assessment should be done by the patient, since it is doubtful that a physician's assessment of a patient's improvement in global IBS symptoms would be more accurate or more reliable than the assessment of the patient.

For *Epidemiology of IBS* studies in the EU, data were extracted about: (a) symptom-based definition of IBS (e.g., Manning criteria or Rome criteria); (b) sample size and case ascertainment technique to identify IBS patients; (c) prevalence, incidence, prevalence of IBS sub-groups, gender distribution, and mean age of onset of symptoms; (d) disease activity (e.g., prevalence of IBS over time and frequency of IBS flares within a specified period of time); (e) quality of life in IBS patients as measured by validated quality of life instruments; and (f) healthcare utilization by IBS patients.

2.1.5 Quantitative assessment of study methodology

Per the ACG monograph [6], 'previous reviews and epidemiologic studies [11–13] have established metho-

dologic criteria that minimize bias and enhance validity of trials about therapy, including the use of randomization, concealed allocation, double blinding, and complete patient follow-up. Additionally, the Rome committees described the preferred design of treatment trials for functional gastrointestinal disorders [10] (Table 2.1.1).^{*} In order to assess the methodologic strength of individual studies about IBS therapies, a quantitative assessment of study quality was performed. Utilizing the 14 study design criteria of the Rome committees, studies that met >10 criteria were considered high quality (level I evidence), studies that met 5–9 criteria were considered intermediate quality studies (level II evidence) and studies that met <5 criteria were considered low quality RCTs (level II evidence) (see next section for further description about levels of evidence).

Although standardized criteria do not exist for rating the methodologic strength of epidemiologic studies, population-based studies are less likely than studies of referral populations to produce inflated estimates of the prevalence and incidence of a disorder. Therefore, epidemiologic studies in this review are limited to population-based studies.

2.1.6 Levels of evidence

Levels of evidence are graded using a system similar to the ACG monograph. Level I evidence is derived from high quality randomized controlled trials (RCTs). Per the ACG monograph [6], ‘these RCTs have few limitations in their study design, which should minimize type I errors. Thus, if the trial does show a significant difference between treatment and placebo, then it will be unlikely that this finding is due to biased study design. High quality RCTs also have adequate power to minimize type II errors. Thus,

if the trial does not show a significant difference between treatment and placebo, then it will be unlikely that this finding is due to an inadequate sample size of patients. Level II evidence represents intermediate quality RCTs. These RCTs have important limitations in their study design, which could produce a type I error. Intermediate quality RCTs may also be susceptible to type II errors due to inadequate sample size.’ Level III–V evidence comes from non-randomized trials or case studies and/or expert opinion. These are observational studies which are prone to multiple biases that produce type I errors. For this review, level III–V evidence was only used to make recommendations about the *Epidemiology of IBS in the European Union* since data about these topics may only be available from observational studies.

Per the ACG monograph system, ‘Grade A recommendations are supported by the strongest (level I) evidence. [Advisory board] members strongly believe that these recommendations are accurate, based on the evidence. Grade B recommendations are supported by intermediate quality (level II) evidence. [Advisory board] members believe that Grade B recommendations may have important limitations due to the intermediate quality of the evidence. These recommendations may change in the future if high quality (level I) evidence becomes available. Grade C recommendations are supported by level III–V evidence. Since these recommendations are based largely on observational studies, the strength of evidence behind these recommendations is limited. Grade C recommendations are only provided because they represent the best evidence about the *Epidemiology of IBS*.’

Table 2.1.1 Quantitative assessment of study methodology scale*

1. Use Rome criteria to identify patients with IBS
2. Randomization
3. Parallel study design (i.e., no crossover studies)
4. Double-blinding
5. Complete follow-up of patients
6. No placebo run-in
7. Baseline observation of patients to assess symptoms
8. Treatment duration of 8–12 weeks or longer
9. Follow-up after treatment to assess symptoms
10. Compliance with the treatment is measured
11. Sample size calculation is provided and adequate sample size enrolled
12. Primary outcome of the trial is improvement in global IBS symptoms
13. Primary outcome is based on patient assessment
14. Validated scale used to measure improvement in IBS symptoms

Adapted from Van Zanten SJO, *et al.* Design of treatment trials for functional Gastrointestinal disorders. *Gut* 1999; **45** (Suppl II):69–77* [10], and Brandt L, *et al.* An evidence based approach to the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002; S1–S26 [6].

*The members of the Committee on Design of Treatment Trials for Functional Gastrointestinal Disorders of the Rome II committee also noted additional recommendations for the design of clinical trials, including a priori defined study endpoint and definition of patient setting (primary care vs. tertiary care). However, published reports of studies rarely provided adequate information to assess the use of these additional techniques in the conduct of treatment trials. Therefore, these additional techniques were not included in the scale.

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- 12 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273**:408–412.
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2.2 Symptom-based criteria for irritable bowel syndrome

The current symptom-based criteria for the diagnosis of IBS are the Rome II criteria, which are used to identify IBS patients for enrollment in clinical trials.

Several symptom-based criteria (e.g., Manning criteria, Rome I criteria, Rome II criteria) have been developed to diagnose IBS. [Note: This advisory board met prior to publication of Rome III criteria for IBS, so Rome II criteria for IBS were used in this report.] These criteria emphasize the association of changes in stool frequency or stool consistency with abdominal discomfort. Advisory board members stated that the Rome II criteria are the most precise criteria for the symptom-based diagnosis of IBS. The precision of these criteria is reflected by their utilization to identify and enroll patients into IBS clinical trials. Therefore, advisory board members stated that Rome II criteria were the most appropriate symptom-based criteria to use when identifying IBS patients.

Per the Rome II criteria, IBS is defined as at least 12 weeks or more, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two out of three features:

- a Relieved with defecation, and/or
- b Onset associated with a change in frequency of stools, and/or
- c Onset associated with a change in form (appearance) of stool

IBS with constipation is defined as the *presence* of abdominal discomfort or pain that is associated with at least one of the following features:

- a Fewer than three bowel movements/week, and/or
- b Hard or lumpy stools, and/or
- c Straining during a bowel movement,

and the *absence* of:

- a More than three bowel movements a day
- b Loose (mushy) or watery stools
- c Urgency (having to rush to have a bowel movement)

IBS with diarrhoea is defined as the *presence* of abdominal discomfort or pain that is associated with at least one of the following features:

- a More than three bowel movements per day
- b Loose (mushy) or watery stools
- c Urgency (having to rush to have a bowel movement),

and the *absence* of:

- a Fewer than three bowel movements per week
- b Hard or lumpy stools
- c Straining during a bowel movement

Reference: Section 2.2

- 1 Thompson WG, Longstreth FG, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; **45** (Suppl II): 43–47.

2.3 Epidemiology of irritable bowel syndrome in the European Union

2.3.1 Prevalence of IBS in the European Union

Although previous estimates of IBS prevalence vary based upon study criteria and symptom-based definitions of IBS, the prevalence of IBS in the European Union (EU) is approximately 4% based upon Rome II criteria. Approximately 16% of IBS patients have constipation-predominant IBS, 21% have diarrhoea-predominant IBS, and 63% have IBS with bowel habits alternating between diarrhoea and constipation. There is a 2:1 female:male predominance among IBS patients in the EU. (Grade C Recommendation)

Thirteen studies [1–13] provided data regarding the prevalence of IBS in one or more EU nations. Table 2.3.1 provides information regarding these studies, including the year of publication, target population, sample size, country of origin, diagnostic criteria used to define IBS, and gender breakdown.

As in North America, the prevalence of IBS depends on the case-finding definition employed and the source

Table 2.3.1 Prevalence of IBS in studies from European nations

Ref.	Year	Population	n	Country	Diagnostic criteria	% IBS		
						Women	Men	All
1	1992	English urban, white=99%	1896	UK	≥ 3 M	13.0	5.0	9.5
2	1992	English urban and suburban, mostly white	1620	UK	≥ 2 M	24.3	18.7	21.6
3	1994	General Danish population	4581	Denmark	Symptom criteria	7.7	5.6	6.6
4	2000	General Swedish population	2707	Sweden	RI	13.3	7.4	10.6
5	2001	General Spanish population	2000	Spain	M	–	–	10.3
					RI			12.1
					RII			4.9
6	2002	General French population	11 131	France	RI	5.3	2.5	4.0
7	2002	General German population	1281	Germany	Patient Report	–	–	12.5
8	2003	Two UK birth cohorts	22 680	UK	Patient Report	–	–	8.26
9	2003	Multinational	41 984	Multinational	M	–	–	6.5
					RI			4.2
					RII			2.9
10	2004	General French population	20 000	France	RII	5.7	3.7	4.7
11	2004	General Finnish population	3650	Finland	≥ 2 M	19.2	13.1	16.2
					≥ 3 M	11.2	8.3	9.7
					RI	6.1	5.1	5.5
					RII	5.3	5.1	5.1
12	2004	Clinic-based population	4807	UK	RII	14.0	6.6	10.5
13	2004	General French population	8221	France	M	3.1	1.7	2.5
					RI	2.8	1.4	2.1
					RII	1.3	0.9	1.1

M, Manning criteria; RI, Rome I criteria; RII, Rome II criteria.

Table 2.3.2 Calculated pooled mean weighted prevalence of IBS in Europe by definition of IBS (study sample size forms basis of pooled weighting calculations)

Definition of IBS	Number of studies	Mean weighed prevalence
Manning	5	6.78%
Rome I	6	4.46%
Rome II	6	3.76%

population interrogated. Table 2.3.2 provides the calculated pooled mean weighted prevalence of IBS for each of the three main IBS definitions employed in the European prevalence studies: Manning, Rome I, and Rome II. These point estimates are generally in line with data from North American studies [14] although the prevalence of Rome II-defined IBS is lower than similar estimates in North America (3.8% in Europe versus roughly 5% in North America).

