Digestion

Guidelines

Digestion
DOI: 10.1159/000540912

Received: June 21, 2024
Accepted: August 10, 2024
Published online: August 19, 2024

Evidence-Based Clinical Guidelines for Chronic Constipation 2023

Eikichi Ihara[a, b] Noriaki Manabe[a] Hidenori Ohkubo[a] Naotaka Ogasawara[a] Haruei Ogino[a] Kazuki Kakimoto[a] Motoyori Kanazawa[a] Hidejiro Kawahara[a] Chika Kusano[a] Shiko Kuribayashi[a] Akinari Sawada[a] Tomohisa Takagi[a] Shota Takano[a] Toshihiko Tomita[a] Toshihiro Noake[a] Mariko Hojo[a] Ryota Hokari[a] Tatsuhiro Masaoka[a] Tomohiko Machida[a] Noboru Misawa[a] Yoshiyuki Mishima[a] Hiroshi Yajima[a] Sayuri Yamamoto[a] Hiroshi Yamawaki[a] Tatsuya Abe[a] Yasumi Araki[a] Kunio Kasugai[a] Takeshi Kamiya[a] Akira Torii[a] Atsushi Nakajima[a] Koji Nakada[a] Shin Fukudo[a] Yasuhiro Fujiwara[a] Hiroto Miwa[a] Hiromi Kataoka[a] Akihito Nagahara[a] Kazuhide Higuchi[a]

[a]Guidelines Committee for Creating and Evaluating the "Evidence-Based Clinical Guidelines for Chronic Constipation 2023, The Japanese Gastroenterological Association, Bunkyo-ku, Japan; [b]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Keywords
Guidelines · Chronic constipation · Definition · Functional constipation · Constipation-predominant irritable bowel syndrome

Abstract
The Japan Gastroenterological Association published the first version of its clinical guidelines for chronic constipation 2023. Based on the latest evidence, these guidelines describe the definition, classification, diagnostic criteria, diagnostic testing methods, epidemiology, pathophysiology, and treatment of chronic constipation. They include flowcharts for both diagnosis and treatment of chronic constipation. In the treatment of chronic constipation, the first step involves differentiating between secondary forms, such as organic disease-associated constipation, systemic disease-associated constipation, and drug-induced constipation. The next step is to determine whether the chronic constipation stems from a motility disorder, a form of primary chronic constipation. For functional constipation and constipation-predominant irritable bowel syndrome, treatment should be initiated after evaluating symptoms like reduced bowel movement frequency type or defecation difficulty type. The first line of treatment includes the improvement of lifestyle habits and diet therapy. The first drugs to consider for oral treatment are osmotic laxatives. If these are ineffective, secretagogues and ileal bile acid transporter inhibitors are candidates. However, stimulant laxatives are exclusively designated for as-needed use. Probiotics, bulk-forming laxatives, prokinetics, and Kampo medicines, for which

karger@karger.com
www.karger.com/dig

Correspondence to:
Eikichi Ihara, ihara.eikichi.167@m.kyushu-u.ac.jp

there is insufficient evidence, are considered alternative or complementary therapy. Providing the best clinical strategies for chronic constipation therapy in Japan, these clinical guidelines for chronic constipation 2023 should prove useful for its treatment worldwide.

Introduction

Chronic constipation is a common disease that not only reduces quality of life (QOL) and social labor productivity but has recently been shown to be associated with long-term prognosis, leading to its recognition as an important disease [1, 2]. In Japan, the following treatments have been approved for chronic constipation therapy (excluding constipation due to organic diseases): the intestinal secretagogues lubiprostone and linaclotide; the ileal bile acid transporter (IBAT) inhibitor elobixibat; and the osmotic laxatives macrogol 4000 and lactulose preparations. For general clinical practice, it was necessary to create the guidelines promptly to incorporate new knowledge and data into chronic constipation therapy. Consequently, in January 2021, the Japan Gastroenterological Association (JGA) decided to create clinical guidelines for chronic constipation. Here we discuss the first version of JGA Evidence-Based Clinical Guidelines for Chronic Constipation 2023. The guidelines were positively evaluated with the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool [3].

