

# An Evidence-Based Approach to the Management of Chronic Constipation in North America

American College of Gastroenterology Chronic Constipation Task Force

Chronic constipation (CC) is characterized by unsatisfactory defecation that results from infrequent stools, difficult stool passage, or both. The pathophysiology of CC is multifactorial and may include dysfunction of intestinal motility, visceral sensitivity, ano-rectal musculature and the enteric nervous system. Because CC is common, this monograph has been developed to educate physicians about its epidemiology, diagnostic approach, and treatment.

In order to assess published data about the management of CC, systematic reviews were performed. Standard criteria for systematic reviews were met, including comprehensive literature searching, use of pre-specified study selection criteria, and use of a standardized and transparent process to extract and analyze data from studies (Section 2.1). A North American perspective was chosen: only epidemiologic studies from North American populations were used and only treatments available in the United States were examined. After analysis of the systematic reviews, Task Force members produced evidence-based recommendations (Section 2.2). Recommendations were graded using a formalized system (Table 1.1) that quantifies the strength of evidence. Recommendations in this monograph may be cross-referenced with the supporting evidence in the following article: "Systematic Review on the Management of Chronic Constipation in North America." The format of this evidence-based position monograph and systematic review has been adapted from the previous evidence-based monograph produced by the American College of Gastroenterology's Functional GI Disorders Task Force (1).

## **SYMPTOM-BASED CRITERIA FOR CHRONIC CONSTIPATION AND THRESHOLD TO TREAT CHRONIC CONSTIPATION (SEE SECTION 2.3)**

*Constipation is a symptom-based disorder defined as unsatisfactory defecation and is characterized by infrequent stools, difficult stool passage, or both. Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool (Grade C Recommendation). CC is defined as the presence of these symptoms for at least 3 months (Grade C recommendation). Available evidence indicates that self-reported constipation is associated with decreased quality of life (Grade C recommendation). Treatment of patients with CC is indicated when the*

*symptoms diminish quality of life (Grade C recommendation).*

Chronic functional constipation has been defined as a symptom-based disorder by an international committee that had its meeting in Rome. These symptom-based so-called "Rome criteria" emphasize  $\geq 12$  wk/year of symptoms, including hard or lumpy stools, straining, a sense of incomplete evacuation, the need to use manual maneuvers to pass stool, or a sense of anorectal obstruction with  $\geq 25\%$  of bowel movements, and/or  $< 3$  bowel movements/week, with no evidence of organic disease. At least two symptoms should be present to make the diagnosis of chronic functional constipation. Although the Rome criteria may identify a uniform group of study patients for a constipation treatment trial, expert opinion suggests that widespread use of these criteria is impractical. Observational studies indicate that most patients who report constipation symptoms do not fulfill Rome criteria for chronic functional constipation. Therefore, Task Force members recommended a broader definition that encompasses the symptoms most commonly expressed by patients who self-report constipation.

Observational studies and expert opinion indicate that CC frequently overlaps with IBS with constipation; the latter is defined as the presence of clinically important abdominal discomfort associated with constipation symptoms. Patients with CC may report minimal abdominal bloating or discomfort associated with their other CC symptoms, creating a spectrum between CC and IBS. In some patients it may be difficult, if not impossible, to differentiate CC and IBS accurately and reliably.

Observational studies of patients who self-report CC suggest that CC is associated with a decreased quality of life. Treatment of CC should be instituted when both the patient and physician have determined that the symptoms diminish the patient's quality of life.

## **EPIDEMIOLOGY OF CHRONIC CONSTIPATION IN NORTH AMERICA (SEE SECTION 2.4)**

*Estimates of the prevalence of CC in North America vary between 2% and 27%. This variation is partly explained by different diagnostic criteria for CC and most studies estimate that the prevalence of CC is approximately 15%. Estimates of CC prevalence based on Rome II criteria are lower than estimates based on self-reporting. Constipation is reported more commonly in women (2–3:1 predominance), the*

**Table 1.1:** Levels of Evidence and Grading of Recommendations\*

<i>Level I Evidence:</i>	RCTs with $p < 0.05$ , adequate sample sizes and appropriate methodology
<i>Level II Evidence:</i>	RCTs with $p > 0.05$ , or inadequate sample sizes and/or inappropriate methodology
<i>Level III Evidence:</i>	Non-randomized trials with contemporaneous controls
<i>Level IV Evidence:</i>	Non-randomized trials with historical controls
<i>Level V Evidence:</i>	Case series
<i>Grade A Recommendations:</i>	Recommendations supported by two or more level I trials without conflicting evidence from other level I trials
<i>Grade B Recommendations:</i>	Recommendations based on evidence from a single level I trial OR recommendations based on evidence from two or more level I trials with conflicting evidence from other level I trials OR supported by evidence from two or more level II trials
<i>Grade C Recommendations:</i>	Recommendations based on level III-V evidence

\*Modified from Cook D, Guyatt G, Laupacis A, Sackett D. Chest 1992;102:305S

elderly, non-whites, and individuals from lower socioeconomic groups (Grade C recommendation).

Population-based studies report that the prevalence of CC in North America varies from 2% to 27%, and most estimates cluster around 15%. This wide range of estimates probably reflects differences in definitions of CC and in study ascertainment techniques rather than true differences in prevalence. There are no rigorously designed studies on the natural history of CC in North America. Ideal longitudinal studies would report on the frequency, duration, and intensity of CC symptoms, frequency of care seeking, medication use, utilization of diagnostic procedures and impact on quality of life. Task Force members support and endorse the execution of properly designed population-based studies about the natural history of CC in North America.

### DIAGNOSTIC APPROACH TO THE PATIENT WITH SYMPTOMS OF CHRONIC CONSTIPATION (SEE SECTION 2.5)

Among CC patients without alarm symptoms or signs, there are inadequate data to make a recommendation about the **routine** use of flexible sigmoidoscopy, colonoscopy, barium enema, thyroid function tests, serum calcium, and other diagnostic tests (Grade C recommendation). Diagnostic studies are indicated in patients with alarm symptoms and signs which may include hematochezia, weight loss  $\geq 10$  pounds, family history of colon cancer or inflammatory bowel disease, anemia, positive fecal occult blood tests, as well as for the acute onset of constipation in elderly persons (Grade C recommendation). A careful history and physical examination should be performed in order to identify symptoms or signs of organic disorders (e.g., hypothyroidism) that may be associated with CC symptoms. Specific diagnostic testing (e.g., thyroid function tests) may be performed in individual patients with additional signs or symptoms of an organic disorder. Routine use of colon cancer screening tools is recommended for all patients  $\geq 50$  years old (Grade C recommendation). Based upon expert opinion, the **routine** approach to a patient with symptoms of CC without alarm signs or

symptoms should be empiric treatment without performance of diagnostic testing (Grade C recommendation).

If the pretest probability of an organic disorder (e.g., hypercalcemia) is similar in patients with CC symptoms and in controls, then the **routine** use of diagnostic testing (e.g., serum calcium) to exclude this disorder cannot be recommended. There are, however, no well-designed studies that assess either the pre-test probability of organic disorders or the utility of routine diagnostic tests among patients with CC symptoms. Available evidence suggests that the likelihood of identifying organic disorders with colonoscopy is similar among patients with CC symptoms and among age-matched, asymptomatic controls. Therefore, the **routine** use of colonoscopy to exclude organic disorders cannot be endorsed in patients with CC symptoms. Task force members emphasize that individual physicians may use diagnostic tests for specific patients if the patient's history and physical examination suggest the presence of an organic disorder associated with CC symptoms. In the absence of adequate data, Task Force members concluded that the **routine** use of a battery of diagnostic tests should be avoided in patients with CC symptoms and that the initial approach to these patients should be empiric treatment. Alarm symptoms or signs indicate a subgroup of patients in whom diagnostic tests are indicated. Given the lack of well-designed studies, Task Force members support and endorse the execution of properly designed studies on this topic.

### THERAPY OF CHRONIC CONSTIPATION: BULKING AGENTS (SEE SECTION 2.6)

Psyllium (e.g., Metamucil<sup>®</sup>, Konsyl<sup>®</sup>) increases stool frequency in patients with CC (Grade B recommendation). There are insufficient data to make a recommendation about the efficacy of calcium polycarbophil (e.g., Perdiem Fiber Therapy<sup>®</sup>, Fibercon<sup>®</sup>), methylcellulose (e.g., Citrucel<sup>®</sup>), and bran in patients with CC (Grade B recommendation).

Bulking agents available in the United States include psyllium, calcium polycarbophil, methylcellulose, and wheat bran. Bulking agents are FDA-approved for the treatment of

occasional constipation. All trials evaluating these therapies demonstrate sub-optimal study design and meet few of the Rome committee recommendations for appropriate design of a treatment trial for a functional gastrointestinal disorder (see Table 2.1.1). Most of these trials had very small sample sizes, short study duration, and were completed before the development of criteria for the performance of therapy trials in patients with functional gastrointestinal disorders. Also, only one poorly designed randomized control trial (RCT) is available to assess the efficacy of multiple bulking agents for the treatment of CC.

There are three placebo-controlled trials of psyllium in patients with CC, and all were of suboptimal design. Generally, these trials demonstrate that stool frequency or stool consistency are improved by psyllium compared with placebo. There are no placebo-controlled trials examining calcium polycarbophil in patients with CC. There is one poorly designed trial comparing calcium polycarbophil with psyllium that examined 32 patients and did not demonstrate any statistically significant difference in stool frequency or stool consistency between the two groups. There are no placebo-controlled trials of methylcellulose. There is one poorly designed trial of 59 patients in which methylcellulose was compared with psyllium. Patients took medication for only 10 days in this trial and no statistically significant differences were demonstrated in stool frequency or stool consistency.

There are three RCTs of wheat bran in patients with CC, but only one is placebo-controlled. All of these trials were poorly designed. The placebo-controlled trial did not demonstrate a statistically significant difference in stool frequency or consistency for bran versus placebo. The other two trials compared wheat bran with either corn biscuit or corn bran and also did not demonstrate significant improvement in stool frequency or consistency.

Data on adverse events were reported for few trials. No statistically significant differences in adverse events were identified between any bulking agent and an active comparator or placebo. Task Force members noted that large quantities of psyllium may be associated with bloating, which may be a bothersome event. Also, mechanical obstruction of the esophagus and colon has been reported with bulking agents, and anaphylactic reactions have been reported with psyllium.