The largest population-based studies may deserve further description because the pooled mean weighted prevalence of IBS is largely dependent on the results from these studies. The study conducted by Hungin *et al.* [9] was conducted by a group of multinational investigators in the UK, Belgium, and Spain. It was a large telephone survey of 41 984 members of the general population of eight European nations (UK, France, Germany, Italy, Holland, Belgium, Spain, and Switzerland). In order to capture representative samples of each nation's population, the investigators used quota sampling applied across age and gender strata commensurate with each country's profile. The survey used random digit dialing within a

probabilistic sampling frame. The authors employed several definitions of IBS, including Manning, Rome I, and Rome II criteria, and self-report. The survey revealed that 11.5% of respondents carried a diagnosis of self-reported IBS. However, the prevalence's of Manning, Rome I, and Rome II IBS were lower at 6.5%, 4.2%, and 2.9%, respectively. The study by Ehlin, *et al.* [8] provides the follow-up results of a long-term birth cohort observational study in the UK. This study aimed to measure the prevalence of several chronic gastrointestinal conditions, including IBS. The investigators followed members of two British birth cohorts (one born in 1958, the other in 1970), and then measured the point prevalence of IBS in the year 2000. There was no formal case-finding definition of IBS, other than patient report of having been diagnosed with IBS. The authors reported an IBS prevalence of 826 per 10 000, or 8.26%, based on the results from 22 680 members of the original birth cohorts. The study from Dapoigny *et al.* [10] described the results of the largest survey in France, which assessed 20 000 members of the general population. The authors used Rome II criteria as their case-finding definitions. The survey found a point prevalence of Rome II IBS of 4.7%, with a higher prevalence in women (5.7%) than men (3.7%). The results of a postal survey administered to a random sample of 5000 members of the general population in Finland indicated that the prevalence of IBS by Rome II criteria was 5.1% [11]. The authors employed several definitions of IBS, including ≥ 2 Manning symptoms, ≥ 3 Manning symptoms, Rome I, and Rome II criteria. There were 3650 responses, yielding an excellent response rate of 73%. The point prevalence

of IBS by Manning 2, Manning 3, Rome I and Rome II criteria was 16.2%, 9.7%, 5.6%, and 5.1%, respectively. The authors concluded that the prevalence of IBS by Rome II criteria was considerably lower than by Manning criteria in Finland.

These epidemiologic studies [8–11] also emphasize two important themes. First, abdominal discomfort is consistently cited as the most troublesome symptom [9–11] with up to 30–40% of IBS patients reporting ‘severe’ or ‘very severe’ abdominal pain [11]. Abdominal discomfort is also the symptom that drives healthcare seeking behaviour in these patients (see Section 2.4). Second, based upon the largest population-based study in the EU, IBS-C accounts for only 16% of IBS patients with IBS-A accounting for 63% and IBS-D accounting for 21% [9], although smaller population-based studies [10] report an equal distribution between IBS-C, IBS-D, and IBS-A. In assessing the prevalence of IBS sub-types, a number of limitations must be borne in mind. First, sub-typing is performed on the basis of symptoms alone which are highly subjective and may not reflect actual changes in stool volume or consistency. Second, it is evident that these sub-types are not stable over time, and the patient who would be classified as IBS-C today may well be classified as IBS-A later on.

Based upon these data, the prevalence of IBS-C (by Rome II criteria) in the European Union is approximately 1% while the prevalence of IBS-D is approximately 1% and the prevalence of IBS-A is approximately 3%.

2.3.2 Impact of irritable bowel syndrome on health-related quality of life

IBS patients in the EU demonstrate clinically important decreases in health related quality of life compared to non-IBS controls. (Grade C Recommendation)

Eight studies provide data regarding HRQOL in IBS patients in EU nations. Table 2.3.3 provides information regarding these studies, including the year of publication, comparison groups, sample size, country of origin, HRQOL instrument employed, and key findings.

The available data support two general conclusions: (1) HRQOL is consistently lower in patients with IBS versus subjects without IBS, and (2) IBS impacts a wide range of HRQOL domains (as measured by validated quality of life questionnaires, including the SF-36 and EuroQOL), and has its largest impact on vitality, bodily pain, social functioning, and role-emotional subscales, patterns reflected by the North American data as well. The largest population-based study in the EU [9] also found that IBS substantially impacted several domains of well-being, including physical relationships, ability to live a normal life, eating out, self-confidence, exercise, concentration, sleep, and diet, among others.

In the EU, IBS patients who consult primary care physicians and IBS patients who consult specialists both suffer substantial decrements in health-related quality of life. A Scottish cross-sectional observational study

Table 2.3.3 Studies reporting HRQOL burden of IBS in Europe

Ref.	Year	Comparison groups	n	Country	HRQOL Instrument	Key findings
15	1999	IBS Patients in US vs. UK-based support groups	1000	US/UK	SF-36	Despite similar use of health care resources between groups, members of the UK group had lower HRQOL than members of the US group.
16	2001	IBS patients with severe symptoms vs. historical controls	257 in IBS group	UK	SF-36	Patients with IBS had clinically and statistically significantly lower HRQOL than historical controls.
17	2001	IBS in primary vs. secondary care	343	Sweden	SF-36	HRQOL was significantly lower in female patients in secondary vs. primary care, but not in male patients.
18	2002	IBS patients from general population vs. non-IBS patients from general population	2000	Spain	SF-36	HRQOL was significantly lower in patients with IBS vs. non-IBS subjects. Large differences were in bodily pain, vitality, social functioning and role-emotional subscales of SF-36.
19	2002	IBS patients from general population vs. non-IBS patients from general population	2400	Germany	SF-36	HRQOL was significantly lower across all subscales in patients with IBS vs. non-IBS subjects.
20	2002	IBS patients from GP practices vs. age- and sex-matched controls	373	UK	SF-36/EuroQOL	HRQOL was significantly lower across all subscales of the SF-36 and EuroQOL.
9	2003	IBS patients from GP practices vs. age- and sex-matched controls	41 984	Multinational	No Formal HRQOL Instrument	IBS patients experienced a larger negative impact, than non-IBS patients, on diet, concentration, ‘long journeys’, physical appearance, ability to eat out, sexuality and physical relationships.
21	2004	IBS in primary vs. secondary care	486	UK	SF-36	There were <i>no</i> significant differences in HRQOL between IBS patients in primary versus secondary care.

reported similar symptom characteristics, symptom frequency, and overall HRQOL in IBS patients seen in primary versus secondary care, and the authors concluded that ‘this study suggests that patients with IBS managed solely in primary care are affected as much as those attending secondary care.’ However, a Swedish cross-sectional survey of 343 patients with Rome I positive IBS found that HRQOL was significantly lower in secondary care versus primary care female IBS patients, but there were no substantial HRQOL differences among male patients stratified by primary versus secondary care. Also, there were no significant HRQOL differences between IBS subtypes.

2.4 Healthcare utilization by IBS patients in the European Union

2.4.1 Healthcare seeking behaviour by IBS patients in the European Union

The majority of IBS patients in the EU have consulted a healthcare provider for treatment of their IBS symptoms, although there is wide variation between different EU countries. The majority of consultations by IBS sufferers in the EU are done with a primary care physician. Abdominal pain is the symptom that most commonly drives healthcare seeking behaviour. (Grade C Recommendation)

Twelve studies were identified that provided data regarding the healthcare seeking behaviour of IBS patients in European nations. Table 2.4.1 provides information regarding these studies, including the year of publication, target

population, sample size, country of origin, diagnostic criteria used to diagnose IBS, and key findings.

These data indicate that patients with IBS in Europe frequently consult healthcare providers for advice and treatment of their symptoms. Specifically, between 33% and 90% of IBS patients sought care for their symptoms. Because this range of values is driven by a heterogeneous group of factors, it is not informative or accurate to calculate a pooled weighted estimate of healthcare seeking prevalence. Most of these data are obtained from community-based samples, suggesting that healthcare seeking is high in the general European population, not just in the subset of IBS patients with severe or longstanding symptoms. Nonetheless, these data demonstrate clear predictors of healthcare seeking: presence of abdominal pain and/or distension, high pain severity, and fulfilling Rome II versus Rome I criteria. These data also indicate that healthcare seeking is higher in IBS patients compared with non-IBS patients.

Studies that reported on these topics support these conclusions. In a cross-sectional survey of 1058 women and 838 men in the UK, the investigators found that abdominal pain was the most important individual symptom that drove healthcare seeking [1]. Additional studies from the UK demonstrated that IBS patients who sought healthcare were more likely to experience visible abdominal distension and have higher mean pain severity scores [22], while Swedish studies [4] demonstrated that healthcare seeking behaviour correlated highly with overall symptom severity [4].

Table 2.4.1 Studies reporting healthcare seeking behaviour of IBS patients in Europe

Ref.	Year	Population	n	Country	Diagnostic criteria	Key findings
1	1992	English urban, white=99%	1896	UK	≥ 3 M	50% had previously consulted a healthcare provider. Presence of abdominal pain drove healthcare seeking.
22	1992	English urban	28	UK	M	Consulters more likely to have abdominal distension and higher pain severity scores than non-consulters.
2	1992	English urban and suburban, mostly white	1620	UK	≥ 2 M	33% had previously consulted a healthcare provider.
23	1999	Clinic-based	53	Netherlands	–	IBS patients averaged 1.6 provider visits per 3-month period vs. 0.8 in general population ($P < 0.001$).
4	2000	General Swedish population	2707	Sweden	RI	Healthcare seeking positively correlated with overall symptom severity.
6	2002	General French population	11 131	France	RI	83.7% of IBS patients had previously consulted a healthcare provider.
7	2002	General German population	1281	Germany	Patient report	49.3% of IBS patients had previously consulted a healthcare provider.
18	2002	General Spanish population	2000	Spain	M RI RII	67.7% of Rome II IBS patients had previously consulted a healthcare provider, versus only 41.8% of Rome I patients.
9	2003	Multinational	41 984	Multinational	M RI RII	90% of IBS patients had previously consulted a healthcare provider, and 17% had been evaluated in a hospital.
10	2004	General French population	20 000	France	RII	80% of IBS patients had previously consulted a healthcare provider, of which 90% saw a GP, 57% a GI, and 50% both.
12	2004	Clinic-based	8386	UK	–	56% of IBS patients had previously consulted a healthcare provider, and 16% had consulted a sub-specialist.
24	2004	General French population	253	France	–	77% of IBS patients had previously consulted a general practitioner, and 43% had consulted a GI.

M=Manning criteria; RI=Rome I criteria; RII=Rome II criteria.

2.4.2 Resource utilization and cost of IBS care in the European Union

IBS sufferers visit the doctor more frequently, undergo more diagnostic tests, use more medications, and are hospitalized more frequently than non-IBS controls. IBS sufferers also miss more days from work and are more likely to reduce their work hours compared to controls. (Grade C Recommendation)

Eleven studies provide data regarding resource utilization, direct costs of care, or indirect costs of care for IBS patients in EU nations. Table 2.4.2 lists these studies, including the year of publication, target population, sample size, country of origin, and key findings. Each individual citation is briefly described in the text that follows the table.

Generally, IBS is associated with significant direct and indirect costs of care in the EU. This occurs because of the high prevalence of IBS in the EU (approximately 4% by Rome II criteria) and because IBS patients in the EU visit the doctor more frequently, use more diagnostic tests, use more medications, miss more work days, have lower work productivity and are hospitalized more frequently than patients without IBS. This resource utilization is positively correlated with worsening symptom severity and poor health-related quality of life.