Scope and Objective

These guidelines primarily aim to provide information that aids in decision-making regarding treatment policies and improving the QOL for patients with the common disease of chronic constipation. Accordingly, these guidelines organize and interpret currently available evidence and provide recommendations for making appropriate clinical decisions, based on patient values. Furthermore, these guidelines are intended for physicians and for health care workers, patients, and their families involved in chronic constipation therapy, facilitating their understanding of treatment protocol. By sharing the information contained in these guidelines, our goal is to provide a resource that will help promote mutual understanding among medical professionals, patients, and their families regarding the treatment of chronic constipation. The Guideline Development Committee decided to classify the clinical questions as follows:

1. Background Question (BQ): for issues about which the conclusion is already clear, and about which past guidelines are in 100% agreement.
2. Clinical Question (CQ): major clinical issues. Questions that can determine recommendations and evidence-based standards through comprehensive literature searches, and that influence the direction of medical treatment.
3. Future Research Question (FRQ): issues for which recommendations and evidence levels cannot be determined through a comprehensive literature search (sufficient evidence is not available for future research topics).

A total of 47 questions were formulated for these guidelines: 15 CQs, 2 FRQs, and 30 BQs. The completed questions were categorized as follows: four addressed the definition, classification, and diagnostic criteria (1 CQ, 1 FRQ, 2 BQ); four addressed epidemiology (4 BQ); ten addressed pathophysiology (4 CQ, 6 BQ); nine addressed diagnostic testing (4 CQ, 5 BQ); and twenty addressed medical therapy (6 CQ, 1 FRQ, 13 BQ).

Creation Process

An evidence search was performed using a systematic method described in a previous report [4]. In short, we searched the PubMed electronic database for articles published in English from January 1983 to September 2021, and the Igaku Chuo Zasshi (ICHUSHI) database for articles published in Japanese. The evidence selection criteria were set as follows: initial assessment A – systematic review, meta-analysis, or randomized controlled trial (RCT); initial assessment C – cohort study, or case-control study; initial assessment D – case series, case report, and expert opinion. Multiple articles were gathered from the literature and their evidence levels ranked based bias risk and specific strengths. The quality of evidence was evaluated as follows: A for high-quality evidence, B for moderate-quality evidence, C for low-quality evidence, and D for very low-quality evidence. Subsequently, the strength of the recommendations was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [5, 6]. The strength of the recommendation was evaluated on four items: (1) certainty (strength) of evidence, (2) patient wishes, (3) benefit and harm, and (4) cost evaluation. Consensus was reached through voting using a modified Delphi method, with decisions requiring 70% or more for approval. If a conclusion could not be reached in the first round, the results were made public, and the voting was repeated after discussions considering the medical landscape in Japan. We determined recommendation strength as either a strong recommendation or objection, or a weak