### **THERAPY OF CHRONIC CONSTIPATION: STOOL SOFTENERS (SEE SECTION 2.7)**

*There are insufficient data to make a recommendation about the efficacy of stool softeners in patients with CC (Grade B recommendation). Stool softeners may be inferior to psyllium for improvement in stool frequency (Grade B recommendation).*

Stool softeners available in the United States include docusate sodium (e.g., Colace<sup>®</sup>) and docusate calcium (e.g., Surfak<sup>®</sup>). Stool softeners are FDA-approved for the treat-

ment of occasional constipation. There are four RCTs that compare stool softeners with active comparators or placebo in patients with CC. Generally, these trials had small sample sizes, only treated patients for 4 weeks, and did not enroll a uniform population of patients. In the trial comparing docusate sodium (Colace<sup>®</sup>) with psyllium, stool frequency was significantly increased by week two with psyllium compared with docusate sodium. One placebo-controlled trial showed no difference in stool frequency or stool consistency among patients taking stool softeners or placebo, but a second placebo-controlled trial demonstrated a significant improvement in stool frequency for stool softeners compared with placebo. Given the small sample sizes and conflicting results in placebo-controlled trials, Task Force members felt that there were insufficient data to make a recommendation about the efficacy of stool softeners. The general consensus of Task Force members was that stool softeners had minimal, if any, effect to improve symptoms of CC. No data on adverse events were provided in these trials.

### **THERAPY OF CHRONIC CONSTIPATION: OSMOTIC LAXATIVES (SEE SECTION 2.8)**

*Polyethylene glycol (PEG) is effective at improving stool frequency and stool consistency in patients with CC (Grade A recommendation). Lactulose is effective at improving stool frequency and stool consistency in patients with CC (Grade A recommendation). There are insufficient data to make a recommendation about the effectiveness of milk of magnesia (MOM) in patients with CC (Grade B recommendation).*

Osmotic laxatives are FDA-approved for treatment of occasional constipation. There are five placebo-controlled RCTs of PEG in patients with CC, and four of these RCTs demonstrate medium-high quality for study design. There are two RCTs that compared PEG with lactulose. All of these trials demonstrated that PEG improves stool frequency and stool consistency among patients with CC. There are three placebo-controlled RCTs that examined the effectiveness of lactulose in patients with CC, and two of these RCTs demonstrate medium-high quality for study design. These trials demonstrated that lactulose is more effective than placebo at improving stool consistency and stool frequency. Only one study reported adverse events, noting that lactulose-using patients suffered more abdominal discomfort than did placebo-using patients. There was only one RCT that assessed the effectiveness of milk of magnesia (MOM) for patients with CC. This crossover trial compared MOM with "laxamucil" and was a low quality study that was difficult to interpret because of multiple crossover periods. Therefore, Task Force members felt that there were insufficient data to make a recommendation about the effectiveness of MOM for patients with CC.

Data on adverse events were not adequately reported for most trials. Multiple electrolyte abnormalities (e.g., hypermagnesemia, hyperphosphatemia, hypercalcemia, hyponatremia, hypokalemia), hypovolemia, and diarrhea have

been reported with these agents, although the precise incidence of these adverse events is unclear. Per FDA-approved prescribing information, high doses of PEG may produce diarrhea and excessive stool frequency, especially in elderly nursing home patients, and nausea, abdominal bloating, cramping and flatulence may occur.

### **THERAPY OF CHRONIC CONSTIPATION: STIMULANT LAXATIVES (SEE SECTION 2.9)**

*There are insufficient data to make a recommendation about the effectiveness of stimulant laxatives in patients with CC (Grade B recommendation).*

Senna (e.g., Senokot<sup>®</sup>, Ex-lax<sup>®</sup>) or bisacodyl (e.g., Dulcolax<sup>®</sup>, Correctol<sup>®</sup>, Carter's Pills<sup>®</sup>) is the active ingredient of most stimulant laxatives available in the United States. Stimulant laxatives are FDA-approved for the treatment of occasional constipation. There are four RCTs that assess the efficacy of stimulant laxatives in patients with CC. None of these RCTs were placebo-controlled, and all of these RCTs demonstrate low quality study design. None of these trials demonstrated that stimulant laxatives were better than other treatments for constipation, although stimulant laxatives were less effective than lactulose in one study. Among trials that reported adverse events, there was no significant difference in adverse events between stimulant laxatives and other treatments for constipation. Abdominal discomfort, electrolyte imbalances, allergic reactions and hepatotoxicity have been reported with these agents. Given the poor quality of study design, lack of placebo-controlled trials, and inconclusive results, Task Force members felt there were insufficient data to make a recommendation about the efficacy of stimulant laxatives for the management of CC, but that available data suggest minimal benefit with these products.

### **THERAPY OF CHRONIC CONSTIPATION: TEGASEROD (SEE SECTION 2.10)**

*Tegaserod is effective at improving the frequency of complete spontaneous bowel movements, straining, stool frequency, and stool consistency in patients with CC (Grade A recommendation).*

Tegaserod is FDA-approved for treatment of CC in men and women younger than 65 years of age. There are two large, well-designed RCTs that compare tegaserod with placebo for

the management of CC. Each of these trials enrolled more than 1,000 patients, was 12 weeks in duration, and demonstrated high quality study design. Each trial demonstrated that patients younger than 65 years old experienced significant improvement in frequency of complete spontaneous bowel movements, total spontaneous bowel movements, straining and global satisfaction with bowel habits with tegaserod compared with placebo. Diarrhea (6.6% vs 3.0%) occurred significantly more often among tegaserod-using patients compared with placebo-using patients, although the diarrhea usually was mild and transient with less than 1% of patients discontinuing tegaserod because of diarrhea.

### **THERAPY OF CHRONIC CONSTIPATION: HERBAL SUPPLEMENTS, ALTERNATIVE TREATMENTS, LUBRICANTS, AND COMBINATION LAXATIVES (SEE SECTION 2.11)**

*There are insufficient data to make a recommendation about the effectiveness of herbal supplements, alternative treatments, lubricants, or combination laxatives in patients with CC (Grade C recommendation).*

There are no published RCTs examining the efficacy of herbal supplements (e.g., aloe) available in the United States in patients with CC. There are no published RCTs on the efficacy of lubricants (e.g., mineral oil) in adult patients with CC, although there are RCTs examining mineral oil in pediatric patients with CC and these trials indicate that mineral oil is more effective than senna-based laxatives and less effective than osmotic laxatives at improving stool frequency and stool consistency. There are no published RCTs of combination laxatives (e.g., psyllium plus senna) available in the United States in patients with CC. There are no published placebo-controlled or sham-controlled randomized trials of biofeedback for the management of patients with CC, although uncontrolled trials indicate that biofeedback techniques improve stool frequency compared with baseline.

### **REFERENCE**

1. American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. Evidence-based position statement on the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002;97(11, Suppl.):S1-S5.



# Systematic Review on the Management of Chronic Constipation in North America

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## 2.1 Methods

Evidence-based guidelines should have:

- (a) a transparent link between the evidence and the recommendations;
- (b) explicit criteria for inclusion of studies to serve as the evidence;
- (c) comprehensive searching of the literature for relevant studies;
- (d) a standardized and explicit system for grading the quality of study design;
- (e) a standardized and explicit system for grading recommendations; and
- (f) recommendations that acknowledge the magnitude of the treatment benefit, the adverse events associated with the treatment, and individual patient preferences that may guide the application of guideline recommendations (1–3).

In order to fulfill these requirements, Task Force members followed the techniques used to produce a previous American College of Gastroenterology evidence-based monograph (4). 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 (5, 6). Data about study methodology and study results were extracted onto standard forms and summaries of data are presented in tables and graphs to insure that the quality of study design was defined and that the magnitude of treatment was quantified. A commonly used system for grading recommendations in evidence-based guidelines (7) was adapted for this document (see Section 2.2) and insured that an explicit and transparent process was used to make recommendations based upon the strength of the evidence. 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 Task Force members contributed their expert advice based upon their clinical experience.

### Literature Search

In order to identify *Chronic Constipation (CC) Therapy Trials*, the following literature search techniques were employed. Separate PUBMED and MEDLINE searches of English language articles from 1966–2003 were performed with different combinations of the following search terms: “constipation,” “laxatives, stimulant,” “laxatives, osmotic,” “laxatives, irritant,” “laxatives, bulk,” “fecal softeners,” “sorbitol,” “lactulose,” “milk of magnesia,” “magnesium sulphate,” “bisacodyl,” “calcium polycarbophil,” “polyethylene glycol,” “danthron,” “cascara,” “ispaghula,” “bran,” “celandin,” “docusate,” “poloxalkol,” “mineral oil,” “glycerine,” “psyllium,” “methylcellulose,” “senna,” and “tegaserod.” Exploded terms were reviewed, and where appropriate, the search was expanded to include them. Manual searches of reference lists from relevant articles also were performed to identify additional studies that may have been missed during the computer-assisted search.

In order to identify relevant studies about the *Epidemiology of CC* and the *Diagnostic Approach to Patients with CC Symptoms*, the following literature search techniques were employed. For *Epidemiology of CC*, only English language articles published in full manuscript form were considered. A search of the MEDLINE database from 1966–2003 was performed using the exploded (exp) MESH terms: exp constipation AND (exp incidence OR exp prevalence OR exp prognosis OR exp natural history OR exp epidemiology OR exp quality of life). For EMBASE, a search from 1998–2002 was performed and modified to include only articles that mentioned constipation in the title: constipation.ti AND (exp incidence OR exp prevalence OR exp prognosis

OR exp natural history OR exp epidemiology OR exp quality of life). The Current Contents database from Week 1, 2002 to Week 6, 2003 was searched with the terms constipation.mp AND (incidence.mp OR prevalence.mp OR prognosis.mp OR natural history.mp OR epidemiology.mp OR quality of life.mp). Manual searches of reference lists from potentially relevant articles also were performed to identify any additional studies that might have been missed during the computer-assisted search. For *Diagnostic Approach to the Patient with CC Symptoms*, a bibliographic database search of MEDLINE from 1966 was performed. The search terms used included “constipation,” “colonic diseases,” “Rome criteria,” “colonoscopy,” “barium enema,” “defecation,” and various systemic or local disorders that cause constipation such as diabetes or colon cancer. Only human studies were considered. Bibliographies from all potentially relevant articles were searched manually.

A medical education and research company (EBMed, LLC, Anaheim Hills, CA) assisted the Task Force with literature searches, application of study selection criteria, data extraction and analysis, and assessment of methodologic quality of individual trials.