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Table 2.4.2 Studies reporting resource utilization and cost of care data for IBS in Europe

Ref.	Year	Population	n	Country	Key findings
25	1995	Italian general population	–	Italy	Estimate that 0.093% of the total Italian National Health Service budget is spent on diagnostic testing alone for IBS.
26	1997	English general population	–	UK	Estimate that £90 (year 1995) are consumed annually in direct costs per IBS patient, which translates to £45.6 million annually in the UK.
27	1999	Clinic-based	53	UK	32% of IBS patients had missed one or more days of work in the previous 2 months because of poorly controlled bowel symptoms, compared with 18% of a matched cohort without IBS.
16	2001	'Severe' IBS patients enrolled in clinical trial	257	UK	Estimate that mean annual patient cost per severe IBS patient is US \$1743.
20	2002	Clinic-based	161	UK	Estimate that IBS cost the UK NHS £123 (year 1999) more per year than patients without IBS. Mean cost per IBS patients was £316/year.
28	2002	Clinic-based	200	Germany	IBS patients had 9 office visits per year. One-third reported missing at least one day of work in previous year. IBS cost 1548 DM per year in direct costs, and 1946 DM in direct+ indirect costs.
9	2003	Multinational general populations	41 984	Multinational	Compared to patients without IBS, IBS patients reported more sick days from work (5.5 vs. 3.1 per year), more days in bed (3.9 vs. 2.7 per year), and more days of limited work activity (10.2 vs. 4.8).
10	2003	Clinic-based/secondary care	1407	France	IBS patients required 5.7 medical visits per year, with 2.3 to GIs. Resource utilization positively correlated with increasing symptom severity.
29	2003	IBS patients in 'routine care' arm of clinical trial	86	UK	Mean annual direct cost of IBS patients undergoing "routine care" was equivalent to US \$1663.
30	2004	General French population	253	France	Mean monthly cost of care of IBS patients was €71.8. 39% of costs from diagnostic tests, and 22% from hospitalizations. Resource utilization positively correlated with increasing symptom severity and poor HRQOL.
10	2004	General French population	20 000	France	67% of IBS patients received additional tests after index diagnosis was made, and on average consumed 3.4 tests per year. 8% of IBS patients were admitted to hospital with an ALOS of 6.6 days. 11% missed work days because of bowel symptoms.

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2.5 IBS study design issues

2.5.1 IBS study design

Trials of IBS therapy may include a broad spectrum of IBS patients or a sub-category of IBS (e.g., constipation-predominant, diarrhoea-predominant) based on the study drug’s profile and mechanism of action. The setting (e.g., primary care, specialist) from which patients are recruited should be stated since it may influence outcome. A run-in observation period without a placebo or treatment prior to randomization is advisable. Randomization, concealed allocation, blinding, and a placebo or appropriate active control group are required. The study duration should be 4–12 weeks with duration based on the study drug’s mechanism of action and onset of activity. (Grade C Recommendation)

Standard recommendations to reduce bias in any therapy trial include randomization, concealed allocation, double-blinding, full accounting of all patients enrolled, intent-to-treat analysis and appropriate calculation of sample sizes [1]. In addition, the Rome II Committee on Functional Gastrointestinal (GI) Disorders developed recommendations specifically related to the design of treatment trials for functional GI disorders [2]:

- Patients should fulfill the Rome II criteria for the functional GI disorder being studied. Inclusion of a broad spectrum was recommended; sub-categorization (e.g., ulcer-like dyspepsia, constipation-predominant IBS) was not generally recommended, although the Rome II sub-committee recognized that limiting studies to sub-groups may be desired. When limiting enrollment to IBS sub-groups, the reasons should be explained and the selection criteria should make clinical sense and reflect normal clinical practice.
- The Rome II Committee recommended that a placebo control should be used because there is currently no ‘standard of care’ for therapy.
- A blinded randomized controlled trial with parallel-group design should be used. Cross-over design should not be used due to potential bias from an ‘order of sequence effect’. Baseline assumptions for cross-over designs, including that symptoms remain relatively

constant over time and return to baseline before cross-over to the second treatment, are not valid in functional GI disorders

- A baseline observation period without treatment or placebo prior to randomization should be employed.
- Minimum treatment duration should be 8–12 weeks.
- Follow-up after treatment should be performed to determine long-term efficacy.
- If short-term efficacy is demonstrated, then perform longer-term studies (6–12 months) to assess continuous safety and efficacy.
- Compliance with treatment should be measured.

Suggested modifications to the Rome II recommendations on study design include the following:

- Enrolling a sub-category of IBS patients in clinical trials is acceptable. Such sub-categorization may be appropriate based on the study drug's mechanism of action and profile. Furthermore, such distinctions are commonly made in clinical practice as well as in the Rome II criteria (e.g., constipation-predominant IBS or diarrhoea-predominant IBS).
- The setting (e.g., primary vs. specialist practice) from which patients are recruited should be stated since outcomes may vary depending on the source of patients in the study.
- Two weeks is an appropriate duration for the run-in observation period prior to randomization.
- The duration of trials may be 4–12 weeks. Earlier assessment of the treatment effect (e.g., at 4 weeks) is acceptable and appropriate for trials of IBS therapy. The duration of the trial also should be based on the mechanism of action and the time to onset of activity of the study drug. For example, a shorter trial duration may be appropriate for an antispasmodic agent but not for an antidepressant.
- Since the Rome II recommendations, significant (albeit relatively modest) benefits have been demonstrated with therapies for IBS in methodologically sound trials. Therefore, an active control also might be appropriate. However, inclusion of a placebo group as well is preferred. This will be especially important if the study drug and active control are not significantly different.

A group of European academic investigators [3] also developed a consensus report which included recommendations regarding design for IBS trials. They made several suggestions that went beyond and/or complemented the Rome II recommendations for trial design:

- The pre-randomization observation period should be two weeks in duration.
- Any diagnostic interventions should be performed before this observation period in order to avoid any

influence of diagnostic testing on the assessment of the effect of active treatment.

- Treatment duration should be 4–12 weeks rather than the Rome Committee's suggestion of 8–12 weeks, indicating that trials as short as 4 weeks are sufficiently valid to assess the efficacy of drug therapy for IBS. They also suggested that this was clinically reasonable because a drug that took longer to act would not be as therapeutically useful for most IBS patients.
- A 4–8 week withdrawal phase after the end of active treatment would be sufficient to ascertain the effect of drug withdrawal.
- The study population should be recruited from all patient population settings (primary, secondary, and tertiary) proportionate to the prevalence of IBS in these three settings.
- The Rome II criteria should be used for determining study eligibility, and physical examination and diagnostic testing (complete blood count and sedimentation rate, stool tests for ova and parasites, and examination of the colon with colonoscopy or flexible sigmoidoscopy, and barium enema) should be negative for inclusion in the study.

Advisory board members believe that these recommendations are also appropriate with the exception of the requirement for diagnostic testing. This guideline and other guidelines [4] agree that the routine use of stool tests for ova and parasites, flexible sigmoidoscopy, barium enema, and colonoscopy are not recommended for patients with IBS symptoms and no 'alarm' symptoms (e.g., haematochezia, weight loss).

2.5.2 Study endpoints in IBS therapy trials

A patient-defined global assessment of IBS symptoms should be the single primary endpoint. A validated IBS instrument may be used as long as the instrument measures changes in global IBS symptoms. A priori, investigators should define what constitutes a 'response' for this primary endpoint (i.e., clinically meaningful improvement), and the primary analysis should compare the proportion of subjects who achieve this response in the treatment and control groups. (Grade C Recommendation)

The recommendations by the Rome II Committee on Functional Gastrointestinal (GI) Disorders for the design of treatment trials for functional GI disorders [2] included suggestions regarding study endpoints:

- The primary outcome measure should integrate the symptoms of the functional disorder into a single global rating. Alternatively, the primary outcome measure can be a summary score of a validated disease-specific questionnaire that evaluates symptoms and disease-related quality of life.
- The main outcome assessment should be performed by the patient.

- A 'response' (change in the outcome measure that is clinically meaningful) should be defined a priori.
- The trial should be designed to compare the proportions of patients who achieve a 'response'.
- Measures of individual symptoms should also be performed.
- Validated outcome measures should be used.
- Symptoms should be recorded at regular intervals to assess treatment response over time.

A patient-defined global assessment of IBS symptoms should be the primary endpoint. The endpoint can be a direct assessment of response to treatment (e.g., dichotomous outcome of satisfactory response) or a measure of global IBS symptoms using an ordinal scale with a predefined score or change in score constituting a response. Endpoints should be measured with instruments validated for IBS and responsive to changes in global IBS symptoms. Advisory board members also felt strongly that a 'response' should be pre-defined in the study protocol and represent a clinically meaningful improvement in global IBS symptoms. Also, the primary analysis should compare the proportion of responders in the study and control groups. Assessment of the proportion responding is the most appropriate and clinically relevant analysis, and it is the analysis that will be most understandable to the physician caring for IBS patients. The panel reasoned that healthcare professionals and patients can understand the concept that 15% more patients improved or responded with the study drug than with a placebo control, but presenting a mean increase in an ordinal scale will provide little if any meaningful or understandable information to patients or their caregivers.

The panel agreed that other individual IBS symptoms should be measured as secondary endpoints to assess consistency with the global outcome measure. They also envisioned situations in which assessment of an individual symptom alone might serve as the primary endpoint. For example, based on its mechanism of action, a new medication might be anticipated to have good effect on abdominal discomfort associated with IBS. Such a medication might be of clinical value if demonstrated to have a marked benefit in this specific individual symptom. The European consensus report from Corazziari *et al.* [3] on IBS trial design also stated that the primary efficacy endpoint could combine the key IBS symptoms (e.g., abdominal pain/discomfort, bowel alterations) into one global assessment, but that if a drug was targeted to one of the specific key symptoms of IBS, the primary endpoint could be chosen accordingly.

2.5.3 Magnitude of benefit of IBS treatments versus placebo

There is no commonly accepted magnitude of benefit over placebo that is clinically important. This varies depending on a variety of individual patient factors, the duration of treatment required

to determine efficacy/lack of efficacy, the availability of other therapies documented to be effective, and the safety of the medication. (Grade C Recommendation)

The recommendations by the Rome II Committee on Functional Gastrointestinal (GI) Disorders for the design of treatment trials for functional GI disorders [2] did not include comments regarding a magnitude of benefit over placebo that would be considered clinically important. Conversely, the European consensus report from Corazziari *et al.* on IBS trial design [3] suggested that a 10–15% improvement over placebo using a global outcome measure should be considered a clinically significant therapeutic gain.

The tremendous number of differences from trial to trial (e.g., inclusion/exclusion criteria, clinical characteristics of patients, primary endpoints, placebo response) and the variability in clinical features and expectations of patients seen in practice make it impossible to identify a specific magnitude as clinically important for all clinical situations. IBS may consist of a heterogeneous group of disorders with different mechanisms underlying the development of symptoms. In this case, this heterogeneity may hide potential therapeutic benefits of new agents in sub-groups of IBS patients. Future advances in our understanding of IBS pathophysiology may allow us to individualize therapy for specific IBS patients.