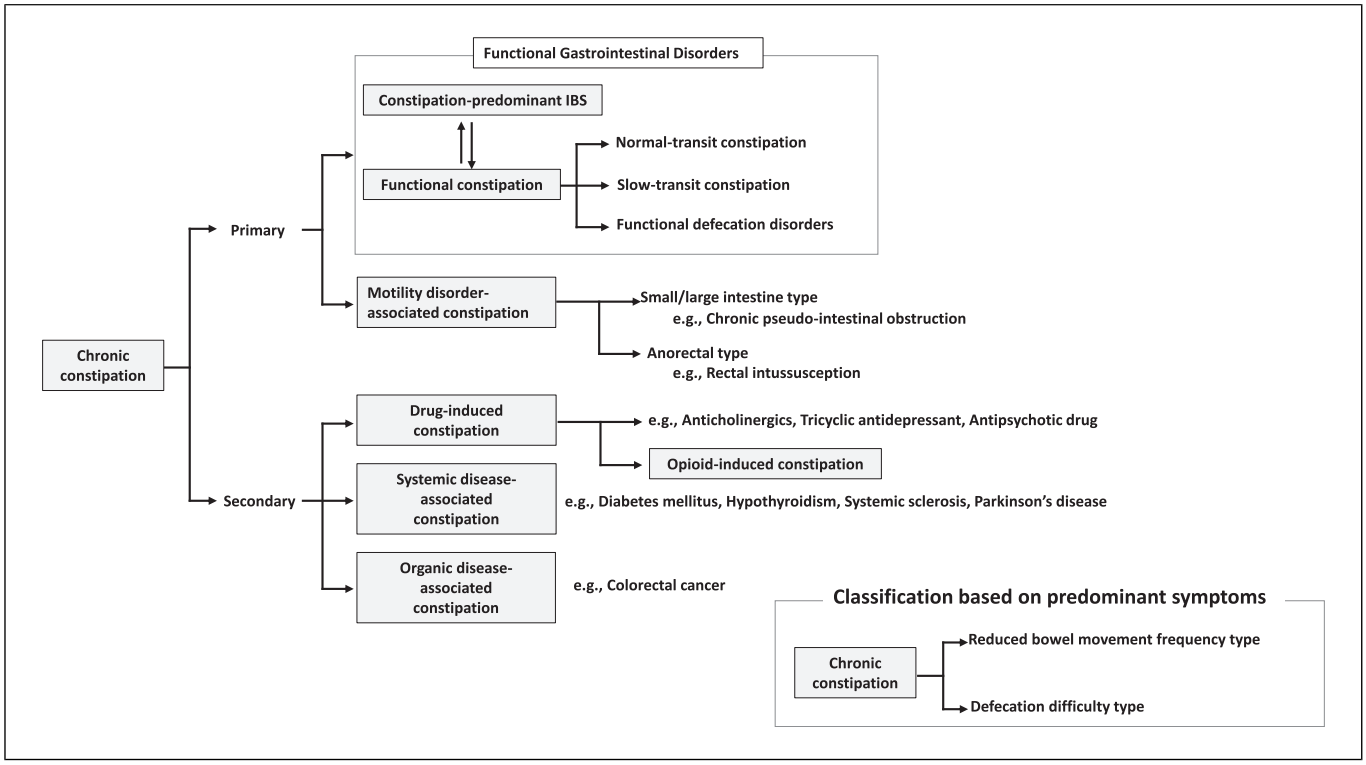

Fig. 1. Classification of chronic constipation. Chronic constipation is classified into primary and secondary constipations. Primary constipation includes functional constipation, constipation-predominant IBS, and motility disorders (small/large intestine type and anorectal type). Secondary constipation includes drug-induced constipation (including OIC), systemic disease-associated constipation, and organic disease-associated constipation. From the viewpoint of symptoms, chronic constipation is classified into "reduced bowel movement frequency type" and "defecation difficulty type." IBS, irritable bowel syndrome.

recommendation or objection, and created evidence-based statements and explanations for each CQ. After the final draft of the guidelines was evaluated by the guideline evaluation committee and modified, it was disclosed to the members from JGA, the Japanese Society of Gastroenterology, the Japan Gastroenterological Endoscopy Society, and the Japan Society of Coloproctology. Furthermore, through discussions on public comments, the current guidelines were completed.

Main Text of the Japanese Chronic Constipation Guidelines

Definition, Classification, and Diagnostic Criteria of Chronic Constipation

CQ1-1. How is constipation defined? Furthermore, how is chronic constipation defined?

- Constipation is defined as "a condition characterized by one or both of the following: retention of feces that should have been excreted from the colon, resulting in lumpy or hard stools and decreased frequency of spontaneous bowel movements; and/or experiencing frustration during defecation leading to excessive straining, sensation of incomplete evacuation, sensation of anorectal obstruction or blockage, and difficulty in defecating."
- Chronic constipation is defined as "a pathophysiology where continued constipation interferes with daily life and potentially causes a variety of diseases."

Recommendation: n.a.

Evidence level: B

Comment: Constipation comes in two forms: either stool produced in the colon cannot be properly transported to the rectum or stool in the rectum cannot be properly excreted. Constipation is a condition in which colonic motility dysfunction prevents feces from being properly transported to the rectum, resulting in lumpy, hard stools, and a decrease in the frequency of bowel movements. The feeling of being unable or inadequately able to appropriately defecate as a result of the anorectal functional abnormality leads patients to

Table 1. Diagnostic criteria for chronic constipation based on Rome IV criteria with modifications