### Study Selection Criteria

The titles and abstracts of all citations identified by the literature searches were reviewed. Potentially relevant studies were retrieved, and the selection criteria were applied. Since a North American perspective was used, only treatments available in the United States were examined and only epidemiologic studies from North American populations were reviewed. For *CC therapy trials*, the selection criteria were: (a) RCT; (b) population of adult patients with CC; (c) comparison of CC therapy *versus* placebo or control therapy; (d) evaluation of relief of CC symptoms; (e) results published in English in full manuscript form (or adequate data available after written communication with investigators); and, (f) therapy available in the United States. For *Epidemiology of CC* studies, the selection criteria were: (a) studies of population-based samples of CC patients in North America; (b) population of adult patients (inclusion of pediatric patients within an adult study population was allowed); (c) results reported on prevalence, incidence, quality of life, or natural history of CC; (d) results published in full manuscript form; and (e) English language only. Case definition for constipation in these epidemiologic trials included patient self-report, physician or ICD-9 diagnosis, consensus criteria from Rome I or Rome II. For trials about the *Diagnostic Approach to the Patient with CC Symptoms*, study inclusion criteria were: (1) population of patients with CC symptoms (note: the definition of constipation is extremely variable or inadequately described in most studies and no single symptom was used to define this condition; therefore, we included any study that stated patients had CC symptoms.); (2) performance of diagnostic tests to diagnose organic disorders responsible for CC symptoms; including complete blood cell count, biochemical laboratory tests, colonoscopy, flexible sigmoidoscopy, barium enema, and plain abdominal radiography; (3) prevalence

of organic disorders responsible for CC symptoms or number of patients with abnormalities on physiologic testing.

### Data Extraction and Analysis

For CC therapy trials, data about study methodology and study results were abstracted onto standard forms for the performance of systematic reviews. Data were extracted about: (a) study population; (b) intervention: dosage and schedule of treatment *versus* placebo or control therapy; (c) study duration; and (d) proportion of patients achieving improvement in global CC symptoms, stool frequency, stool consistency, and adverse events. The Rome committee recommended study design techniques to minimize bias in trials of functional GI disorders (8) (Table 2.1.1). Data about the use of these techniques were extracted. We also used a single grading system that has been validated for appropriate study design of therapy trials examined in a systematic review or meta-analysis (9) (Table 2.1.2). Data about the use of proper randomization, blinding and follow-up were extracted from each study and summarized in tabular form. Because of wide variation in study design, study endpoints, and dosages of study medication, however, no attempt was made to combine results into meta-analyses. Based on Rome Committee recommendations (8), global improvement in symptoms is the ideal endpoint for these trials because this endpoint encompasses improvement in the multiple symptoms (*e.g.*, straining, sense of incomplete evacuation, bloating, etc.) of CC. Because few trials evaluated this endpoint, however, Task Force members agreed to expand the endpoints to include stool frequency and stool consistency. Results of individual RCTs are presented in tabular form. When individual RCTs reported numerical results, these results were included in the tables. When individual RCTs provided graphs or declarative statements without numerical results, then declarative statements were included

**Table 2.1.1.** Qualitative Assessment of Study Methodology Scale\*#

1. Rome criteria to identify patients with chronic constipation
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 wks 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 CC symptoms
13. Primary outcome is based on patient assessment
14. Validated scale used to measure improvement in CC symptoms.

\*Data from van Zanten SJO, Talley NJ, Bytzer P, et al. Design of treatment trials for functional gastrointestinal disorders. *Gut* 1999;45 (Suppl II):II69–77.

#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 an *a priori*-defined study endpoint and definition of patient setting (primary care vs tertiary care). Published reports, however, rarely provide 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.

in the tables. Due to the lack of RCTs, no data about the management of pelvic floor disorders are included.

For *Epidemiology of CC* studies, data about study methodology and study results also were abstracted onto standard forms. Data were abstracted about: (a) symptom-based definition of CC (e.g., patient self-report or Rome Criteria); (b) sample size and case ascertainment technique to identify CC patients; (c) prevalence, incidence, prevalence of CC subgroups, gender distribution, race distribution, socioeconomic distribution, diseases associated with CC, and mean age of onset of symptoms; and (d) disease activity (e.g., prevalence of CC over time and frequency of CC flares within a specified period of time) and/or quality of life data. For trials about the *Diagnostic Approach to the Patient with CC Symptoms*, data were abstracted about: (a) symptom-based criteria used to identify CC patients; (b) diagnostic evaluation performed; (c) prevalence of confirmed organic GI disease, resulting in an alternative diagnosis to explain CC symptoms or prevalence of abnormal results on diagnostic tests.

## 2.2 Levels of Evidence and Grading of Recommendations

### *Quantitative Assessment of Study Methodology*

Previous reviews and epidemiologic studies (10–12) have established criteria that minimize bias in trials about therapy, including the use of randomization, concealed allocation, double-blinding, and complete patient follow-up. A single grading system has been validated for appropriate study design of therapy trials examined in a systematic review or meta-analysis (9) (Table 2.1.2). In order to assess the strength of individual studies about CC therapies, data about the use of these techniques were extracted, summarized in a quantitative scale, and presented in tabular form. This scale estimates the rigor of an individual trial: a trial with a low quality score may be more likely to produce inaccurate or biased results and a trial with a high quality score may be more likely to produce accurate and unbiased results (8–10). Additionally, the Rome committees described the preferred design of treatment trials for functional gastrointestinal disorders (8) (Table 2.1.1). Data about use of these additional Rome committee criteria for appropriate design of treatment trials also were extracted and are presented in descriptive form.

No standard criteria are available to rate the quality of study design of epidemiologic studies in a systematic review. Population-based studies may be preferable to studies of referral populations because referral populations may provide inflated estimates of the prevalence and incidence of a disorder. Therefore, epidemiologic studies in this review are limited to population-based studies.

### *Levels of Evidence*

Levels of Evidence have been defined previously (see Table 1.2). Level I evidence represents high quality RCTs. These RCTs have few limitations in their study design, which should minimize Type I errors. Thus, if a RCT shows a significant difference between treatment and placebo, then this finding probably did not result from biased study design. These RCTs also have adequate power to minimize Type II errors. Thus, if a RCT does not show a significant difference between treatment and placebo, then this finding probably did not occur because of 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 also may be susceptible to Type II errors because of inadequate sample size. Level III–V evidence comes from non-randomized trials or case series. These are observational studies that are prone to multiple biases that produce Type I errors. For this review, Level III–V evidence was not used to make recommendations about *CC therapies*. Level III–V evidence was used only to make recommendations about the *Diagnostic Approach to the Patient with CC Symptoms* or about *Epidemiology of CC* because data on these topics are available only from observational studies.

### *Grading of Recommendations*

Recommendations are listed as Grade A, Grade B, or Grade C (see Table 1.2). Grade A recommendations are supported by the strongest (Level I) evidence. Task Force members strongly believe that these recommendations are accurate based upon the evidence. Grade B recommendations are supported by intermediate quality (Level II) evidence. Task Force members believe that Grade B recommendations may have

**Table 2.1.2.** Jadad Criteria-Validated Scale to Assess Quality of Study Design for Treatment Trials in a Systematic Review or Meta-Analysis

Randomization	
+2	Randomized with Concealed Allocation and Appropriate Description of Randomization Process
+1	Trial described as randomized, but no further information provided
0	Not randomized
Blinding	
+2	Double-blind with appropriate description of techniques used to insure double-blinding (e.g., double-dummy technique)
+1	Trial described as double-blind, but no further information provided
0	Not blinded
Complete Follow-Up	
+1	Statement about number of patients lost to follow-up and reason for loss to follow-up provided
0	No statement about number of patients lost to follow-up or reason for loss to follow-up provided

Jadad A, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized controlled trials: Is blinding necessary? *Controlled Clin Trials* 1996;17:1–12. Scores of 4–5 are consistent with a well-designed RCT, while scores of 1–2 are consistent with a poorly-designed trial.



important limitations because of 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 observational studies (Level III–V evidence). The strength of evidence behind these recommendations is limited, and Grade C recommendations are provided only because they represent the best evidence about the *Epidemiology of CC* and the *Diagnostic Approach to Patients with CC Symptoms*.

## REFERENCES: SECTION 2.1 AND 2.2

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## 2.3 Symptom-based Criteria for Diagnosing Chronic Constipation and Threshold to Treat Chronic Constipation

*Constipation is a symptom-based disorder defined as unsatisfactory defecation and is characterized by infrequent stools, difficult stool passage, or both. Difficult stool passage in-*

*cludes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool (Grade C Recommendation). CC is defined as the presence of these symptoms for at least 3 months (Grade C recommendation). Available evidence indicates that self-reported constipation is associated with decreased quality of life (Grade C recommendation). Treatment of patients with CC is indicated when the symptoms diminish quality of life. (Grade C recommendation).*

CC may be associated with dysfunction of intestinal motility, visceral sensitivity, ano-rectal musculature and the enteric nervous system, but no structural, biochemical, or physiological abnormalities are demonstrated consistently in CC patients; therefore, the definition of CC is symptom-based. Symptoms of CC include decreased stool frequency, difficult stool passage or both. Symptoms of difficult stool passage include straining, a sense of difficulty passing stool or of incomplete evacuation, hard/lumpy stools, prolonged time to stool, and need for manual maneuvers to pass stool (1).

Symptom-based criteria for the diagnosis of CC have been developed by functional bowel disorder experts to facilitate the diagnosis of CC (2). These symptom-based criteria, also known as the Rome criteria (Table 2.3.1), are used to identify CC patients for research studies, but they are probably too detailed for use in the primary care setting. In fact, few primary care physicians use Rome criteria to identify patients with irritable bowel syndrome (IBS) (3). Furthermore, both the Rome criteria (2) and physicians (4) emphasize that CC is defined by less than 3 bowel movements per week, although many patients who report CC pass  $\geq 3$  bowel movements per week (4). These patients report CC because of difficult stool passage (e.g., straining, sense of incomplete evacuation, etc.). Given the uncertain clinical utility of Rome criteria for identification of patients with CC, Task Force members suggest that physicians use a broad definition of CC: “*unsatisfactory defecation characterized by infrequent stools, difficult stool passage or both. Difficult stool passage includes straining, a sense of difficulty passing stool, incomplete evacuation, hard/lumpy stools, prolonged time to stool, or need for manual maneuvers to pass stool.*” In order to define constipation as a chronic disorder, Task Force members felt that some combination of these symptoms should be present for at least three of the previous 12 months (5).

Task Force members noted that the symptom-based criteria for CC and IBS might overlap. Task Force members therefore emphasized that the presence of clinically important abdominal discomfort associated with constipation symptoms defines IBS with constipation. Most patients with CC may report minimal abdominal bloating or discomfort associated with their other CC symptoms, creating a spectrum between CC and IBS (Fig. 2.3.1). Indeed, in some patients it may be difficult, if not impossible, to differentiate CC and IBS accurately and reliably.