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2.6 Efficacy of currently available traditional IBS-C therapies

2.6.1 Bulking agents

Bulking agents are not more effective than placebo at improving global IBS symptoms. (Grade B Recommendation)

An American College of Gastroenterology (ACG) systematic review identified 13 RCTs that evaluated bulking agents available in the US for the treatment of IBS [1]. These trials were low to intermediate quality with quality scores of 5–9 on a scale of 0–14. None of the trials used

Rome Committee criteria to identify IBS patients since all of these trials were conducted before the first Rome Committee conference was held. None of the trials used a validated instrument or followed patients after the end of study drug treatment. Few trials were ≥ 8 weeks and seven utilized a cross-over rather than parallel study design. None presented sample size calculations, and most trials had small sample sizes (< 30 patients).

A single study of corn fibre (quality score = 8) reported that pain severity, stool frequency or stool consistency improved with both corn fibre and placebo, but there was no significant difference between corn fibre and placebo [2]. Pain frequency and duration were not significantly improved with either. A single study of calcium polycarbophil (quality score = 7) reported no significant difference in overall preference, but did report preference for calcium polycarbophil in patients with constipation or alternating constipation and diarrhoea. There was no significant difference in abdominal pain between active agent and placebo [8]. Of the five trials of wheat bran [3–7] (quality scores 5–6), only one study [4] without a placebo control found improvement in pain frequency and severity and stool frequency. The other four noted similar effects with wheat bran and placebo. The single study of psyllium (quality score = 9) found that no IBS symptoms were improved with psyllium compared to placebo. Overall symptoms were a little or much better in over 70% of both groups at the end of the study [9]. Four of five studies with ispaghula husk (quality scores 6–9) noted improvement in global symptoms of bowel habits but no improvement in abdominal pain [10–14]. Patients in the negative study were all taking 30 g/day of bran in addition to husk or placebo.

The ACG systematic review concluded that none of the trials of bulking agents demonstrated high quality methodology and sample sizes in most trials were particularly small [1]. Nevertheless, available evidence indicates that corn and wheat fibre are ineffective for global IBS symptom improvement. Neither calcium polycarbophil nor psyllium was shown to be more effective than placebo for global IBS symptom improvement. Although the majority of ispaghula husk studies demonstrated improvement in bowel habits, they did not demonstrate improvement in abdominal discomfort. Therefore, fibre was considered appropriate for treatment of constipation, but it was not recommended for treatment of IBS.

A more recent European systematic review [15] identified six RCTs of fibre not included in the ACG review [16–21] although only two were placebo-controlled [18,21]. These two studies were parallel design RCTs, included with only 49 and 28 patients and had quality scores of 8 and 9. Cereal and fruit fibre were assessed in one study [18] and wheat bran in the second study [21]. One study demonstrated no difference between fibre and placebo for relief of abdominal pain/discomfort, constipa-

tion and global symptom scores [18]. The second study showed an improvement for mean stool weight for fibre compared with placebo but no difference in other bowel function measurements or in symptoms [21].

The European systematic review concluded that although bulking agents are widely used in clinical practice, there is no evidence to suggest that they are effective in the treatment of the global symptoms of IBS [15]. Level II evidence indicates that bulking agents may have some benefits in treating constipation [15].

A Cochrane systematic review also reported no significant benefit of bulking agents in IBS [22]. Their pooled analysis of global assessment of improvement in IBS symptoms revealed marked heterogeneity among the nine studies included and the random effects model relative risk was 1.09 (95% CI, 0.78–1.50).

In conclusion, bulking agents are not significantly better than placebo at improving global IBS symptoms. Some evidence suggests that bulking agents such as ispaghula husk may improve constipation.

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2.6.2 Laxatives

No data are available from randomized controlled trials to assess the efficacy of laxatives in patients with IBS.

Laxatives (e.g., osmotic, stimulant, surfactant) are widely used by IBS patients with constipation and are available to patients over the counter. Both the ACG [1] and European [2] systematic reviews found no RCTs with osmotic, stimulant or surfactant laxatives in IBS patients. Therefore, there is no evidence regarding the efficacy of laxatives in the management of patients with IBS. Laxatives are commonly used in patient with IBS-C and anecdotal experience suggests that laxatives may provide benefit with respect to bowel habits.

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2.6.3 Antispasmodic agents

There are insufficient data to make a recommendation about the effectiveness of antispasmodic agents for improvement in global IBS symptoms. Some antispasmodic agents may improve abdominal pain. (Grade B Recommendation)

The ACG systematic review [1] focused on antispasmodic agents available in the US and identified only three RCTs [2–4] evaluating such agents. These trials of dicyclomine and hyoscyamine [2–4] were low–intermediate quality (quality scores of 5–7 on a scale of 0–14). None of these trials used Rome Committee criteria (or Manning criteria) to identify IBS patients, and none of the trials followed patients after discontinuation of therapy. Only one trial [4] was ≥ 8 weeks. Sample sizes were not calculated a priori in any of these trials, and all of these trials included fewer than 100 patients.

One [3] of the studies demonstrated a statistically significant improvement in global IBS symptoms with dicyclomine compared to placebo. However, this study had poor study design (quality score of 5) and used a very high dose of dicyclomine (40 mg, four times daily), which led to significantly more adverse events among dicyclomine-using patients (69% vs. 16% of placebo treated patients). Also, 15% of dicyclomine-treated patients withdrew from the study, while no placebo-treated patients withdrew. In the other two studies [2,4], no significant differences in outcomes were noted between patients treated with the active drug vs. placebo.

More antispasmodic agents are available in Europe than in the US, and the European systematic review [5] identified a large number of additional RCTs of mebeverine, pinaverium, otilonium, cimetropium, trimebutine, and pirenzepine. Ten placebo-controlled comparisons, of at least 3 weeks in duration were provided in nine articles [6–14] and are shown in Table 2.6.1. Studies were low to intermediate quality (quality scores of 4–9), most included small numbers of patients and only one used Rome (or Manning) diagnostic criteria. Abdominal pain was improved in seven of the 10 comparisons [7,8,10–12,14] and bowel symptoms improved in three comparisons [12,14]. Global symptoms were reported to be improved with antispasmodic agents in four studies [6–8,11].

The European systematic review concluded that there is level II evidence to suggest that antispasmodics may

Table 2.6.1 Placebo-controlled RCTs not included in the ACG review of at least three weeks in duration reporting on the efficacy of antispasmodic agents for IBS [5]

Ref.	Study design	Treatment	ITT population	Findings	Quality score
6	3-month, randomized, double-blind, placebo-controlled, parallel	Cimetropium bromide 50 mg t.i.d. vs. placebo	30 IBS-C; Rome criteria not used	Improvement in global clinical symptoms ($P < 0.01$) with cimetropium bromide compared with placebo	8
7	6-month, randomized, double-blind, placebo-controlled	Cimetropium bromide 50 mg t.i.d. vs. placebo	48 IBS (IBS-C and IBS-D); Rome criteria not used	Cimetropium was associated with reduction in abdominal pain ($P < 0.01$) and anxiety ($P < 0.05$) and more patients considered themselves globally improved ($P < 0.01$) compared with placebo	9
8	3-month, double-blind, randomized, placebo-controlled, parallel	Cimetropium bromide 50 mg t.i.d. vs. placebo	70 IBS (subtype not specified); Rome criteria not used	Cimetropium bromide was associated with reductions in abdominal pain intensity ($P = 0.0005$) and number of pain episodes ($P = 0.001$). More patients considered themselves to be globally improved ($P = 0.039$) compared with placebo	8
9	16-week, randomized, double-blind, placebo-controlled, parallel	Mebeverine 100 mg q.i.d. vs. placebo vs. open-label wheat bran 5 g t.i.d.	120 IBS (subtype not specified); Rome criteria not used	No significant difference in efficacy was observed between mebeverine and placebo. Wheat bran had a superior short-term effect ($P < 0.05$) but this was not confirmed at the end of the trial	8
10	4-week, double-blind, placebo-controlled Parallel	Otilonium bromide 40 mg t.i.d. vs. placebo	72 IBS (subtype not specified)	Abdominal pain and bloating were significantly improved with otilonium bromide compared with placebo ($P < 0.02$). No difference was observed for the frequency of bowel movements	8
11	15-week, double-blind, randomized, placebo-controlled parallel	Otilonium bromide 40 mg t.i.d. vs. placebo	Rome criteria not used 378 IBS (subtype not specified); Rome I	Otilonium bromide was associated with a reduced number of pain episodes ($P < 0.01$), severity of abdominal distention ($P < 0.05$), improvements in well-being ($P < 0.05$) and global symptom assessment ($P < 0.01$) compared with placebo. There was no difference in bowel symptom improvement between groups	8
12	3-week, double-blind, placebo-controlled, parallel	Pinaverium bromide 50 mg t.i.d. vs. placebo	40 IBS (all subtypes) Rome I	Improvements in abdominal pain duration, stool frequency and stool consistency were observed with pinaverium bromide compared with placebo ($P \leq 0.01$), but differences in total symptom score, pain frequency, pain severity and distention were not significant	7
13	4-week, randomized, double-blind, placebo-controlled, parallel	Pirenzepine 50 mg b.i.d. vs. placebo	24 IBS (subtype not specified); Rome criteria not used	No significant difference between pirenzepine and placebo was shown for overall well-being, bowel habit or abdominal pain	6
14	60-day, randomized, double-blind, placebo-controlled, parallel	Rociverine 20 mg t.i.d. vs. trimebutine 100 mg t.i.d. vs. placebo	90 IBS (subtype not specified); Rome criteria not used	Rociverine and trimebutine showed similar efficacy and both were more effective than placebo for pain relief and improvement of bowel symptoms ($P < 0.05$).	9

improve abdominal pain, but there is a lack of clinical trial data to support an effect on global IBS symptoms. Furthermore, there are insufficient trial data to draw conclusions on the relative efficacy of the different agents or classes of agent.

A Cochrane systematic review included 16 studies reporting on global assessment of improvement in IBS symptoms [15]. Marked heterogeneity of the studies was noted ($P = 0.0006$), suggesting that pooling in a meta-analysis to provide a summary statistic may not be appropriate. In their discussion, the authors concluded that the evidence for efficacy for antispasmodics in IBS was weak and that it was unclear which antispasmodic subgroups were individually effective [15]. Another recent meta-analysis concluded that the heterogeneity of trials, the differing spectrum of patients' symptoms and efficacy measures, the low numbers of patients

included, and the high number of drop-outs during follow-up rendered judgment of the therapeutic value of anti-spasmodics impossible [16].

In conclusion, systematic reviews indicate that antispasmodic agents have not been consistently documented to be better than placebo for improvement in global IBS symptoms. Marked heterogeneity of the studies, methodological shortcomings, and small sample sizes are concerns in interpreting the available evidence. However, some available antispasmodic agents may improve abdominal pain.