1. Diagnostic criteria for "Constipation"
Must include 2 or more of the following
Constipation-related quantitative signs
QS1 Lumpy or hard stools (BSFS 1–2) more than one-fourth (25%) of defecations
QS2 Fewer than 3 spontaneous bowel movements per week
Defecation-related subjective symptoms
SS1 Straining more than one-fourth (25%) of defecations
SS2 Sensation of incomplete evacuation more than one-fourth (25%) of defecations
SS3 Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations
SS4 Manual maneuvers to facilitate more than one-fourth (25%) of defecations
2. Diagnostic criteria for "Chronic"
Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
In general clinical practice, the application of these criteria is left to the discretion of the attending doctor
Lacy BE 2016 [11].

experience sensations of straining, sensations of incomplete evacuation, sensations of anorectal obstruction, and difficulty in defecating [7–9]. Chronic constipation, however, is a condition requiring medical intervention because the continuous state of constipation causes symptoms that affect activities of daily life, including schoolwork, employment, and sleep, and can cause various diseases beyond the gastrointestinal tract, including increased risk of onset of coronary heart disease [2] and neurodegenerative disease [10]. We believe it is significant that the definition of chronic constipation states that it reduces QOL and labor productivity and has the potential to affect long-term prognosis.

BQ1-1. How is chronic constipation classified?

- For primary constipation, chronic constipation is classified into functional constipation, constipation-predominant irritable bowel syndrome (IBS-C), and motility disorders (small/large intestine type and anorectal type).
- For secondary constipation, chronic constipation is classified into drug-induced constipation (including opioid-induced constipation [OIC]), systemic disease-associated constipation, and organic disease-associated constipation. From the viewpoint of symptoms, chronic constipation is classified into "reduced bowel movement frequency type" and "defecation difficulty type."

Comment: Disorders of gut-brain interaction (DGBI, former functional gastrointestinal disorders) that cause chronic constipation are functional constipation and IBS-C, which can be considered diseases on a continuous spectrum [11]. In these guidelines, constipation caused by gastrointestinal motility disorders, such as chronic intestinal pseudo-obstruction and rectal intussusception, are classified as motility disorders (small/large intestine type and anorectal type), and further classified along with DGBI as a primary constipation. Secondary constipation is classified into drug-induced constipation, such as OIC; systemic disease-associated constipation, as from diabetes mellitus and sclerosis; and organic disease-associated constipation, as with colorectal cancer. Functional constipation and IBS-C are classified into normal-transit constipation or slow-transit constipation (STC), and functional defecation disorders may coexist with either of them [11] (Fig. 1).

BQ1-2. What are the diagnostic criteria for chronic constipation?

Chronic constipation is diagnosed according to Rome IV criteria by assessing constipation-related quantitative signs (stool form, frequency of bowel movements) and defecation-related subjective symptoms (sensations of straining, sensation of incomplete evacuation, sensations of anorectal obstruction/blockage, and manual assistance required).

Comment: The diagnostic criteria for chronic constipation align with the definition in the Rome IV criteria [11]. However, these guidelines take a unique approach by classifying the six items proposed in the Rome IV criteria into two groups: constipation-related quantitative signs (stool form and frequency of bowel movements) and defecation-related subjective symptoms (anger, sensation of incomplete evacuation, sensation of anorectal obstruction/difficulty, manual assistance required). If two or more of the six items are present, constipation is

diagnosed. While constipation-related quantitative signs indicate "feces that should have been excreted become stuck in the colon, resulting in lumpy or hard stools and decreased frequency of spontaneous bowel movements," defecation-related subjective symptoms pertain to the "feeling of frustration during defecation leading to excessive straining, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, and difficulty in defecating." The academic criteria for a chronic diagnosis based on the Rome IV criteria are that the patient has had symptoms for 6 months and has met the criteria for constipation for the past 3 months. However, the application of these criteria is left to the discretion of the attending doctor in general clinical practice (shown in Table 1).

FRQ1-1. How is refractory chronic constipation defined?

While there is no official definition, the current standard is "chronic constipation that does not show sufficient improvement despite appropriate treatment based on pathophysiology."

Comment: No specification exists in the Rome criteria, and currently, there is no official definition. One study has defined it as "inadequate improvement in constipation evaluated with an objective scale despite adequate therapy (i.e., pharmacological and/or behavioral) that is based on the underlying pathophysiology of constipation," [12]. However, in a recent meta-analysis, the authors consider "suboptimal response to management" to be "refractory" but conclude there is no clear "consensus on the choice of drug, order of usage, and dosage or treatment duration" [13]. In the field of pediatrics, guidelines from ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) and NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition) define "intractable constipation" as "Constipation not responding to optimal conventional treatment for at least 3 months" [14].