**Table 2.3.1.** Rome Criteria for the Diagnosis of Chronic Functional Constipation (2)

1. Two or more of the following symptoms for at least 12 wks (which need not be consecutive wks) in the preceding 12 months
  - Straining during >25% of bowel movements
  - Lumpy or hard stools for >25% of bowel movements
  - Sensation of incomplete evacuation for >25% of bowel movements
  - Sensation of anorectal blockage for >25% of bowel movements
  - Manual maneuvers to facilitate >25% of bowel movements (*e.g.*, digital evacuation or support of pelvic floor)
  - <3 bowel movements per week.
2. Loose stools are not present.
3. Insufficient criteria for the diagnosis of irritable bowel syndrome
4. No organic disorder responsible for chronic constipation symptoms is present

Several physiologic sub-types of CC have been described, including colonic inertia (*e.g.*, decreased colonic transit), outlet delay constipation (*e.g.*, pelvic floor dyssnergia), and functional constipation without delays in colonic transit or outlet delay. There are no symptom-based criteria, however, that effectively identify the different sub-types of CC and these sub-types may coexist in individual patients.

In one study, CC symptoms were associated with a significant decrease in quality of life among CC patients who sought medical care for their symptoms (6). This study also demonstrated decreased mental and physical sub-scores on the SF-36 questionnaire in a population-based sample of Canadians with constipation when these patients were compared with control patients without any functional GI disorder. Based on these data, the Task Force members stated that self-reported CC is associated with a clinically important decrease in quality of life.

Although limited evidence indicates that CC diminishes quality of life, there are no data available to guide recommendations about the threshold to treat CC. Therefore, Task Force members developed an expert-based recommendation: treatment should be initiated when the patient *and* physician feel that CC symptoms are diminishing the quality of life of the patient. Treatment may include lifestyle modification (*e.g.*, increases in daily fiber, increased water consumption, increased exercise) and/or drug therapy, although lifestyle modifications have not been proven effective at increasing stool frequency or stool consistency. Task force members also noted that treatment may be appropriate if constipation symptoms potentially could worsen another disorder or condition (*e.g.*, a patient who recently has had a myocardial infarction or a demented nursing home patient with a history of constipation and fecal impaction.)

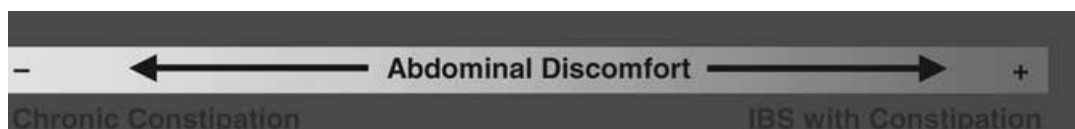
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**2.4 Epidemiology of Chronic Constipation in North America**

*Estimates of the prevalence of CC in North America vary between 2% and 27%. This variation is partly explained by different diagnostic criteria for CC. Most studies estimate that the prevalence of CC is approximately 15%. Estimates of CC prevalence based on Rome II criteria are lower than estimates based on self-reporting. Constipation is more commonly reported in women (2–3:1 predominance), the elderly, non-whites, and individuals from lower socioeconomic groups (Grade C recommendation).*

Understanding the epidemiology and natural history of CC facilitates physician and patient education. In this portion of



**Figure 2.3.1.** Spectrum of chronic constipation and irritable bowel syndrome (IBS) with constipation.

**Table 2.4.1.** Prevalence of Constipation in Representative Population Samples in North America

Study	Population	Year	Ascertain	N (% response)	Case Criteria	Prevalence per 100
Hammon	ACS	1964	Mail survey	890,394 (NR)	Self-report	27.1
Sandler	NHANES I	1971–5	FTF	15,014 (NR)	Self-report	12.8
Everhart	NHANES I	1971–5	FTF	11,024 (74.4)	Self-report	15.8
Johanson	NHIS	1983–7	FTF	NR (NR)	Self-report	1.9
Harari	NHIS	1989	FTF	42,375 (NR)	Self-report	3.4
Talley	Olmsted whites	1991	Mail survey	835 (82)	(Strain AND Hard) OR <3/wk	17.4†
Talley	Olmsted whites	1993	Mail survey	690 (83)	Self-report	5.0*
					Rome I FC	19.2*
					Rome I OD	11.0*
Drossman	Household	1993	Mail survey	5,430 (66)	Rome I FC	3.6
					Rome I Dyschezia	13.8
Stewart	US EPOC	1997	Phone survey	10,018 (53.6)	Rome II, FC or OD or IBS-C	14.7
Pare	Canada	2000	Mail survey	1,149 (57)	Self-report	27.2
					Rome I	16.7
					Rome II	14.9

NR = not reported; FTF = face-to-face interview; FC = functional constipation; OD = obstructive defecation.

†Age- and gender-adjusted prevalence.

Age-adjusted prevalence NHANES: National Health and Nutrition Examination Survey; NHIS: National Health Interview Survey; US EPOC: United States epidemiology of constipation; ACS: American Cancer Society volunteers; Reproduced from Higgins P, Johanson J. Epidemiology of chronic constipation: A systematic review. *Am J Gastroenterol* 2004;99:750–9.

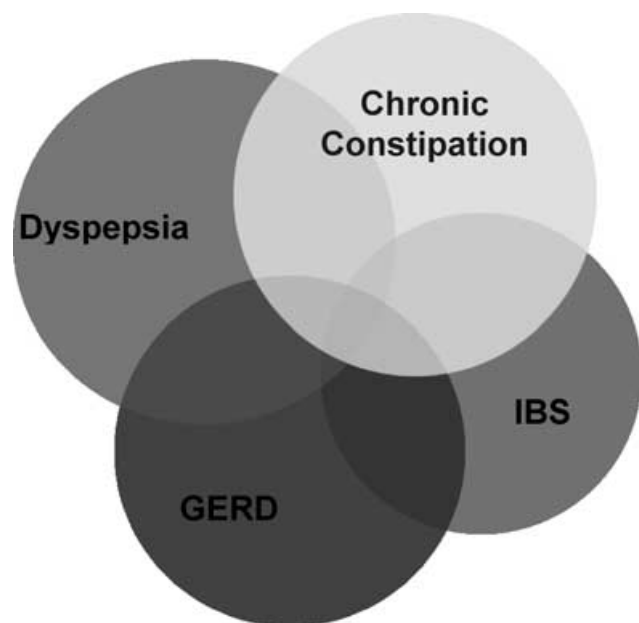
the monograph, our objectives were to review the epidemiology literature systematically about: (a) the prevalence of CC in North America; (b) the age, gender, and socioeconomic status of patients with CC in North America; and, (c) to characterize the natural history of constipation (1).

Ten population-based North American studies (2–11) quantify the prevalence of CC or provide other epidemiologic data about CC in North America. Literature search techniques, study selection criteria, and data analysis are outlined in Section 2.1. In these studies, the diagnosis of CC was made based on self-reports, Rome I or Rome II criteria (Table 2.4.1).

The reported prevalence of CC varied between 2% and 27% (2–11), although most studies estimated prevalence at 10–15 % (Table 2.4.1). Differences in the reported prevalence of CC probably reflect differences in study design (e.g., mailed surveys versus face-to-face interviews) or variation in the symptom-based definitions of CC (e.g., Rome I versus Rome II criteria versus different criteria for self-reports of CC).

Multiple factors were associated with CC. Specifically, women report CC approximately twice as often as do men. Task Force members noted that the greater prevalence of CC in women may arise from the increased prevalence of pelvic floor dyssynergia in women. Also, low socioeconomic grouping (e.g., annual income less than \$20,000), age older than 65 years, and non-White race have been associated with an increased prevalence of CC (1). Task Force members noted that the increasing prevalence of CC with advancing age might reflect the increased prevalence of secondary causes of constipation (e.g., an increased prevalence of Parkinson's disease or diabetes mellitus). There are no definitive data to suggest that the colonic musculature atrophies with advancing age, and, therefore, new onset constipation symptoms in the elderly should be investigated. Task Force members also noted that the increased prevalence of CC in non-White individuals in North America may reflect dietary issues and that this is another area for further research. Finally, the association between CC and low socioeconomic grouping is the exact opposite of IBS, which is associated with higher socioeconomic grouping (12).

CC is frequently associated with other gastrointestinal motility and sensory disorders, including functional dyspepsia, functional heartburn, and GERD (13, 14) (Fig. 2.4.1). In fact, 29% of GERD patients also report CC (14). Given this overlap, Task Force members hypothesized that there may be common pathophysiologic mechanisms (13) for these disorders and that this too is another area for further research.

**Figure 2.4.1.** Overlap between functional GI disorders.

The literature search did not reveal any North American population-based studies about the natural history of CC. One study (15) surveyed the population in Olmsted County, MN, on two separate occasions over 12–20 months. This study indicated that the prevalence of chronic constipation is 17.4% (95% CI: 14.8–20.0%), and 89% of CC patients still had similar symptoms during repeat survey 12–20 months later. The incidence of CC symptoms is approximately four per 100 person-years of follow-up.

Overall, Task Force members noted that the quality and quantity of epidemiologic studies about CC are limited. Appropriately designed studies about the natural history of CC should be completed. Task Force members proposed that additional studies should be performed about the impact of CC on quality of life. Comprehensive epidemiologic studies may determine why certain risk factors, including race, gender, socioeconomic status, and age, are associated with an increased prevalence of CC. Such studies may also identify symptoms that better define sub-types of CC.

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## 2.5 Diagnostic Approach to the Patient with Chronic Constipation Symptoms

*Among CC patients without alarm symptoms or signs, there are inadequate data to make a recommendation about the routine use of flexible sigmoidoscopy, colonoscopy, barium enema, thyroid function tests, serum calcium, and other diagnostic tests (Grade C recommendation). Diagnostic studies are indicated in patients with alarm symptoms and signs which may include hematochezia, weight loss  $\geq 10$  pounds, family history of colon cancer or inflammatory bowel disease, anemia, positive fecal occult blood tests, and the acute onset of constipation in elderly persons (Grade C recommendation). A careful history and physical examination should be performed in order to identify symptoms or signs of organic disorders that may be associated with CC symptoms (e.g., hypothyroidism). Specific diagnostic testing (e.g., thyroid function tests) may be performed in individual patients with additional signs or symptoms of an organic disorder. Routine use of colon cancer screening tools is recommended for all patients  $\geq 50$  yr (Grade C recommendation). Based upon expert opinion, the routine approach to a patient with symptoms of CC without alarm signs or symptoms should be empiric treatment without performance of diagnostic testing. (Grade C recommendation).*

The symptoms of CC may be due to dysfunction of intestinal motility, visceral sensitivity, ano-rectal musculature, or the enteric nervous system. Also, CC symptoms may be secondary to an organic disorder, including metabolic disorders (e.g., hypothyroidism), myopathies (e.g., amyloidosis), neurologic disease (e.g., the Parkinson disease), or medications (e.g., opiates) (1). Numerous diagnostic tests, including laboratory tests (e.g., complete blood count, thyroid function tests, serum calcium) and structural tests of the colon (e.g., colonoscopy, flexible sigmoidoscopy, barium enema), have been recommended to exclude secondary causes of CC symptoms although “data do not exist to strictly evaluate and define the tests that need to be done” (1).