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2.6.4 Antidepressants

There are insufficient data to make a recommendation about the effectiveness of antidepressant agents (tricyclic antidepressants

and SSRIs) for improvement in global IBS symptoms. Tricyclic antidepressants are more effective than placebo at relieving abdominal discomfort in patients with IBS. (Grade B Recommendation)

The ACG systematic review [1] included six RCTs on the effectiveness of tricyclic antidepressants (TCAs) in the treatment of patients with IBS [2–7]. A seventh RCT was excluded because the dropout rate was 45% [8]. All six trials included were low quality (quality scores of 5–6 on a scale of 0–14), sample sizes were small (31 patients per treatment arm), and five of the six studies were 4–6 weeks in duration. Because the primary and secondary endpoints were poorly defined and results were not presented in a straightforward fashion, interpretation of study results was difficult. Improvement in abdominal pain was noted in three of the six studies, but significant improvement in global IBS symptoms was documented in only one of the six studies [6]. The authors concluded that evidence was inadequate to support the effectiveness of TCAs for improvement of global IBS symptoms, but that there was limited evidence that TCAs may decrease abdominal pain.

The European systematic review [9] identified an additional intermediate-quality RCT of amitriptyline, which enrolled small numbers of patients [8]. In this study amitriptyline was significantly more effective than placebo in improving global IBS symptoms, improving feelings of well-being, reducing abdominal pain/discomfort, and increasing satisfaction with bowel movements.

Two recent high-quality RCTs of the selective serotonin reuptake inhibitor (SSRI) paroxetine for treatment of IBS were also identified in the European systematic review [10,11], but only one was placebo-controlled [11]. This trial examined IBS patients not responding to a high fibre diet and reported significantly greater improvement in overall well-being with paroxetine than placebo. However, no improvements in abdominal pain/discomfort, bloating or social functioning were seen [11]. Another small placebo-controlled trial of intermediate quality found no significant benefit of fluoxetine [12]. The antidepressant RCTs included in the European systematic review are presented in Table 2.6.2.

The European systematic review concluded that there is level II evidence that TCAs have some benefits in treating abdominal pain associated with IBS, but there are no convincing data to support the efficacy of TCAs in improving global IBS symptoms. They also concluded that the data on SSRIs in IBS are limited and consistent improvement in the multiple symptoms of IBS has not been documented.

Table 2.6.2 RCTs of the efficacy of antidepressants for IBS not included in the ACG systematic review [9]

Ref.	Study design	Treatment	ITT population	Findings	Quality score
8	12-week, randomized, double-blind, placebo-controlled, parallel	Amitriptyline (25 mg q.d. Week 1, 50 mg q.d. Week 2 and 75 mg q.d. thereafter) vs. placebo	40 IBS (subtypes not specified) Rome I	Amitriptyline was more effective than placebo at improving global symptoms ($P < 0.01$), increasing feelings of well-being ($P < 0.001$), reducing abdominal pain ($P < 0.01$) and increasing satisfaction with bowel movements ($P < 0.05$)	7
12	6-week, randomized, double-blind, placebo-controlled, parallel	Fluoxetine 20 mg q.d. vs. placebo	40 IBS (all subtypes) Rome I	Fluoxetine did not alter rectal sensitivity. No significant differences in abdominal pain or global symptom relief scores were observed	9
10	3-month, randomized, controlled, parallel	Psychotherapy 8 sessions vs. 20 mg paroxetine q.d. vs. routine care	257 IBS (all subtypes) Rome I	Psychotherapy and paroxetine were superior to routine care in improving physical aspects of HRQoL ($P < 0.001$) but not the psychological components or abdominal pain. Similar patient-reported overall improvements were observed with psychotherapy and paroxetine compared with routine care ($P = 0.001$)	12
11	12-week, randomized, double-blind, placebo-controlled	High fiber diet (HFD) with paroxetine 10 or 20 mg q.d. vs. HFD with placebo	110 IBS (all subtypes) Rome I	Improvement in overall well-being was greater with paroxetine than placebo ($P = 0.01$), as was decreased food avoidance ($P = 0.03$). Abd pain and social function did not differ between groups	10

A very recent placebo-controlled trial of fluoxetine in a small number ($n = 44$) of constipation-predominant IBS patients was published after the cut-off date for the literature search of the European systematic review [13]. This study showed significant improvement in abdominal discomfort, bloating, and bowel habits with fluoxetine, but global assessment of symptoms was not performed.

A Cochrane systematic review included only four studies reporting on global assessment of improvement in IBS symptoms with antidepressants [14]. Heterogeneity among the studies was noted ($P = 0.08$), and no significant improvement in IBS symptoms was observed (RR = 1.16; 95% CI: 0.78–1.73). No significant improvement in abdominal pain was observed. They noted that their conclusions may be more negative than other reviews/meta-analyses because they excluded several studies that were included in other reviews, due to methodological weaknesses that were included in other reviews.

In conclusion, there is inadequate evidence to indicate that TCAs or SSRIs improve global IBS symptoms, although TCAs do appear to be more effective than placebo at relieving abdominal pain in IBS.

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2.6.5 Anti-diarrhoeal agents

Anti-diarrhoeal agents (i.e., loperamide) are not more effective than placebo at relieving global IBS symptom (Grade B recommendation). Anti-diarrhoeal agents (i.e., loperamide) are more effective than placebo at improving stool consistency and decreasing stool frequency in IBS patients.

IBS patients with diarrhoea demonstrate accelerated transit through the GI tract [1,2]. Thus, agents which delay intestinal transit (i.e., anti-diarrhoeal agents) may be helpful for IBS patients with diarrhoea. Only one anti-diarrhoeal agent, loperamide, has been examined in IBS treatment trials, which limits evidence-based recommendations about other anti-diarrhoeal agents.

Three trials examined the effectiveness of loperamide [3–5] (Table 2.6.3). These trials were low–intermediate quality (quality scores ranging from 5–7 out of possible 14). All trials were shorter than 5 weeks in duration, none used Rome criteria to identify IBS patients, and no trials provided sample size calculations. None of the trials had more than 100 patients, and these small sample sizes may have led to type II errors.

In one study [3], loperamide significantly decreased the proportion of unformed stools (60% to 31%), decreased stool frequency (1.9/day to 1.3/day), and minimized the incidence of urgency (2.4 days/week to 1.1 days/week). Placebo had no effectiveness on these outcomes. There was no significant improvement in global IBS symptom improvement or abdominal discomfort with loperamide. In another study [4], patients with painless diarrhoea had improvements in stool frequency (100% vs. 40%), stool consistency (100% vs. 50%), and overall symptoms (100% vs. 25%) with loperamide. Patients who alternated between constipation and diarrhoea without pain did not demonstrate significant improvement with loperamide. Patients who alternated between constipation and diarrhoea with pain did demonstrate significant improvement for stool frequency (95% vs. 25%) and stool consistency (95% vs. 45%). In the final study [5], loperamide significantly improved stool frequency

(35% vs. 10%) and stool consistency (50% vs. 20%). There was no significant difference in abdominal pain and global IBS symptom improvement was not reported.

Based on these data, loperamide is an effective treatment for diarrhoea, but it does not improve global IBS symptoms or abdominal discomfort. Loperamide should not be used in IBS patients with constipation, and it should be used with caution in IBS patients alternating between diarrhoea and constipation.

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2.6.6 Tegaserod

Tegaserod is more effective than placebo for improvement of global IBS symptoms in women with IBS with constipation and in patients who alternate between constipation and diarrhoea (IBS-M). (Grade A Recommendation)

The American College of Gastroenterology monograph, ‘An evidence-based approach to the management of irritable bowel syndrome in North America’ [1], reviewed four RCTs that evaluated the effectiveness of tegaserod 6 mg b.i.d. in the management of IBS [2–6]. Their findings are reprinted here with permission:

All of these trials were high quality trials (quality scores of 12–13 out of possible 14) based on Rome committee criteria for the design of treatment trials for functional gastrointestinal disorders. Trial duration was 12 weeks in all trials. The patient population in these trials were > 80% women, > 80% Caucasian and had a mean age of approximately 45 years old and mean duration of IBS symptoms of > 10 years. Patients met Rome I criteria for the diagnosis of IBS. Most patients met

Table 2.6.3 Trial characteristics: anti-diarrhoeal agents

Author (reference)	Treatment	Dose	Study type	Patients (% female)	Duration	Outcome measures	Quality score (range: 0–13)
Cann [3]	Loperamide	2–12 mg q.d.	Crossover	28 (75%)	5 weeks	Sxs, SGA	7
Kovdenak [4]	Loperamide	4 mg	Parallel	58	3 weeks	Sxs, SGA	6
Efskind [5]	Loperamide	2–6 mg q.d.	Parallel	69 (80%)	5 weeks	Sxs	5

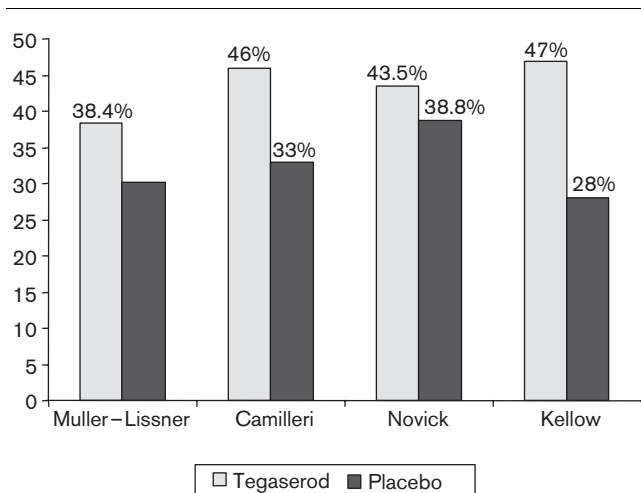
criteria for IBS with constipation, although a minority of patients had IBS with bowel habits alternating between constipation and diarrhoea.

Global IBS symptom improvement was determined based on IBS symptoms during the last four weeks of 12 week trials, although numerically larger differences between tegaserod and placebo were seen with 12-week longitudinal analyses or analyses of IBS symptoms during the first four weeks. In the most recent study [2], improvement in global IBS symptoms was measured during the first four weeks of the trial with a binary endpoint (i.e., IBS symptoms improved vs. IBS symptoms not improved). This trial produced the largest numerical benefit observed with tegaserod. Thus, the definition of global IBS symptom improvement appears to influence the magnitude of benefit observed with tegaserod.

All ... trials of tegaserod 6 mg b.i.d demonstrated statistically significant improvement in global IBS symptoms for tegaserod-using patients compared to placebo-using patients. Based on the prescribed endpoint, approximately 5–19% more tegaserod-using patients had significant improvement in global IBS symptoms compared to placebo-using patients (Fig. 2.6.1). In further analysis, tegaserod-using patients experienced less bloating, less abdominal discomfort, and improved satisfaction with their bowel habits compared to placebo-using patients. The magnitude of these improvements varied across trials due to the use of different scales to measure individual symptoms in different trials.

Two RCTs, the ZAP study [2] and the TENOR study [7], assessed the efficacy of tegaserod in non-D IBS patients.

Fig. 2.6.1



Percentage of patients with improvement in global IBS symptoms.