Epidemiology

BQ2-1. What is the prevalence of chronic constipation?

The prevalence of chronic constipation, including functional constipation and IBS-C, is estimated to be approximately 10–15%, although there are variations.

Comment: An internet survey conducted on 10,000 ordinary people in Japan between the ages of 20 and 69 found the prevalence of chronic constipation to be 4.4% according to Rome IV criteria, and 38% according to the criteria in the chronic constipation guidelines 2017 [15]. A large-scale internet survey (n = 54,127) using Rome IV criteria conducted simultaneously in 33 countries found the prevalence of functional constipation to be 11.7% (95% CI: 11.4–12.0), while in Japan it was 16.6% (95% CI: 15.1–18.0) [16]. Furthermore, a meta-analysis using 45 studies (n = 275,260) revealed the prevalence of functional constipation to be 10.4% (95% CI: 6.5–14.9) using Rome III criteria and 10.1% (95% CI 8.7–11.6) using Rome IV, with a higher prevalence among women [17]. The prevalence varies by country and region and by the diagnostic criteria used. The study stated that it is necessary to consider factors such as the environment, ethnicity, diet, and genetics.

BQ2-2. What is the risk of onset of chronic constipation?

Background factors and risk of onset for chronic constipation include: gender (female), decreased physical activity, low subjective health, certain underlying diseases (such as mental illness or neurological disease), history of abdominal surgery, and certain drugs.

Comment: Chronic constipation is more common in women, with a global systematic review reporting a female/male ratio of 2.22 [18]. Moreover, multiple epidemiological surveys have shown that decreased physical activity [19] and a history of abdominal surgery in the anorectal area or gynecological area increase the risk of developing chronic constipation [20–23]. Moreover, it has been shown to be associated with certain underlying diseases, aging, and certain drugs [24]. However, there is currently a lack of evidence regarding its relationship with obesity, dietary habits, such as reduced dietary fiber and water intake, and socioeconomic status, such as income and education levels.

BQ2-3. Does chronic constipation decrease QOL?

Chronic constipation reduces QOL.

Comment: SF-36 and SF-12, two comprehensive scales for health-related QOL, report that patients with chronic constipation experience decreased QOL compared to that in healthy people [25]. A large-scale survey of Japanese people using a database reported that the QOL and labor productivity of patients with chronic constipation declined significantly, leading to an annual economic loss of approximately 1.22 million yen [26]. The Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire, a disease-specific measure for chronic constipation whose Japanese version had its reliability and validity verified [27], revealed a relationship between PAC-QOL and

stool form, with type 4 of the Bristol Stool Form Scale (BSFS) showing the highest QOL score [28].

BQ2-4. Does chronic constipation affect long-term prognosis?

Because chronic constipation is associated with an increased risk of cardiovascular disease and death and an increased risk of onset for Parkinson's and renal disease, there is a possibility it could affect long-term prognosis.

Comment: Excessive "straining" during defecation can put a load on the circulatory system [29]. Additionally, in chronic constipation, dysbiosis causes changes in intestinal metabolites, which may be involved in the development of various diseases [30]. Although constipation has been reported to increase the risk of cardiovascular events such as coronary artery disease, angina pectoris, myocardial infarction, coronary revascularization procedures, and ischemic cerebrovascular accident [2, 31, 32], there have been conflicting results [33]. Patients with constipation are at increased risk of developing Parkinson's disease, chronic kidney disease, and end-stage renal disease [10, 34]. Constipation may increase the risk of developing colorectal cancer because bile acids, which are carcinogenic, have a prolonged contact with the intestinal mucosa [35]. However, the contribution of chronic constipation to the incidence of colorectal cancer is controversial, given the conflicting results reported [36].

Pathophysiology

CQ3-1. Is small intestinal function involved in the pathophysiology of chronic constipation?

Small intestine dysmotility can be observed in patients with chronic constipation; however, such dysmotility is unlikely to affect small intestinal transit time. Small intestine dysmotility may be partly involved in the pathophysiology of chronic constipation.

Recommendation: n.a.