If the pre-test probability of an organic disorder (e.g., hypercalcemia) is similar in patients with CC symptoms and in control patients, then the routine use of additional diagnostic testing for that disorder (e.g., serum calcium) cannot be

**Table 2.5.1.** Specialized Diagnostic Testing in Patients with Chronic Constipation Symptoms (8, 9)

1. *Colon Transit Studies.* The patient swallows a capsule containing 24 radio-opaque markers. Over the following 5 days, the patient should maintain a high fiber diet, but abstain from using laxatives, enemas, or medicines that affect bowel function. On Day 5, the patient undergoes an abdominal plain film. If > 20% of the radio-opaque markers are retained in the colon, then slow-transit constipation is confirmed.
2. *Defecography.* Thickened barium, which approximates the consistency of stool, is inserted into the rectum. The patient then sits on a radiolucent commode. During evacuation of the barium, fluoroscopy is utilized to assess ano-rectal anatomy and structures, including the ano-rectal angle, perineal descent, and any abnormalities. Pelvic floor dyssynergia is diagnosed by the observation of insufficient descent of the perineum (< 1 cm) and less than a normal change in the anorectal angle (< 15 degrees). Rectoceles and intussusceptions also may be diagnosed by this technique. Defecography is operator dependent and has poor reliability.
3. *Anorectal manometry with balloon expulsion.* Provides measurements of the internal and external anal sphincter pressure, relaxation of the internal anal sphincter during rectal distention and straining, and rectal sensation to distention. Appropriate internal anal sphincter relaxation excludes Hirschprung disease. This may be the screening test of choice for outlet obstruction.

recommended. In this portion of the monograph, our objectives were to review the literature systematically to determine: (a) the pre-test probability of underlying organic disorders among patients who present with CC symptoms; and (b) to assess the utility of diagnostic tests (e.g., CBC, serum calcium, thyroid function tests, flexible sigmoidoscopy, colonoscopy, barium enema) to diagnose organic disorders producing CC symptoms. Literature search techniques, study selection criteria, and data analysis are outlined in Section 2.1.

No appropriately designed studies estimate the pre-test probability of organic disorders among patients with CC symptoms or assess the utility of testing to diagnose organic disorders producing CC symptoms. Appropriately designed studies perform a prospective evaluation of a diagnostic test in a consecutive sample of patients with pre-defined symptom criteria. If possible, the diagnosis of an organic disorder is confirmed with a "gold standard" diagnostic test (2–3). In order to define the current state of the literature, Task Force members reviewed retrospective studies of non-consecutive patients with CC symptoms.

No studies examined the utility of laboratory testing (e.g., CBC, serum calcium, thyroid function tests) in the evaluation of patients with CC symptoms. A retrospective study of patients with CC symptoms who underwent colonoscopy (N = 358) or flexible sigmoidoscopy (N = 205) revealed a 1.6% prevalence of colon cancer (including one malignant polyp) and a 14.4% prevalence of adenoma (4). The authors reported that no patient with colon cancer had constipation as the sole indication for colonoscopy or flexible sigmoidoscopy. This study did not include controls to determine if the prevalence of colorectal neoplasia in patients with CC symptoms was similar to an appropriate population of control patients, although the authors suggested that the rates of colon cancer and adenoma in their study were similar to prior studies of screening colonoscopy in asymptomatic patients. Based upon these data, Task Force members concluded that the *routine* use of colonoscopy to exclude organic disorders cannot be endorsed in patients with CC symptoms, although the routine use of colonoscopy for colon cancer screening is recommended for all patients  $\geq$  50 yr. This recommendation is consistent with current recommendations from the American Society for Gastrointestinal Endoscopy (ASGE) (5).

Barium enemas were evaluated in a select group of 62 patients with CC symptoms prior to undergoing an anorectal myectomy and no "organic lesions" or narrowed segments were identified in any patient (6). Another study assessed 791 patients with positive findings on a barium enema, 22% of whom had constipation (7). They reported that the frequency of constipation was nearly identical among patients regardless of whether the barium enema was normal or abnormal (ratio = 0.95).

Among patients with CC symptoms who do not respond to conventional therapy, the diagnosis of slow transit constipation, pelvic floor dyssynergia, and other disorders of ano-rectal musculature may be considered. Diagnosis of these disorders is possible with specialized physiologic and radiologic testing (Table 2.5.1); however, no appropriately designed studies have been performed to determine the utility of routinely performing these tests among patients with CC symptoms. Ano-rectal manometry with balloon expulsion and defecography facilitate diagnosis of outlet obstruction, Hirschprung disease, and pelvic floor dyssynergia. These specialized physiologic and radiologic tests are recommended for patients whose symptoms have not responded to conventional therapies and who complain of excessive straining or the need to use digital manipulation to evacuate stool (8, 9). Colon transit studies, which diagnose slow transit constipation, may be utilized in patients with severe constipation unresponsive to multiple therapies or when surgical treatment of severe, refractory constipation is being considered (8).

Based upon their clinical experience and available evidence, Task Force members did not endorse the *routine* use of a battery of diagnostic tests among patients with CC symptoms. They proposed that the initial approach to patients with CC symptoms should be empiric therapy. Task Force members emphasized that a detailed history and physical examination are needed to identify disorders that may produce CC symptoms. Physicians may selectively utilize specific diagnostic tests (e.g., thyroid function tests) if a patient's history and physical examination suggest an organic disorder (e.g., hypothyroidism) associated with CC symptoms. Alarm symptoms or signs indicate a subset of patients in whom diagnostic tests are indicated (Table 2.5.2). Task Force members acknowledged that there is inadequate evidence to make a



**Table 2.5.2.** Alarm Symptoms/Signs in Patients with Chronic Constipation

1. Hematochezia
2. Family history of colon cancer
3. Family history of inflammatory bowel disease
4. Anemia
5. Positive fecal occult blood test
6. Weight loss $\geq$ 10 pounds
7. Severe, persistent constipation that is unresponsive to treatment
8. New onset constipation in elderly patient without any evidence of a possible primary cause of constipation

This table is not intended as an exhaustive list of all possible alarm symptoms/signs that may indicate the need for additional diagnostic testing.

strong recommendation about the appropriate diagnostic approach to patients with CC symptoms, and they endorsed the execution of properly designed studies about this topic.

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## 2.6 Effectiveness of Bulking Agents in the Treatment of Chronic Constipation

*Psyllium (e.g., Metamucil<sup>®</sup>, Konsyl<sup>®</sup>) increases stool frequency in patients with CC. (Grade B recommendation). There are insufficient data to make a recommendation about the efficacy of calcium polycarbophil (e.g., Perdiem Fiber Therapy<sup>®</sup>, Fibercon<sup>®</sup>), methylcellulose (e.g., Citrucel<sup>®</sup>) and bran in patients with CC (Grade B recommendation).*

Among patients with CC, stools may be deficient in water content. Bulking agents are organic polymers that retain water in the stool. By adding water and additional solid material to stool, these agents may improve CC symptoms.

Several of these agents (e.g., psyllium), undergo bacterial fermentation in the colon thereby producing gas with resultant bloating. Bulking agents available in the United States include psyllium (Metamucil<sup>®</sup>, Konsyl<sup>®</sup>), calcium polycarbophil (Perdiem Fiber Therapy<sup>®</sup>, Fibercon<sup>®</sup>), methylcellulose (Citrucel<sup>®</sup>), and bran. Mechanical obstruction of the esophagus and colon has been reported with bulking agents, and anaphylactic reactions have been reported with psyllium (1). Bulking agents are FDA-approved for the treatment of occasional constipation.

### *Psyllium*

Psyllium husk is the outer coat of the psyllium seed (known in India as ispaghula seed) from the plant *Plantago ovata*. Five RCTs were found (Table 2.6.1), three of which are placebo controlled (2–4). Only one of these was of high quality (4), and it was the only one lasting more than 4 wk. It included only 22 patients and met only 5 of 14 Rome criteria. Two trials compared psyllium with “active” agents, but neither was of high quality (5, 6). The largest trials were low quality (3, 5, 6). In two of the three placebo-controlled trials, psyllium resulted in greater stool frequency, better stool consistency, and greater ease of defecation (3, 4). In the third study, there was no significant increase in stool frequency, and stool consistency and stool weights were not improved (2). When compared with other laxatives, patients taking psyllium noted a higher percentage of normal, well-formed stool and fewer hard stools compared with baseline (5). The incidences of soiling, diarrhea, and abdominal pain also were reduced. Both psyllium and lactulose improved stool frequency and consistency compared with baseline, but there were no significant differences in magnitude of improvement between the lactulose-using patients and psyllium-using patients (6). Overall, these trials display weak study design, including small sample sizes, short study duration ( $\leq$ 14 days), or both. Based on low-intermediate quality RCTs, psyllium appears to improve stool frequency and consistency (Grade B recommendation). There were no statistically significant differences in side effects among psyllium, placebo, and lactulose.

### *Calcium polycarbophil*

Only one trial of calcium polycarbophil is available and it is not placebo-controlled (7). This crossover study in 32 bed-ridden nursing home patients compared Fibercon<sup>®</sup> with psyllium, each taken for 3 wk. It had a quality score of 1. There were no significant differences in stool frequency (7.2 stools/wk vs 7.22 stools/wk), stool consistency, and ease of defecation. Because of the lack of data, it is not possible to make any recommendation about calcium polycarbophil as treatment for constipation. There was no reporting of adverse events in this study, so the frequency of diarrhea or other adverse events with calcium polycarbophil cannot be determined.