Patients enrolled in these RCTs met Rome II criteria for non-D IBS. These trials were high quality trials (quality scores of 12–13 out of possible 14) based on Rome committee criteria for the design of treatment trials for functional gastrointestinal disorders. The primary study endpoint was improvement in global IBS symptoms. This improvement was measured by asking: ‘Over the past week, do you consider that you have had satisfactory relief of your symptoms of IBS?’ Patients answered this question with a ‘Yes’ or ‘No’ reply. Both RCTs demonstrated that tegaserod was significantly better than placebo at producing global IBS symptom relief. In a week-by-week examination of the ZAP study, 51–68% of tegaserod-using patients noted satisfactory relief of their global IBS symptoms compared to 28–54% of placebo-using patients (Fig. 2.6.2).

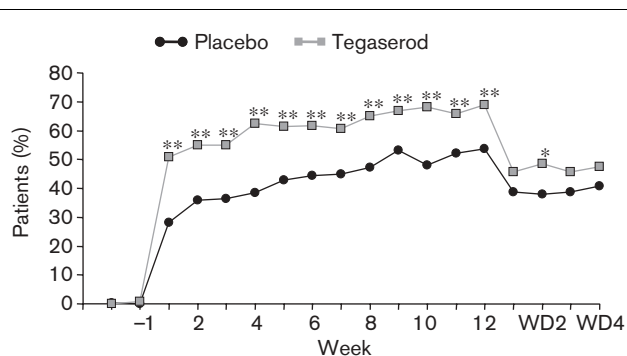
In a week-by-week evaluation of the TENOR study, 19–40% of tegaserod-using patients experienced satisfactory relief of their global IBS symptoms compared to 14–28% of placebo-using patients. In the most recently published RCT [8], tegaserod was compared to placebo among patients with IBS-M (IBS patients whose bowel habits alternate between constipation and diarrhoea). In this RCT of over 300 patients, tegaserod-treated patients were significantly more likely than placebo-treated patients to experience satisfactory relief of their global IBS symptoms (52% vs. 36%, $P < 0.03$).

In conclusion, tegaserod is clearly and consistently more efficacious than placebo for improvement in global IBS symptoms and for improvement of stool frequency and stool consistency in women with IBS-C and IBS-M. Furthermore, based upon the design of these RCTs, tegaserod demonstrates ‘level I’ evidence of efficacy for treatment of IBS-C and IBS-M in women.

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Fig. 2.6.2



Satisfactory relief by week (ITT) in the ZAP study.

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2.6.7 Re-treatment therapies for patients with IBS with constipation

No randomized controlled trials have assessed the efficacy of re-treatment cycles with traditional therapies (bulking agents, laxatives, antispasmodic agents, and antidepressant agents). Tegaserod is more effective than placebo at relieving global IBS symptoms in IBS-C patients in re-treatment trials. (Grade A Recommendation)

Re-treatment of patients with IBS has not been assessed with traditional therapies in RCTs, so no statements on the efficacy of bulking agents, laxatives, antispasmodic agents, or antidepressants can be made. RCTs with a single re-treatment cycle are appropriate to be certain that treatment efficacy does not diminish on the subsequent cycle (e.g., ‘tolerance’ does not develop). This is a clinically relevant issue because, due to the cyclic nature of IBS, patients commonly employ intermittent courses of therapy.

In response to requests from the European Committee for Medicinal Products for Human Use (CHMP) ‘Points to Consider’, a re-treatment study (Fig. 2.6.3) with tegaserod in IBS patients was performed [1]. This re-treatment study was a prospective, double-blind, random-

Fig. 2.6.3



Re-treatment study design. The study incorporated the following points:

- Criterion for entering treatment-free interval: relief in 2 out of 4 weeks ($n = 1194$)
- Response: relief in 3 out of 4 weeks (75% rule)
- Criterion to enter randomization for re-treatment: $\frac{3}{4}$ weeks lack of satisfactory relief for both variables, overall and disc/pain relief ($n = 983$)
- 106 patients ended the treatment-free interval without symptom recurrence
- 105 patients discontinued during the treatment-free interval

mized, multicentre trial, which included a 4 week screening period, a 2 week baseline period (no study medication), and two 4 week placebo-controlled treatment periods (first and repeated treatments), separated by a treatment-free interval (TFI) (Fig. 2.6.3).

During the first treatment, patients received either tegaserod 6 mg twice daily or placebo for four weeks (allocation ratio 4:1). Patients with at least a partial response (satisfactory relief of either overall IBS symptoms for at least two of the first four treatment weeks or abdominal discomfort/pain in at least two of the first four treatment weeks) entered the treatment free interval (TFI). The TFI (2–12 weeks) depended on the time to recurrence of IBS symptoms after the end of first treatment. If symptoms recurred within 12 weeks (absence of satisfactory relief of overall IBS symptoms for at least three out of four consecutive weeks and abdominal discomfort/pain for at least three out of four consecutive weeks) patients were eligible for repeated treatment. Subjects without recurrence of their symptoms within 12 weeks were not studied further. Patients who received tegaserod during first treatment were re-randomised to either tegaserod or placebo (ratio 1:1); those receiving placebo during first treatment were mock randomised to tegaserod in the repeated treatment period. This allowed for the treatment blind to be maintained while ensuring that each patient who experienced at least a partial response during first treatment received active treatment during at least one four week cycle [9].

Primary efficacy was assessed using a binary scale based on the patient answers to the following weekly questions: 'Did you have satisfactory relief of your overall IBS symptoms during the last week?', and 'Did you have satisfactory relief of you abdominal discomfort or pain during the last week?' All study patients were women who met Rome II criteria for IBS with constipation.

Tegaserod was significantly superior to placebo for all four primary efficacy variables (response for relief of overall IBS symptoms and relief of abdominal discomfort/pain during both first and repeated treatment) (Fig. 2.6.4) [9].

Patients treated with tegaserod had significantly greater work productivity in the first treatment period than those receiving placebo as measured by the WPAI:IBS-C, including less presenteeism (less impairment while at work), less absenteeism (less work time missed), less work impairment (combination of presenteeism and absenteeism), and less activity impairment ($P < 0.05$) [1].

Reference: Section 2.6.7

1 Tack J, Muller-Lissner S, Bytzer P, Corinaldesi R, Chang L, Viegas A, *et al.* A randomised controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. *Gut* 2005; **54**:1707–1713.

2.7 Tolerability and safety of current IBS therapies

2.7.1 Additional data sources for evaluation of tolerability and safety

The ACG systematic review [1], briefly mentioned adverse events in studies available through 2001, while neither the European systematic review [2], nor the

Cochrane systematic reviews [3], were designed to provide a systematic assessment of tolerability and safety. However, a recent systematic review by a group of European investigators was specifically designed to assess the safety and tolerability of pharmacological agents of IBS treatments available in Europe [4]. The literature search for this systematic review was designed to identify clinical trials of IBS therapies that provided information on safety or adverse events through June 2005. They also assessed methodologic quality of studies employing the quality score used in the ACG review [1], and the European systematic review of efficacy [2], dividing studies into low, intermediate, and high quality based on a 14-point scoring system.

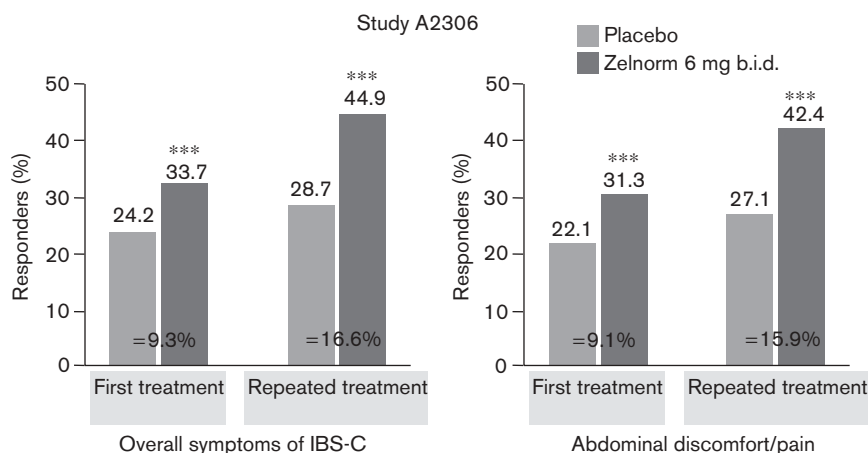
References: Section 2.7.1

- 1 Brandt LJ, Bjorkman D, Fennerty MB, Locke GR, Olden K, Peterson W, *et al.* for the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. An evidence-based approach to the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002; **97** (Suppl):S1–S26.
- 2 Tack J, Fried M, Houghton L, Spicak J. An evidence-based review of the treatments for irritable bowel syndrome: a European perspective. *Aliment Pharmacol Ther* 2006; **24**:183–205.
- 3 Quartero AO, Meineche-Schmidt V, Muris J, Rubin G, de Wit N. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. *Cochrane Database System Rev* 2005; **4**.
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2.7.2 Bulking agents

In small randomized controlled trials, bulking agents are not associated with significantly more adverse events than placebo

Fig. 2.6.4



Clinical efficacy: primary endpoints. *** $P < 0.001$; Response: relief in 3 out of 4 weeks (75% rule); First treatment: Placebo $n = 525$, Zelnorm $n = 2135$; Retreatment: Placebo $n = 488$.

among IBS patients (Grade B Recommendation). Survey data and clinical experience suggest that bulking agents may cause bloating and distension and potentially exacerbate IBS symptoms in some patients. (Grade C Recommendation)

The ACG systematic review noted that data on adverse events associated with bulking agents were not reported in the trials, precluding evidence-based statements on adverse events associated with bulking agents [1]. They did state that bowel gas is produced by metabolism of fibre by intestinal bacteria and that anecdotal experience of IBS experts suggested that fibre products may increase intestinal gas, bloating, and abdominal discomfort in IBS patients [1].

The more recent European systematic review of safety and tolerability [2], identified five studies with information on safety of bulking agents [3–7]; four of the studies were placebo-controlled [3–5,7]. Two of the placebo-controlled trials assessed ispaghula husk, [3,4], one assessed cereal and fruit fibre [5], and one trial examined calcium polycarbophil [7]. The quality scores of these trials was intermediate–high, although all studies included small numbers of patients (40 patients per arm). The studies reported that bulking agents were well tolerated, with few withdrawals due to side effects. They described an adverse event frequency similar to placebo. In the included studies, there were two withdrawals in the placebo groups for adverse events (nausea in one patient; flatulence, abdominal distension, and borborygmi in one patient) [3,5], while there was one withdrawal for adverse events in the bulking agent groups (flatulence in a patient taking ispaghula husk) [3]. The authors of the European systematic review on safety and tolerability [2] indicated that these agents may have the potential to increase bowel gas, bloating and abdominal discomfort in IBS patients, and they cite survey data [8], suggesting that bran exacerbated the symptoms of IBS, including bowel disturbance, abdominal distension and pain.

