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 ≥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 ≥25% of bowel movements, and/or <three 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
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 ≥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 ≥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®, Konsyl®) 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®, Fibercon®), methylcellulose (e.g., Citrucel®), 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®) and docusate calcium (e.g., Surfak®). 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. 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®) 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®, Ex-lax®) or bisacodyl (e.g., Dulcolax®, Correctol®, Carter’s Pills®) 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**