Evidence level: C

Comment: Studies using small intestinal manometry have shown that, compared to that in healthy participants, patients with STC often have abnormal migrating motor complexes in the proximal jejunum and terminal ileum [37–40]. In a prospective study using a wireless motility capsule, Rao et al. [41] showed that the small intestine transit time of patients with STC was approximately 4 h, which was the same as that of healthy participants. However, a study using scintigraphy showed that the small intestinal transit time of patients with STC was longer than that of healthy participants [42]. A study using radiopaque markers demonstrated that approximately 20% of both patients with constipation and patients with diarrhea had prolonged small intestinal transit time [43]. This finding suggests that small intestinal transit time may be involved in the pathophysiology of constipation, but further research is needed.

BQ3-1. Is colonic function involved in the pathophysiology of chronic constipation?

Colon dysfunction, represented by changes in colonic sensation and decreased colonic motility, is involved in the pathophysiology of chronic constipation.

Comment: The colon absorbs water and sodium, producing stool and transporting it to the rectum. The sensation and movement of the colon facilitated by the vagus nerve and sacral parasympathetic outflow is integral in this process. Colonic motor activity consists of segmental contractions and propagated contractions. These coordinated movements regulate absorption and transport [44]. Additionally, periodic rectal motor activity is observed in the rectosigmoid portion of the rectum, which increases during sleep and prevents stool and intestinal gas from flowing into the rectum. When propagated contractions increase after waking or eating, stool flows into the rectum and promotes defecation [44]. Impairment of any of these steps will cause constipation. After accounting for the pathophysiology, constipation is classified as DGBI based on colorectal transit time into normal-transit constipation or STC. Functional defecation disorders may coexist with either of them. However, it has been reported that the above activities and responses are significantly decreased in STC, in particular [44].

BQ3-2. Is anorectal function involved in the pathophysiology of chronic constipation?

Anorectal dysfunction, including decreased rectal sensation and dyssynergic defecation, is involved in chronic constipation.

Comment: Transporting feces stored in the sigmoid colon to the rectum expands the rectal wall, and when this stimulation is transmitted to the cerebral cortex via the sacral nerve, the urge to defecate is felt. Additionally, due to the rectoanal reflex caused by the stretching of the rectal wall by feces, a portion of the rectal contents approaches the dentate line, where the rectal contents are sensed and the characteristics (solid, liquid, gas) are discerned by a sampling function. This capacity to perceive this sequence leads to the action of defecation [45]. At this point, as the rectum itself responsively contracts to defecate, simultaneously the diaphragm and trunk muscles voluntarily contract to increase intra-abdominal pressure, which in turn increases intra-rectal pressure and

relaxes the pelvic floor muscles (puborectalis and external anal sphincter) to excrete stool. This unconscious movement, involving contraction of the trunk muscles and the relaxation of the pelvic floor muscles, is called rectoanal coordination. Impairment of any of these anorectal functions will inhibit fecal excretion from the rectum.

CQ3-2. Is rectal sensation (urge to defecate) involved in the pathophysiology of chronic constipation?

Increased rectal sensory threshold (loss of urge to defecate) is involved in the pathophysiology of chronic constipation.

Recommendation: n.a.

Evidence level: A

Comment: A large-scale internet survey showed that many patients with chronic constipation have lost the urge to defecate [46]. Additionally, a study of a large number of patients with intractable functional constipation observed rectal hypesthesia in 25% of patients, which was shown to be associated with the severity of constipation [47]. To comfortably excrete feces, the appropriate sensation of fecal masses that have been transported to the rectum by colonic movements (= feel the urge to defecate) and quick performance of defecation are essential. Hence, the rectal sensory threshold must be normal during the final stage of defecation [48].

BQ3-3. Are there any underlying diseases that are secondary causes of chronic constipation?

Multiple underlying diseases can cause chronic constipation.

Comment: Multiple underlying diseases can cause chronic constipation. Among endocrine/metabolic diseases, diabetes mellitus and hypothyroidism have been reported to cause chronic constipation [49]. Among mental illnesses, chronic constipation is reported to be common in depression and schizophrenia [50]. As for neurodegenerative diseases, Parkinson's disease has been reported to be associated with chronic constipation [51]. Systemic sclerosis frequently causes constipation, requiring caution due to decreased small intestinal peristalsis which may result in chronic intestinal pseudo-obstruction, a disease associated with a poor prognosis. Furthermore, patients on dialysis are reported to have a high incidence of constipation [52].