The European systematic review [2], concluded that bulking agents are well tolerated, although this statement is based on small patient numbers, and that bulking agents may increase bowel gas, bloating and abdominal distension with a potential to exacerbate IBS symptoms. However, they stated that there was no evidence that use of these agents in IBS patients is associated with clinically significant safety concerns.

In conclusion, small, randomized, controlled trials show that bulking agents are not associated with significantly more adverse events than placebo among IBS patients, but survey data and clinical experience suggest that bulking agents may cause bloating and distension and potentially exacerbate IBS symptoms in some patients.

References: Section 2.7.2

- 1 Brandt LJ, Bjorkman D, Fennerty MB, *et al.*, for the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. An evidence-based approach to the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002; **97** (Suppl):S1–S26.
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2.7.3 Laxatives

No data are available from randomized controlled trials to assess the safety or tolerability of laxatives in patients with IBS.

Neither the ACG systematic review [1], nor the European systematic review [2], identified published studies assessing the safety and tolerability of laxatives in the treatment of IBS patients. Therefore no evidence-based conclusions can be drawn regarding the safety and tolerability of laxatives in IBS.

Anecdotal experience suggests that laxatives are commonly used in patients with IBS-C and are generally well-tolerated. Uncommon side effects including volume depletion and electrolyte abnormalities may occur, especially in patients with underlying comorbidities (e.g., congestive heart failure, renal insufficiency, liver disease), and laxatives are contraindicated in patients with known or suspected intestinal obstruction. Overall, trials in constipated patients indicate that osmotic laxatives are usually safe and well-tolerated in these patients, and it is doubtful that the safety profile is substantially different in IBS-C patients.

References: Section 2.7.3

- 1 Brandt LJ, Bjorkman D, Fennerty MB, *et al.*, for the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. An evidence-based approach to the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002; **97** (Suppl):S1–S26.

2 Heading R, Bardhan K, Hollerbach S, Lanas A. An evidence-based review of the safety and tolerability of pharmacological agents for treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2006; **24**:207–236.

2.7.4 Antispasmodic agents

In small RCTs, antispasmodic agents are not associated with significantly more adverse events than placebo among IBS patients. However, an increase in adverse events with antispasmodic agents is seen in some studies and frequency of adverse events may be dose related. (Grade B Recommendation)

Among the three studies evaluated in the ACG systematic review, a placebo-controlled RCT of maximal dose dicyclomine (40 mg, four times daily) noted significantly more adverse events with the active agent (69% vs. 16%) and a higher rate of withdrawal from the study (15% vs. 0) [2]. The authors of the ACG systematic review wrote that antispasmodic agents may exhibit atropine-like side effects at higher doses and this may lead to intolerance due to visual disturbances, urinary retention, dry mouth, or constipation. They indicated that specific data on frequency of bowel movements in constipated patients were lacking but that constipation was a potential complication of antispasmodic agents due to their muscle relaxant properties. Therefore, the ACG

Task Force members therefore felt that antispasmodic agents should be used with caution among patients with constipation [1].

The European systematic review [3], identified 21 trials of antispasmodic agents that included some safety information. The trials were generally low-intermediate quality, and only 10 were placebo-controlled RCTs. The nine placebo-controlled trials of at least 2 weeks in duration that provided information on the tolerability or safety of antispasmodic agents for IBS treatment are shown in Table 2.7.1.

The European systematic review [3], concluded that the 21 trials provided limited clinical data on the tolerability of antispasmodics. The available trials demonstrated varied design and duration and generally included only small sample sizes. The available data indicated that antispasmodics were generally well tolerated, with the most frequently reported side effects being anticholinergic effects of dry mouth, nausea, and constipation. They further suggested that constipation may limit the use of antispasmodics, particularly in IBS-C patients. However, from the published data, there is no evidence that use of these agents in IBS patients is associated with clinically significant safety concerns.

Table 2.7.1 Placebo-controlled randomized controlled trials at least 2 weeks in duration that report on the tolerability or safety of antispasmodic agents for IBS treatment [3]

Ref.	Study design	Treatment	No.	Duration of treatment	Key findings
4	Randomized, double-blind, prospective + open branch trial	Mebeverine 100 mg q.i.d. vs. placebo	80	16 weeks	<ul style="list-style-type: none"> Clinically relevant side effects were not observed during the study
5	Double-blind, placebo-controlled	Otilonium bromide 40 mg t.i.d. (n=34) vs placebo (n=37)	71	4 weeks	<ul style="list-style-type: none"> 'Symptoms' were reported: nausea, abdominal pain, dry mouth, general malaise and constipation One AE reported: mild nausea during otilonium therapy No withdrawals due to AEs reported
6	Randomized, double-blind, placebo-controlled, parallel-group	Otilonium bromide 40 mg t.i.d. (n=160) vs. placebo (n=165)	325	15 weeks	<ul style="list-style-type: none"> Three patients withdrew due to AEs (otilonium: prostate disturbance, dizziness; placebo: skin rash)
7	Double-blind, placebo-controlled	Cimetropium bromide 50 mg t.i.d. (n=15) vs placebo (n=15)	30	3 months	<ul style="list-style-type: none"> AEs reported by five patients Cimetropium: dry mouth (n=2), dizziness (n=2) Placebo: dizziness (n=1) All mild severity, no withdrawals
8	Randomized, double-blind, placebo-controlled, parallel-group	Cimetropium bromide 50 mg t.i.d. (n=23) vs placebo (n=21)	44	6 months	<ul style="list-style-type: none"> Cimetropium: 18 AEs reported by 11 patients (48%). Dry mouth (11 AEs), sleepiness (5 AEs), epigastric fullness (1 AE), dizziness (1 AE) Placebo: seven AEs reported by six patients. Epigastric fullness (two AEs) and 1 AE each of dry mouth, sleepiness, pyrosis, insomnia and nausea No withdrawals due to AEs
9	Randomized, double-blind, placebo-controlled, parallel-group	Cimetropium bromide 50 mg t.i.d. (n=35) vs placebo (n=35)	70	3 months	<ul style="list-style-type: none"> Cimetropium: dry mouth (n=6) Placebo: insomnia (n=1) No withdrawals due to AEs
10	Randomized, double-blind, parallel-group	Rociverine 20 mg t.i.d. vs. trimebutine 100 mg t.i.d. vs. placebo	90	60 days	<ul style="list-style-type: none"> Both treatments were well tolerated
11	Randomized, double-blind, placebo-controlled, parallel-group	Dicyclomine 40 mg q.i.d. vs. placebo	97	2 week	<ul style="list-style-type: none"> Dicyclomine: 33 patients (69%) reported at least 1 AE. Most frequently reported AEs were dry mouth, dizziness and blurred vision Placebo: 8 patients (16%) reported at least 1 AE
12	Randomized, double-blind, placebo-controlled	Pinaverium bromide 50 mg t.i.d. vs. placebo	40	3 weeks	<ul style="list-style-type: none"> Pinaverium: 1 patient complained of headache

A meta-analysis of smooth muscle relaxants concluded that there was no significant difference between these agents and placebo in the rate of adverse events (risk difference of treatment vs. placebo: 2%; 95% CI, 1% to 5%) [13]. However, there was significant heterogeneity ($P = 0.04$) in this meta-analysis, and the authors excluded dicyclomine and peppermint oil because they were known to have higher rates of adverse events.

In conclusion, there is no significant overall increase in adverse events in small, randomized, controlled trials of antispasmodic agents, but an increase was seen in some studies, and effects may be dose-related. Dicyclomine, at least in higher doses, does appear to demonstrate a higher rate of reported adverse events. The anticholinergic effects of these agents, especially constipation, may limit their use in the IBS-C patient.

References: Section 2.7.4

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- Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2001; **15**:355–361.

2.7.5 Antidepressants

Insufficient data is available to make a recommendation about the safety and tolerability of antidepressants in IBS patients. Side effects may be relatively common and dose-related with tricyclic antidepressants. (Grade B recommendation)

The ACG systematic review [1], reported that adverse events were sporadically reported in the antidepressant trials reviewed. They pointed out that constipation was significantly more frequent with desipramine than with placebo in one trial [2], and that ‘tiredness’ was significantly worse with trimipramine than control during the first 2 weeks of another trial [3]. The review concluded that TCAs may cause constipation and should be used with caution in IBS patients with constipation.

The European systematic review [4], identified five trials that included safety information on the use of antidepressants in patients with IBS: two trials of trimipramine [3,5], one of desipramine [2], one trial of doxepin [6], and one of fluoxetine [7]. Most trials included small sample sizes and were not well designed; all five were placebo-controlled. The adverse event data and study characteristics are presented in Table 2.7.2.

The European systematic review [4], concluded that antidepressants are frequently prescribed by physicians to treat IBS, but the safety and tolerability of the doses used have not been well documented. None of the five published studies described the severity of adverse events. The authors also concluded that because TCAs may cause constipation they should be used with caution in patients with IBS-C.

A placebo-controlled RCT of desipramine in functional bowel disease was not included in the systematic review because it was not performed exclusively in IBS patients, although 78% of the patients had IBS [8]. Nevertheless, 135 patients received desipramine, initially at a dose of 50 mg daily and advancing to 150 mg daily by week 3 if tolerated, and 55 patients received placebo. Side effects that were higher in the desipramine group included constipation (26% vs. 9%), dry mouth (48% vs. 26%), flushing (23% vs. 4%), nausea (13% vs. 6%), and decreased appetite (10% vs. 2%).

Table 2.7.2 Placebo-controlled randomized controlled trials that report on the tolerability or safety of antidepressants for IBS treatment [4]

Reference	Study design	Treatment	No.	Duration of treatment	Key findings
5	Prospective, double-blind, placebo-controlled	Trimipramine 50 mg/day vs placebo	61	4 weeks	<ul style="list-style-type: none"> • No adverse side effects were recorded
3	Randomized, double-blind	Trimipramine (various doses; 30–50 mg/day) vs. placebo	428	6 weeks	<ul style="list-style-type: none"> • No significant difference from placebo in palpitations, dizziness or dry mouth • Tiredness was more pronounced during the first 2 weeks of active treatment in the trimipramine group • No withdrawals due to AEs reported
2	Randomized, double-blind, crossover	Desipramine 50–150 mg/day vs. atropine 0.4–1.2 mg/day vs. placebo	28	3 × 6 weeks	<ul style="list-style-type: none"> • Desipramine: 9 patients reported AEs leading to withdrawal in 3 patients (dose reduction was required in the other 6). Most frequently reported AEs were anxiety, tremulousness, palpitations, sweating, xerostomia and constipation • Atropine: 7 patients reported AEs (xerostomia, constipation and palpitations) • Placebo: 3 patients reported AEs leading to withdrawal of 2 patients. AEs were tremulousness, xerostomia, nausea and urticaria
6	Randomized, double-blind, placebo-controlled	Doxepin 75 mg q.i.d. vs. placebo	50	4 weeks	<ul style="list-style-type: none"> • Doxepin: 6/25 patients (24%) reported drowsiness leading to withdrawal in 2
7	Randomized, double-blind placebo-controlled	Fluoxetine 20 mg q.i.d. vs. placebo	40	6 weeks	<ul style="list-style-type: none"> • 8 patients in the placebo group and 10 patients in the fluoxetine group reported AEs • Most frequent AEs were dizziness, drowsiness; less frequent were diarrhea, constipation, headaches, nausea and itching • 4 placebo and 2 fluoxetine patients withdrew due to intolerable side effects.