**Table 2.6.1.** Trial Characteristics: Psyllium

Trial	Study Type	Treatment	Dose	Control	N	Duration	Outcomes Measured	Quality Score
2 (Cheskin)	Crossover	Psyllium (Konsyl)	24 g/d	Placebo	10	4 wks each arm	SF, SC	3
<i>Result:</i> No significant difference in stool frequency/wk with psyllium compared with placebo (1.3 vs 0.8, respectively; $p > 0.05$ ). No difference in stool weights or stool consistency.								
3 (Fenn)	Parallel	Psyllium (Regulan)	6.4 g sachets (3.6 g psyllium t.i.d.)	Placebo	183	2 wks	SF, SC	3
<i>Result:</i> The median number of formed stools/wk (9 vs 3), loose stools/wk (1 vs 0), and total stools/wk (14 vs 9) was significantly greater with psyllium compared with placebo. A significant decrease in abdominal discomfort (87% vs 46%, respectively; $p < 0.05$ ) and straining (89% vs 48%, respectively; $p < 0.05$ ) was observed.								
4 (Ashraf)	Parallel	Psyllium (Metamucil)	5 gm b.i.d.	Placebo	22	8 wks after 4 wk placebo run-in	SF, SC, EOD	4
<i>Result:</i> Stool frequency/week (3.8 vs 2.9, respectively), stool consistency-Likert scale measurement (3.2 vs 3.8, respectively), and ease of defecation-Likert scale measurement (2.0 vs 2.6, respectively) were significantly better with psyllium compared with placebo.								
5 (Dettmar)	Parallel	Psyllium (Fybogel)	3.5 g b.i.d.	"Other laxatives"	381	4 wks	SF, SC	2
<i>Result:</i> Percentage of normal, well-formed stools and hard stools were significantly improved with psyllium compared with "other laxatives." Incidence of soiling, diarrhea, and abdominal pain was significantly lower with psyllium compared with placebo. No interpretable numbers provided in study results.								
6 (Rouse)	Parallel	Psyllium (Fybogel)	3.5 g b.i.d.	Lactulose 30 mL/d	112	4 wks	SF, SC, SGA	2
<i>Result:</i> Psyllium and Lactulose improved stool frequency/wk (6.5 and 7.5) and stool consistency compared with baseline, but there were no significant differences between psyllium and lactulose. Psyllium was more likely than lactulose to be considered unpalatable (15.7% vs 4.2%, respectively; $p < 0.05$ ).								

SF = stool frequency; SC = stool consistency; EOD = ease of defecation; SGA = subjective global assessment of bowel habits.

### Methylcellulose

Only one study of methylcellulose (Citrucel®) is available (8). This was a parallel design study in which 59 patients took one of three doses of methylcellulose or psyllium for only 10 days after a 1 week placebo run-in period. The quality score was only 2. There were no significant differences in stool frequency, stool consistency or ease of defecation among the treatments. Each one led to improvement compared with the placebo run-in period. Because of the lack of data, it is not possible to make any recommendation about

methylcellulose as treatment for constipation. There was no reporting of adverse events in this study.

### Bran

Three RCTs were found (Table 2.6.2). One trial was placebo-controlled and it had a quality score of 4, with 10 Rome criteria met (9); however, it was a crossover design with only 24 patients and the duration on each arm was only 4 wk. The other two studies were of very poor quality (10, 11) with quality scores of 1.

**Table 2.6.2.** Trial Characteristics: Bran

Trial	Study Type	Treatment	Dose	Control	N	Duration	Outcomes Measured	Quality Score
9 (Badiali)	Crossover	Wheat Bran	6.6 g t.i.d.	Placebo	24	4 wks each arm after 3 wks	SF	4
<i>Result:</i> Wheat bran and placebo increased stool frequency/wk compared with baseline, but there were no significant differences between treatments.								
10 (Anderson)	Parallel	Corn Biscuit or Wheat Bran	10 g/day	No Bran	40	2 wks after 2 wk	SF, SC	1
<i>Result:</i> Corn biscuit and wheat bran increased stool frequency/wk and improved stool consistency compared with baseline. Wheat bran significantly increased stool frequency/wk compared with no treatment (data not shown in study).								
11 (Graham)	Parallel	Wheat Bran	10 g b.i.d.	Corn Bran	10	2 wks	SF, SGA	1
<i>Result:</i> Wheat bran significantly increased stool frequency/wk (data from figure not interpretable). Subjective Global Improvement in bowel function, measured on a Likert scale, favored corn bran (5/5) over wheat bran (0.5).								

SF = stool frequency; SC = stool consistency; SGA = subjective global assessment of bowel habits; Likert scale = 5-point or 7-point scale for assessing severity of specific symptoms (e.g., straining)

In the first study, stool frequency was significantly greater with bran than with placebo if placebo was given first, but not if bran was given first (9). This suggests a placebo run-in effect. Both treatments increased stool frequency compared with the 3-wk baseline period. Other symptoms were not significantly different between bran and placebo. The other two studies were of such low quality that their results are impossible to interpret (10–11). Given the lack of data, it is not possible to make any recommendation about bran as treatment for constipation. There was no reporting of adverse events.

Overall, studies of bulking agents were of sub-optimal design and only one study met as many as 10 Rome criteria for appropriate design of a treatment trial for a functional gastrointestinal disorder (9). Most of the trials had very small sample sizes, were of short duration, and were performed before the advent of what are now the generally accepted criteria for treatment trials in patients with functional disorders. Data from two systematic reviews (12–13) provide conflicting results. One systematic review (12) performed sub-group analysis of bulking agent trials and concluded that bulking agents were more effective than placebo at improving stool frequency, while a more recent meta-analysis (13) combined RCTs of multiple agents (e.g., stimulant laxatives, bulking agents, and osmotic laxatives) and did not find evidence that active agents were better than placebo in trials of 5–12 week duration.

Data on adverse events were reported in only a few trials but, where reported, revealed no statistically significant differences in adverse events identified between the bulking agent studied and the comparator. Nevertheless, bloating and severe adverse events, including esophageal and colonic obstruction and anaphylactic reactions, have been reported with bulking agents (1).

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## 2.7 Effectiveness of Stool Softeners in the Treatment of Chronic Constipation

*There are insufficient data to make a recommendation about the efficacy of stool softeners in patients with CC (Grade B recommendation). Stool softeners may be inferior to psyllium for management of CC symptoms (Grade B recommendation).*

“Stool softeners” are surface-acting agents, that function primarily as detergents (*i.e.*, they allow water to interact more effectively with solid stool, thereby “softening” the stool). Stool softeners available in the United States include docusate sodium (Colace<sup>®</sup>) and docusate calcium (Surfak<sup>®</sup>). Stool softeners are FDA-approved for the treatment of occasional constipation.

There are four RCTs that compare stool softeners with active comparators or placebo in patients with CC (1–4) (Table 2.7). Three of these RCTs demonstrate high quality study design (1, 2, 4), and one of these RCTs (4) had a large sample size, although it also had a placebo run-in period and only treated patients for 2 wk. Two of the RCTs (1–2) were placebo controlled and met 7–8 Rome criteria, although these trials had very small sample sizes. The fourth study had no control group other than “no therapy” (3).

In the placebo-controlled crossover trial of docusate calcium *versus* placebo, there were no differences in stool frequency or consistency (1). In the parallel study of docusate calcium and two doses of docusate sodium *versus* placebo, docusate calcium increased stool frequency (3). No regimen improved stool consistency. The crossover study of docusate sodium *versus* placebo showed significant improvement in stool frequency and subjective global assessment of symptoms with docusate sodium (2). In the comparison of docusate sodium with psyllium, psyllium caused a significant increase in stool frequency compared with docusate sodium during the second week (4). Given the small sample sizes and conflicting results in placebo-controlled trials, it is not possible to make a recommendation about the efficacy of stool softeners as

**Table 2.7.** Trial Characteristics: Stool Softeners

Trial	Study Type	Treatment	Dose	Control	No.	Duration	Outcomes Measured	Quality Score
1 (Castle)	Crossover	DCS	240 mg bid	Placebo	15	3 wks each after 2 wk run-in	SF, SC	4
<i>Result:</i> No significant difference in stool frequency/wk (4.3 vs 4.1, respectively; $p > 0.05$ ) or stool consistency between DCS and placebo.								
2 (Hyland)	Crossover	DSS	100 mg tid	Placebo	34	4 wks each	SF, SGA	4
<i>Result:</i> Significant improvement in percentage of patients with increased stool frequency (1 more stool/wk) and Subjective Global Assessment of Effectiveness with DSS compared with placebo.								
3 (Fain)	Parallel	DCS DSS DSS	240 mg/d 100 mg/d 100 mg/d	None	46	3 wks after 2 wk placebo run-in	SF, SC	3
<i>Result:</i> Significant improvement in stool frequency/wk with DCS compared with placebo (2.83/wks vs 1.75/wks, respectively; $p < 0.05$ ). No significant difference was observed with either dose of DSS. No significant change in stool consistency was observed with any regimen.								
4 (McRorie)	Parallel	DSS	100 mg bid	Psyllium 5.1 gm bid	170	2 wks after 2 wks placebo run-in	SF	5
<i>Result:</i> Significant improvement in stool frequency/wk with psyllium compared with DSS (3.5/wk vs 2.9/wk, respectively; $p < 0.05$ ) during wk 2.								

DSS: docusate sodium (Colace); DCS: docusate calcium (Surfak); SF = stool frequency; SC = stool consistency; SGA = subjective global assessment of bowel habits.

treatment for CC symptoms. There were no statistically significant differences in adverse effects among subjects given stool softeners and placebo.

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## 2.8 Effectiveness of Osmotic Laxatives in the Treatment of Chronic Constipation

*Polyethylene glycol (PEG) is effective at increasing stool frequency and stool consistency in patients with CC (Grade A recommendation). Lactulose is effective at increasing stool frequency and stool consistency in patients with CC (Grade A recommendation). There are insufficient data to make a recommendation about the effectiveness of magnesium hydroxide in patients with CC (Grade B recommendation).*

Osmotic laxatives contain poorly absorbed ions or molecules and create an osmotic gradient within the intestinal lumen, thereby retaining water in the intestinal lumen. Osmotic laxatives available in the United States include lactulose (e.g., Kristalose<sup>®</sup>), polyethylene glycol (e.g., Miralax<sup>®</sup>), and magnesium hydroxide (e.g., milk of magnesia<sup>®</sup>). These agents are FDA approved for the treatment of constipation (e.g., Kristalose<sup>®</sup>) or occasional constipation (e.g., milk of

magnesia<sup>®</sup>). Polyethylene glycol is approved for the treatment of occasional constipation and may be used for 2 wk or less.

Multiple electrolyte abnormalities (e.g., hypermagnesemia, hyperphosphatemia, hypercalcemia, hyponatremia, hypokalemia), hypovolemia, and diarrhea have been reported with these agents, although the precise incidence of these adverse events is unclear (1). Per FDA-approved prescribing information, high doses of polyethylene glycol may produce diarrhea and excessive stool frequency, especially in nursing home patients, and nausea, abdominal bloating, cramping, and flatulence may occur.

### Lactulose

Trial characteristics of the three RCTs of lactulose are shown in Table 2.8.1 (2–4).

All three trials are placebo-controlled, and two trials demonstrate high quality study design (3–4). Only one trial entered a substantial number of patients ( $n = 103$ ) (4). In the first of these studies (2), both lactulose and placebo significantly increased stool frequency compared with baseline values, and the effect of lactulose was numerically greater than the effect of placebo (2). Lactulose, but not placebo, significantly improved stool consistency. In the second trial (3), the mean number of bowel movements/day was significantly greater with lactulose than with placebo and lactulose relieved all assessed symptoms more often than did placebo. Patients in the lactulose group had significantly fewer fecal impactions ( $n = 6$ ) than did patients in the placebo group ( $n = 66$ ). In the third trial, the “success rate” with lactulose (80%) was significantly greater than with placebo (60%) (4). Even though there are only three trials, two are of high quality and the results all favor lactulose. One study reported that significantly more patients experienced abdominal pain with lactulose.