BQ3-4. Does aging contribute to chronic constipation?

Aging contributes to chronic constipation, with the prevalence of chronic constipation increasing with age. The causative factors are manifold, including aging-related decreases in the intestinal smooth muscle contractility and neurological activity responsible for peristalsis, decreased rectal sensation, and altered anorectal function, along with changes in living environment.

Comment: With aging, there is a decrease in the neurotransmitters responsible for intestinal peristalsis and decrease in intestinal smooth muscle contractility due to acetylcholine. This age-related decrease in responsiveness of intestinal smooth muscle contractility to acetylcholine results from impairment of smooth muscle intracellular signal transduction pathways [53]. Additionally, it has been reported that nerve cells of Auerbach's plexus degenerate with age, with a tendency for a decrease in the number of normal ganglia [54]. Concerning anorectal function, the rectal sensation threshold tends to be higher in the older adults than that in younger people, suggesting that impairment of rectal sensation progresses with age, leading to onset of chronic constipation.

BQ3-5. Are there any drugs that cause chronic constipation?

Many drugs cause chronic constipation.

Comment: Numerous drugs cause chronic constipation, with anticholinergic drugs, psychotropic drugs, and opioids being popular examples. Among these, opioids frequently cause constipation by suppressing intestinal smooth muscle contractions, peristalsis, and intestinal fluid secretion [55–58]. Parkinson's disease can induce constipation due to autonomic neuropathy; however, caution is required as anti-Parkinson's drug therapy can exacerbate constipation by increasing dopamine activity and decreasing acetylcholine activity [59, 60]. Other drugs that can cause constipation include anticancer drugs such as plant alkaloids and taxanes, calcium channel blockers, diuretics, aluminum-containing gastric antacids, adsorbents, and anion exchange resins [61–64].

BQ3-6. Do psychological abnormalities contribute to the pathophysiology of chronic constipation?

Many patients with chronic constipation have higher scores for psychological abnormalities such as depression and anxiety than those in healthy people, suggesting that psychological abnormalities are involved in the pathophysiology of chronic constipation.

Comment: Patients with chronic constipation have been shown to have psychological abnormalities such as depression and anxiety [65, 66]. A systematic review showed that the decline in QOL due to chronic constipation was more pronounced on psychological items

than on physical items [67]. Another study reported that patients with functional constipation have significantly higher values on the Self-Rating Anxiety Scale (SAS) [68]. An internet survey conducted in Japan using the BSFS revealed that participants with stool forms other than type 4 had higher anxiety and depression scores than those with type 4 [28]. Furthermore, the severity of constipation has been demonstrated to correlate with the severity of depression and negatively impact both mental and physical QOL [69].

CQ3-3. Are intestinal bacteria involved in the pathophysiology of chronic constipation?

Intestinal bacteria are involved in the pathophysiology of chronic constipation.

Recommendation: n.a.

Evidence level: C

Comment: Studies comparing the intestinal bacteria of patients with chronic constipation (functional constipation) and healthy adults have shown that there are significant differences in the balance of intestinal bacteria between the two groups [70]. However, there is variability in the occupancy rate of specific intestinal bacteria varies across studies, and no consensus has been reached. The mechanisms through which intestinal bacteria are believed to contribute to chronic constipation include (1) the composition of intestinal bacteria contributing to stool hardness [71]; (2) short-chain fatty acids produced by intestinal bacteria influencing nerve activity to stimulate production of polypeptide YY [72], and impacting enterochromaffin cells to enhance serotonin production, which regulates intestinal motility [73]; (3) involvement of intestinal bacteria in bile acid metabolism, affecting enterochromaffin cells to induce serotonin and calcitonin gene-related peptides, which in turn affects intestinal motility [74, 75]; (4) intestinal bacteria are involved in intestinal permeability [76]; and (5) methane-producing bacteria contribute to intestinal motility [77]. Furthermore, given that studies have reported symptoms can be improved by treatments related to intestinal bacteria, including symbiotic [78], prebiotics (BQ5-02), probiotics (BQ5-03), and fecal transplants [79], intestinal bacteria are likely to play a role in the pathophysiology of chronic constipation.

CQ3-4. What functional gastrointestinal disorders overlap with chronic constipation?