AE, adverse event.

In conclusion, data on the safety and tolerability of antidepressants in IBS patients are limited by small sample sizes. However, side effects may be relatively common and dose-related with tricyclic antidepressants based on data in other patient populations, and these agents should be used cautiously in IBS patients with constipation. Virtually no information is available regarding the adverse effects of SSRIs in IBS patients which precludes evidence-based statements regarding their safety and tolerability. However, there are no data to suggest that the safety profile of SSRIs is different in IBS patients as compared to other patient populations.

References: Section 2.7.5

- 1 Brandt LJ, Bjorkman D, Fennerty MB, *et al.*, for the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. An evidence-based approach to the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002; **97** (Suppl):S1–S26.
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- 8 Drossman DA, Toner BB, Whitehead WE, Diamant NE, Dalton CB, Duncan S, *et al.* Cognitive-behavioural therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders. *Gastroenterology* 2003; **125**:19–31.

2.7.6 Anti-diarrhoeal agents

There are no reported increases in adverse events in small randomized controlled trials of loperamide for IBS. (Grade B Recommendation)

Only one study [1] reported data about adverse events. In this trial, 29% of loperamide-treated patients reported adverse events versus 36% of placebo-treated patients ($P > 0.05$). No other details were provided. Due to the relative lack of adverse event data, no evidence-based comments about possible adverse events associated with loperamide can be made.

Reference: Section 2.7.6

- 1 Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci* 1984; **29**:239–247.

2.7.7 Tegaserod

Diarrhoea occurs in up to 10% of tegaserod-treated patients, but no more than 2% discontinue tegaserod due to diarrhoea. In clinical studies, tegaserod-associated diarrhoea typically is mild, occurs in the first week of treatment, and resolves without discontinuing treatment. Headache occurs more frequently in tegaserod-treated patients versus placebo-treated patients in pooled analysis (15% vs. 12%, respectively). (Grade A Recommendation)

In the ACG monograph [1], investigators noted that ‘diarrhoea is the most common adverse event associated with tegaserod use... diarrhoea was reported as an adverse event in 9–10% of tegaserod-using patients vs. 4–5% of placebo-using patients. Approximately 1–2% of tegaserod-using patients discontinued medication due to this adverse event’ [1]. Discontinuation of study medication due to diarrhoea probably reflects a clinically important adverse event and this occurred in approximately 1–2% of patients. In pooled analysis of clinical studies, the incidence of a diarrhoea-associated serious adverse event (e.g., dehydration or syncope associated with tegaserod-induced diarrhoea which led to emergency department evaluation) is less than 0.04%.

In pooled analysis of phase III trials in 2001 [2], the incidence of headache was 3% higher among tegaserod-using patients compared to placebo-using patients (15% vs. 12%). In all individual studies, the incidence of headache was similar in tegaserod-using patients and placebo-using patients. Withdrawal of study medication due to headache was infrequent (less than 1.2%) in tegaserod-treated patients and placebo-treated patients.

Phase III RCTs demonstrated a numeric imbalance in the incidence of cholecystectomy among tegaserod-treated patients vs. placebo-treated patients (0.17% vs. 0.06%, *P* = 0.22, respectively) (Table 2.7.3).

US FDA personnel initially suggested that this finding could represent a ‘signal’ that tegaserod had a deleterious effect on gallbladder motility. However, review of these cases revealed that several surgeries, including three cholecystectomies, were unrelated to tegaserod use [3] (e.g., one patient had documented symptomatic cholelithiasis for one year prior to entry into the phase III trial

Table 2.7.3 Abdominal and pelvic surgeries in phase III trials of tegaserod in IBS patients with constipation

	Tegaserod (<i>n</i> = 2965)	Placebo (<i>n</i> = 1740)	<i>P</i> value
Pelvic	4 (0.13%)	4 (0.23%)	0.71
Abdominal, non-cholecystectomy	4 (0.13%)	2 (0.11%)	1.00
Cholecystectomy	5 (0.17%)	1 (0.06%)	0.22
Total	13 (0.44%)	7 (0.40%)	0.63

and had scheduled an elective cholecystectomy before entering the trial). Also, a randomized, double blind, placebo-controlled cross-over study demonstrated no difference in gallbladder emptying, gallbladder contractility, or common bile duct diameter in healthy volunteers and IBS patients whether these patients were treated with either tegaserod or placebo [4]. Based upon these data, advisory board members concluded that there is no RCT evidence that tegaserod-treated patients are more likely to undergo cholecystectomy or experience symptomatic cholelithiasis. There is no evidence to suggest that tegaserod use should be avoided in patients with a history of small bowel obstruction or abdominal adhesions. The only reported case of bowel obstruction due to abdominal adhesions in a tegaserod RCT occurred in patient treated with placebo [3].

Multiple epidemiologic studies [5], demonstrate that IBS patients are more likely to be diagnosed with ischemic colitis than healthy controls (Table 2.7.4).

This observation may reflect an ascertainment bias (i.e., IBS patients undergo colonoscopy much more frequently than healthy controls and may be more likely to be diagnosed with a condition that usually causes transient colonic mucosal inflammation in response to transient decreases in mucosal blood flow to the colonic mucosa). It could also reflect decreased colonic mucosal blood flow in response to defects in serotonin receptors in the enteric nervous system of IBS patients.

With respect to tegaserod-treated patients in clinical trials, there have been no reports of ischemic colitis. There has been at least one case of ischemic colitis in a placebo-treated patient in these clinical trials. Based on over 2 500 000 tegaserod prescriptions in post-marketing surveillance, the rate of ischemic colitis in tegaserod-treated patients is approximately 20 cases per 100 000 patient-years. This result is comparable to the rate of ischemic colitis in the healthy control population and is two to five times less than the rate of ischaemic colitis in the general IBS population. Based upon these data, advisory board members stated that there is no evidence for an increased rate of ischemic colitis among tegaserod-treated IBS patients.

Table 2.7.4 Rates of ischaemic colitis in healthy controls and IBS patients

Background incidence rate of ischaemic colitis in United Health Care database	
● IBS cohort	43/100 000 patient-years
● Non-IBS cohort	7/100 000 patient-years
● RR = 3.4	(95% CI 2.6–4.5)
Study of Medi-Cal adult population between 1995 and 2002	
● IBS cohort	179/100 000 person-years
● Non-IBS cohort	47/100 000 person-years
● RR = 3.15	(95% CI 2.5–3.9)

References: Section 2.7.7

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2.8 Patient satisfaction with currently available IBS therapies in the European Union

A majority of IBS patients are not satisfied with traditional IBS therapies. A majority of IBS patients switch or combine medications due to lack of efficacy and poor tolerability. (Grade C Recommendation)

Survey data have addressed satisfaction of IBS patients with traditional IBS therapies. A survey from the International Foundation for Functional GI Disorders from 2002 indicated that more than two-thirds of IBS sufferers were dissatisfied with traditional medications for IBS therapy [1]. Lack of symptom relief (e.g., persistence of abdominal pain or discomfort and persistence of abnormal bowel habits) was a major cause of dissatisfaction [1]. Another survey noted that a majority of IBS patients failed to achieve adequate symptom relief with their initial medication [2]. Among IBS patients taking prescription medications, 55% reported their therapy as not effective (22%) or only somewhat effective (33%), while among IBS sufferers taking over-the-counter medications, 73% reported their therapy was not effective (40%) or only somewhat effective (33%). The lack of satisfaction with IBS therapy presumably leads to nearly two-thirds of patients switching or augmenting their initial prescription for IBS [3]. Zacker *et al.* reported that among a cohort of 3149 IBS patients, 22% switched and 42% augmented their initial prescription for IBS therapy [3].

Hungin *et al.* performed a community survey in nearly 42 000 people living in eight western European countries [4]. A group of 1838 IBS patients from this survey underwent an in-depth interview regarding their IBS. Among all sufferers with current symptoms, 69% had taken some form of therapy. When asked to categorize the overall satisfaction with the treatments they used, 38% said they were completely or very satisfied. When questioned about individual symptoms, complete

relief with treatment was reported for abdominal pain in 24%, bloating in 11%, constipation in 15%, and trapped wind in 12%.

Another survey was performed among 666 patients diagnosed with IBS in a US health maintenance organization (HMO) [5]. This study provides useful information since it examined a group of patients who had sought medical care (relevant because these are the IBS sufferers who will potentially be prescribed medications) and because effectiveness of treatment was specifically evaluated 6 months after their initial visit. Satisfaction was assessed with a binary question regarding ‘satisfactory relief of your bowel symptoms’ and with a seven-point ordinal scale regarding change in bowel symptoms over the six months. Satisfactory relief was reported in 57% at their 6-month follow-up visit. When scoring their change in bowel symptoms, 49% reported they were somewhat or markedly better. However, only 22% reported a $\geq 50\%$ reduction in symptom severity. This ‘real-world’ assessment of IBS patients also reported a relatively high rate of side-effects from medical treatments: moderate to severe side effects were reported among 19% of patients taking antispasmodic agents, 16% of those taking laxatives, and 24% of those taking antidepressants.

A survey in France revealed that 87% of subjects with IBS in the general population had taken some form of medication. There was clear evidence of switching and combining of medications: 53% of IBS patients used anti-spasmodics, 42% used laxatives, 52% used anti-diarrhoeals, and 57% used other unspecified bowel therapy [6]. Mebeverine, an anti-spasmodic agent, was commonly used by IBS patients. A study of pharmacy directors in the Netherlands revealed that mebeverine use was associated with a significantly increased use of more than 20 different types of medications, including laxatives (OR = 7.3; 95% CI: 6.0–8.7), prokinetics (OR = 1.9; 95% CI: 1.3–2.6), and psychotropics (OR = 1.4; 95% CI: 1.1–1.7) [7].

In conclusion, available survey data consistently documented that a substantial number of patients with IBS are not satisfied with their medical therapy. Depending on the definition of satisfaction, half or more of patients fail to achieve satisfactory relief with traditional medications. Furthermore, a survey of usual medical care for IBS suggests high rates of moderate-severe side effects (~15–25%) among patients taking traditional IBS therapies such as antispasmodics, antidepressants, or laxatives. The limited data available also suggest that a majority of IBS patients switch or augment their initial medications. Although studies directly assessing the influence of efficacy and tolerability on decisions to alter therapy were not identified, lack of efficacy and tolerability issues are likely to be the primary reasons for changes in therapy.

References: Section 2.8

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