**Table 2.8.1.** Trial Characteristics: Lactulose

Trial	Type	Treatment	Dose	Control	No.	Duration	Outcomes Measured	Quality Score
2 (Bass)	Parallel	Lactulose	60 mL/d	Placebo	24	1 wk after 1 wk baseline	SF, SC	3
<i>Results:</i> Stool frequency/wk increased more with lactulose compared with placebo (4.5/wk vs 2.8/wk, respectively; $p < 0.05$ ). Stool consistency (Likert scale measurement) improved significantly more with lactulose than with placebo (4.3 vs 3.8, $p = 0.01$ ).								
3 (Sanders)	Parallel	Lactulose	30 mL/d	Placebo	47	12 wks after 2 wk baseline	SF, Sxs, FI	4
<i>Results:</i> Stool frequency/day was significantly greater with lactulose compared with placebo (0.6–0.8/d vs 0.5–0.6/d, respectively; $p < 0.05$ ). Fecal impactions were significantly lower with lactulose compared with placebo (6 vs 66, respectively; $p < 0.05$ ). Multiple symptoms of constipation were significantly improved with lactulose compared with placebo.								
4 (Wesselius-De Casparis)	Parallel	Lactulose	15–30 mL/d	Placebo	103	3 wks after 2 wk baseline	“Success rate”	4
<i>Result:</i> “Success rate” was significantly greater for lactulose compared with placebo (80% vs 60%, respectively; $p < 0.05$ ).								

SF = stool frequency; SC = stool consistency; Sxs = miscellaneous CC symptoms, including straining; FI = fecal impaction.

**Polyethylene Glycol**

There are five placebo-controlled RCTs of polyethylene glycol (PEG), and two RCTs comparing PEG and lactulose (Table 2.8.2) (5–11).

Of the five placebo-controlled trials of PEG (4–8), four are high quality by Jadad criteria and four met 8 or more Rome criteria (5–8). A sixth trial compared PEG with lactulose and placebo in patients with opiate-induced constipation (10), and the seventh (a high quality trial) compared PEG and

lactulose (11). Four of the trials were of parallel design (7–9, 11) and four enrolled more than 50 patients (8–11). The study duration was  $\geq 8$  wk in only two trials (7–8).

In the five placebo-controlled trials, PEG resulted in increased stool frequency and improvement in stool consistency compared with placebo (5–9). In the sixth study, both PEG and lactulose produced more “non-hard” stools than did placebo, with PEG producing the loosest stools (10). In the final study, stool frequency was significantly greater with PEG

**Table 2.8.2.** Trial Characteristics: PEG

Trial	Study Type	Treatment	Dose	Control	No.	Duration	Outcomes Measured	Quality Score
5 (Andorsky)	Crossover	PEG (Colyte)	8–16 oz/d	Placebo	32	5 days with 2 day WO	SF, SC	5
<i>Result:</i> Stool frequency significantly improved compared with placebo with either dose of PEG. Stool consistency improved significantly with the 16 oz/d dose of PEG vs placebo.								
6 (Cleveland)	Crossover	PEG (Miralax)	17 g/d in 250 mg	Placebo	23	14 days each after 7 days	SF, SC, EOD	3
<i>Results:</i> Stool frequency (1 BM/d vs 0.5 BM/d, respectively), stool consistency, ease of defecation, cramping were significantly improved with PEG compared with placebo.								
7 (Corazziari)	Parallel	PEG	17.5 g in 250 mL bid	Placebo	48	8 wks after 4 wk placebo RI	SF, SC	5
<i>Result:</i> Stool frequency significantly improved with PEG compared with placebo (4.8/wks vs 2.8/wks, respectively; $p < 0.05$ ). Stool consistency and straining also improved significantly with PEG compared with placebo.								
8 (Corazziari)	Parallel	PEG (Normopeg)	17.5 g in 250 mL bid	Placebo	70	20 wks after 4 wks PEG RI	SF	5
<i>Result:</i> Stool frequency significantly improved with PEG compared with placebo (7.4/wk vs 5.4/wk, respectively; $p < 0.05$ ).								
9 (DiPalma)	Parallel	PEG (Miralax)	17 gm/d in 8 oz	Placebo	151	2 wk after 1 wk baseline	SF, SC, EOD, SGA	4
<i>Result:</i> Stool frequency significantly improved with PEG compared with placebo (4.5/wk vs 2.7/wk, respectively; $p < 0.05$ ). Stool consistency and ease of defecation were significantly improved with PEG compared with placebo.								
10 (Freedman)	Crossover	PEG (Go-Lytely)	240 mL/d	Placebo or Lactulose	57	2 wk each after 1 wk RI	SF, SC, EOD	3
<i>Result:</i> Non-hard stools were significantly more frequent with lactulose or PEG compared with placebo (data from figure).								
11 (Attar)	Parallel	PEG (Movicol)	13 gm in 125 mL bid	Lactulose 10 g bid	99	4 wk	SF	5
<i>Result:</i> Stool frequency was significantly higher with PEG compared with lactulose (1.3/d vs 0.9/d, respectively; $p < 0.05$ ). Straining and overall effectiveness was significantly improved with PEG compared with lactulose.								

SF = stool frequency; SC = stool consistency; EOD = ease of defecation; SGA = subjective global assessment of bowel habits.

compared with lactulose, straining occurred significantly less often with PEG, and overall effectiveness was significantly better with PEG (11). Adverse events were not adequately reported in most trials, and no statistically significant differences in adverse events were reported among patients taking PEG, placebo, or lactulose. Discontinuation of medication because of diarrhea was not reported in any trials. Incidence of diarrhea in PEG-treated patients ranged from 2–40% in individual trials. Per FDA-approved prescribing information, high doses of PEG may be associated with diarrhea and excessive stool frequency, especially in nursing home patients, and nausea, abdominal bloating, cramping, and flatulence may occur. Multiple electrolyte abnormalities (e.g., hypermagnesemia, hyperphosphatemia, hypercalcemia, hyponatremia, hypokalemia), and hypovolemia have been reported with osmotic laxatives (1).

### **Magnesium Hydroxide**

Only one, very low quality trial evaluated magnesium hydroxide in comparison with “laxamucil,” a compound not available in the United States (12). In this crossover study, 64 patients were treated for 8 wk with one treatment and then crossed over to the other treatment. There were 2.8 more defecations and one less bisacodyl dose used over the last 4 wk with magnesium hydroxide. No reporting of adverse events was provided in this trial. Given the poor quality of study design, Task Force members felt that it was not possible to make any recommendation about magnesium hydroxide as treatment for constipation.

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## **2.9 Effectiveness of Stimulant Laxatives in the Treatment of Chronic Constipation**

*There are insufficient data to make a recommendation about the effectiveness of stimulant laxatives in patients with CC (Grade B recommendation).*

Stimulant laxatives include compounds containing senna (e.g., Senokot<sup>®</sup>, ExLax<sup>®</sup>) or bisacodyl (e.g., Dulcolax<sup>®</sup>, Correctol<sup>®</sup>, Carter’s Pills<sup>®</sup>). These agents are FDA approved for the treatment of occasional constipation. The mechanism of their action is believed to involve stimulation of sensory nerve endings upon their contact with colon mucosa, and they may also inhibit water absorption by affecting epithelial transport of water and electrolytes. Abdominal discomfort, electrolyte imbalances, allergic reactions and hepatotoxicity have been reported with these agents (1). Senna-containing compounds also have been associated with melanosis coli. Although cathartic colon (a syndrome characterized by colonic dilatation and loss of haustration) has been reported in patients using stimulant laxatives, this entity has not been reported in long-term users of currently available stimulant laxatives (1). It is arguable if the long-term use of stimulant laxatives induces any permanent injury to either the colonic mucosa or the enteric nervous system (1).

Four RCTs of these compounds were found (Table 2.9) (2–5). There are no placebo-controlled trials of stimulant laxatives, and study design was low quality (1–2 out of 5) in all studies. The comparator agent in two studies is not available in the United States (2, 4). In the first three trials, there was no difference between the stimulant laxative and control laxative in stool frequency or consistency (2–4). In the last study (5), 58% of patients taking lactulose were passing a normal stool by day 7 compared with 42% of patients taking the stimulant laxative. Given the poor quality of study design, it is not possible to make any recommendation about the efficacy of stimulant laxatives for the treatment for constipation. There were no statistically significant differences in adverse events between stimulant laxatives and control agents, although adverse events were not reported adequately in most studies.

**Table 2.9.** Trial Characteristics: Stimulant Laxatives

Trial	Study Type	Treatment	Dose	Control	No.	Duration	Outcomes Measured	Quality Score
2 (MacLennan)	Parallel	Senna	2 tabs/d	Na Picosulfate	50	2 wk	SF, SC	2
<p><i>Results:</i> Stool frequency was similar with senna and sodium picosulphate (4.4/wk vs 5.0/wk). Loose or unformed stools were more common with sodium picosulfate compared with senna (43% vs 21%, respectively; <math>p &lt; 0.05</math>).</p>								
3 (McCallum)	Parallel	Senna (Senokot)	10 mL daily or 3x/wk	Bran 10 gm as 3 biscuits or unrefined	23	3 wk each	SF, SC	1
<p><i>Results:</i> Stool frequency was similar with either bran preparation compared with sennokot (5.6/3 wk and 5.2/3 wk vs 5.8/wk, respectively).</p>								
4 (Rider)	Crossover	Bisacodyl	10 mg/d	Bisoxatin 60 mg/d	51	4 wk each	SF, SC	2
<p><i>Results:</i> Stool consistency and stool frequency was similar with bisacodyl compared with bisoxatin (2.1/d vs 1.7/d, respectively).</p>								
5 (Connolly)	Crossover	“Irritant Laxative”	?	Lactulose 30 mL/d	194	1 wk each and 1 wk without	SC	2
<p><i>Results:</i> Percentage of patients passing normal stools by day 7 was significantly greater with lactulose compared with “irritant” laxative (58% vs 42%, respectively; <math>p &lt; 0.05</math>).</p>								

SF = stool frequency; SC = stool consistency.

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**2.10 Effectiveness of Tegaserod in the Management of Chronic Constipation**

*Tegaserod is effective at improving the frequency of complete spontaneous bowel movements, straining, stool frequency, and stool consistency in patients with CC (Grade A recommendation).*

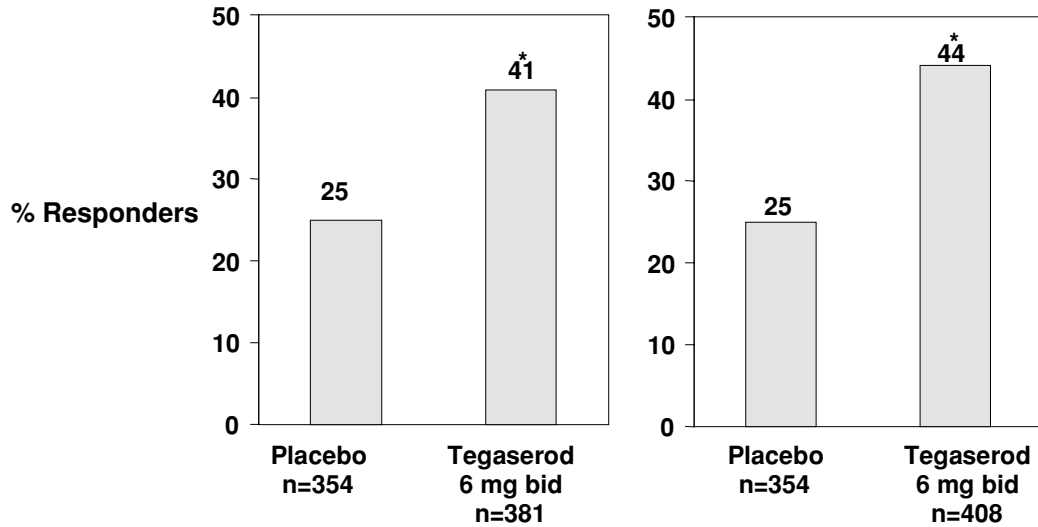
Tegaserod is an agonist of the 5-HT<sub>4</sub> (serotonin) presynaptic receptor. Through its action on 5-HT<sub>4</sub> receptors in the enteric nervous system, tegaserod stimulates the peristaltic reflex, increases colonic motility, decreases visceral hypersensitivity, and facilitates secretion into the colonic lumen (1–3). Tegaserod is FDA-approved for the treatment of IBS with constipation in women and for the treatment of CC in

**Table 2.10.1**

Trial	Study Type	Treatment	Dose	Control	No.	Duration	Outcomes Measured	Quality Score
1	Parallel	Tegaserod	2 mg bid 6 mg bid	Placebo	1264	12 wk	*CSBM SF, SC Global improvement	5
<p><i>Result:</i> Percentage of patients with one additional complete spontaneous bowel movement per week was significantly greater with tegaserod compared with placebo (41% vs 25%, respectively; <math>p &lt; 0.05</math>). Percentage of patients with significant improvement in global satisfaction with their bowel habits was significantly greater with tegaserod compared with placebo (40% vs 30%, respectively; <math>p &lt; 0.05</math>). Stool frequency, stool consistency, and straining (Likert scale measurement) were significantly improved with tegaserod compared with placebo.</p>								
2	Parallel	Tegaserod	2 mg bid 6 mg bid	Placebo	1348	12 wk	*CSBM SF, SC Global Improvement	5
<p><i>Result:</i> Percentage of patients with one additional complete spontaneous bowel movement per week was significantly greater with tegaserod compared with placebo (44% vs 25%, respectively; <math>p &lt; 0.05</math>). Percentage of patients with significant improvement in global satisfaction with their bowel habits was significantly greater with tegaserod compared with placebo (44% vs 31%, respectively; <math>p &lt; 0.05</math>). Stool frequency, stool consistency, and straining (Likert scale measurement) were significantly improved with tegaserod compared with placebo.</p>								

CSBM = complete spontaneous bowel movement.

SF = stool frequency; SC = stool consistency; Global Improvement = subjective global improvement in satisfaction with bowel habits.



\* P < 0.0001. Responder = increase of  $\geq 1$  CSBM/week.  
 Johanson JF, et al. Clin Gastroenterol Hepatol. 2004; 2:796-805.  
 Kamm MA, et al. Am J Gastroenterol. 2005;100:372-82.

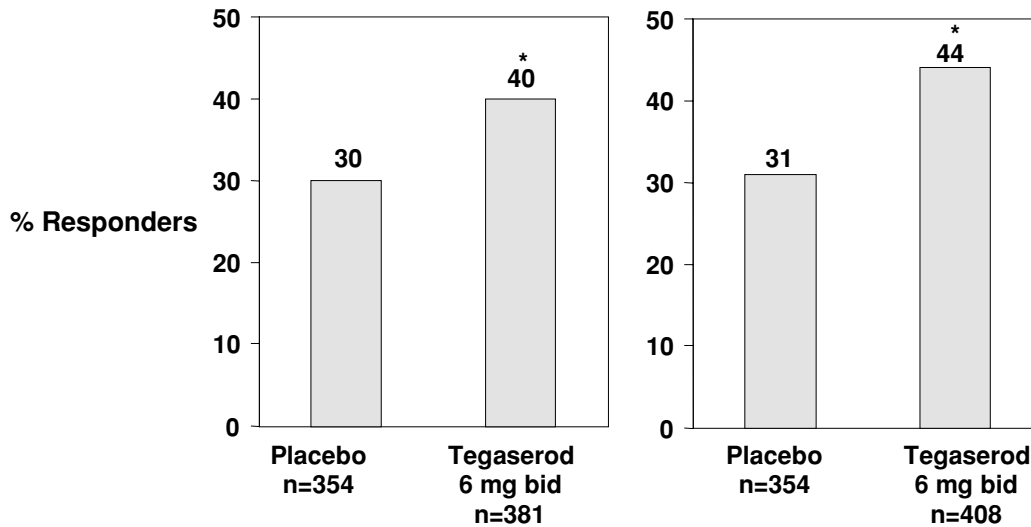
**Figure 2.10.1.** Percentage of responders with an increase in complete spontaneous bowel movements among male and female CC patients <65 years with tegaserod and placebo.

men and women younger than 65 years of age. Diarrhea is associated with tegaserod use in CC patients.

Two RCTs have evaluated the effectiveness of tegaserod in the management of CC (4-5) (Table 2.10.1). Both of these trials were high quality trials (5/5 Jadad criteria and 13/14 Rome criteria), and each trial enrolled over 1000 patients. More than 80% and 85% of the patient populations in these

trials were female and Caucasian, respectively. Patients had a mean age of 46 years, and met modified Rome II criteria for the diagnosis of constipation (4, 5).

Both trials assessed the efficacy of tegaserod in doses of 2 mg BID and 6 mg BID for improvement of complete spontaneous bowel movements (primary objective), stool frequency, stool form, straining, sense of complete evacuation,



\* P < 0.0001. Responder = increase of one point in a five point Likert scale measuring global satisfaction with bowel habits.  
 Johanson JF, et al. Clin Gastroenterol Hepatol. 2004; 2:796-805.  
 Kamm MA, et al. Am J Gastroenterol. 2005;100:372-82

**Figure 2.10.2.** Percentage of responders with improved global satisfaction with their bowel habits among male and female CC patients <65 years with tegaserod and placebo.



and global satisfaction with bowel habits. Based on the prescribed primary end point (*i.e.*, an increase of one complete spontaneous bowel movement/wk), 16–19% more tegaserod-using patients younger than 65 years were responders compared with placebo-using patients younger than 65 years (Fig. 2.10.1). Tegaserod 6 mg BID also increased spontaneous bowel movements (mean increase of 2 bowel movements/wk) and produced significant improvements in stool form and straining. Tegaserod-using patients younger than 65 years were 10–13% more likely to demonstrate improvement in global satisfaction with bowel habits compared with similarly aged placebo-using patients (Fig. 2.10.2).

Tegaserod 6 mg BID was associated with a statistically significant increase in diarrhea compared with placebo (6.6% vs 3.0%), however, there was no statistically significant difference in discontinuation of study drug because of diarrhea, in tegaserod-using patients (<1%) and placebo-using patients. New FDA-approved prescribing information includes a precaution that ischemic colitis has been reported among tegaserod-treated patients. When evaluating this precaution, physicians may wish to consider the following data (6): (1) in clinical trials, no cases of ischemic colitis have been reported among >11,400 tegaserod-treated patients and only one case of probable ischemic colitis has been reported among >2500 placebo-treated patients; (2) in post-marketing surveillance, the rate of ischemic colitis in tegaserod-treated patients is ~10 per 100,000 patient-years of follow-up compared with a rate of ~8 per 100,000 patient-years in the general population and a rate of 44–47 per 100,000 patient-years in the IBS population. Because of these data, the FDA did not issue a “warning,” which is defined as “reasonable evidence of an association between a drug (*e.g.*, tegaserod) and an adverse event (*e.g.*, ischemic colitis)” (6).

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## 2.11 Effectiveness of Herbal Supplements, Alternative Therapies, Lubricants and Combination Laxatives in the Management of Chronic Constipation

*There are insufficient data to make a recommendation about the effectiveness of herbal supplements, lubricants, alternative therapies, or combination laxatives in patients with CC (Grade C recommendation).*

There are no published RCTs examining the efficacy of herbal supplements (*e.g.* aloe) available in the United States in patients with CC. A single RCT examined an aloe and psyllium-based treatment that is not available in the United States (1). This study demonstrated a significant improvement in stool frequency and stool consistency, although the study design was poor and may have led to biased results. There are no published RCTs on the efficacy of mineral oil, a lubricant, in adult patients with CC. RCTs (2–3) have evaluated the efficacy of mineral oil for the treatment of constipation in pediatric populations, and these studies indicate that mineral oil was superior to senna-based laxatives for stool frequency and stool consistency (3), but inferior to osmotic laxatives (2). There are several combination laxatives available, including senna plus psyllium and senna plus docusate, however, there is no RCT evidence examining the efficacy of these products in adult CC patients.

Biofeedback has been examined in multiple trials as a therapy for pelvic floor dyssynergia or outlet-type constipation (4), however, there are no placebo-controlled or sham-controlled randomized trials of these therapies in adult CC patients. No biofeedback technique (*e.g.*, peri-anal EMG biofeedback, intra-anal EMG biofeedback, balloon defecation training, intrarectal balloon distention training) has proved to be consistently more effective than another biofeedback technique in an appropriately designed study. Available studies (4) indicate that biofeedback improves physiologic outcomes (*e.g.*, propulsive force of evacuation) and clinical outcomes (*e.g.*, stool frequency) compared with baseline data.

Given the absence of RCT data in adults with CC, Task Force members concluded that these data were inadequate to make a recommendation about the efficacy or safety of these therapies.

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**Potential Conflicts of Interest Reported by Members  
of the ACG Functional GI Disorder Task Force**

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