Functional dyspepsia (FD) and gastroesophageal reflux disease (GERD) can overlap with chronic constipation.

Recommendation: n.a.

Evidence level: B

Comment: A multicenter study conducted by the Rome Committee, using a questionnaire based on the Rome IV criteria, reported that 22% of functional constipation cases were complicated by FD [80], while a Japanese study reported that functional constipation is a complication in 13.8% of FD cases [81].

A Japanese study using an internet survey on complications of chronic constipation reported a complication rate of GERD as 56.7%, while 26% of these participants used oral laxatives [15]. Many studies from other countries reported about the complications of chronic constipation, FD, and GERD [82–84]. These findings suggest an association between FD and GERD with chronic constipation.

Diagnostic Tests

BQ4-1. What medical questionnaires are useful for determining the treatment approach for chronic constipation?

Several questionnaires have been devised for chronic constipation therapy, but it is unclear which one is useful.

Comment: Several types of medical questionnaires have been developed in Europe and America [85, 86], a few of which have been translated into Japanese [87]. However, it is difficult to ascertain the commonly used type of questionnaire in general clinical practice in Japan. Any general comparison between the various questionnaires is complicated by the fact that their intended uses are different, and the characteristics of chronic constipation in Westerners and Japanese people are not necessarily the same. Going forward, the development of questionnaires is suited to the realities facing Japanese people.

BQ4-2. What physical examinations are useful for determining the treatment approach for chronic constipation?

Physical examinations useful for treating chronic constipation include abdominal examination (visual examination, auscultation, percussion, and palpation) and rectoanal examination (visual examination and digital rectal examination).

Comment: Abdominal examination (visual examination, auscultation, percussion, palpation) enable physicians to assess abdominal swelling, variation in loudness of intestinal peristaltic sounds, presence and location of tympanic sounds, and tenderness or the presence of masses. If there are symptoms of difficulty in defecating, perform a visual examination of the rectum to check for anal prolapse and stool leakage, and then perform a manual anorectal examination. Subsequently, examine

the patient for the presence of anal stenosis, fecal masses, lumps, and blood adhesion. The contractile function of the internal anal sphincter can be determined by the tightness of the anus at rest, while the contractile function of the puborectalis and external anal sphincter can be determined by the tightness of the anus during contraction. Moreover, it is possible to detect the presence of paradoxical puborectalis contractions, in which the anal canal does not relax even though the patient engages in the action of defecation (straining). This is a sign of pelvic floor motor dysfunction. Physical examinations can help diagnose the presence of organic disease-associated constipation and defecation disorders.

BQ4-3. What tests are appropriate for determining the treatment approach for chronic constipation?

Underlying disease and pathophysiology are inferred from medical interviews and physical examinations, while the need for blood tests, colonoscopies, and abdominal/intestinal X-rays to differentiate secondary constipation is determined on an individual basis and implemented.

Comment: If anemia is shown on complete blood count, malignant disease should be considered [8]. Biochemical tests for blood sugar, thyroid function tests (free T4, TSH), and serum calcium measurements are used to differentiate between endocrine and metabolic diseases, such as diabetic neuropathy, hypothyroidism, and hyperparathyroidism [88–90]. Fecal occult blood testing is a useful screening test for colorectal cancer [91]. Colonoscopy is useful for differentiating constipation resulting from organic disease-associated constipation linked to neoplastic and inflammatory diseases. In particular, patients with warning symptoms, risk factors, or abnormalities on laboratory test results should undergo colonoscopy [89]. However, the prevalence of neoplastic diseases at colonoscopy in patients with chronic constipation is similar to that in asymptomatic patients [92]. Abdominal X-ray examination is useful for distinguishing intestinal obstruction and colonic volvulus, while barium enema is used to exclude organic disease-associated constipation.

CQ4-1. What are the warning symptoms and signs of chronic constipation?

Symptom and sign indicative of organic disease include rapid changes in bowel habits, bloody stools, unexpected weight loss of 3 kg or more within 6 months, fever, joint pain, and abnormal physical findings (palpation of abdominal masses, abdominal undulations, palpation of masses or blood adhesion via rectal examination, etc.).

Recommendation: n.a.

Evidence level: B

Comment: In patients with "warning symptoms and signs" of chronic constipation, the possibility of secondary constipation resulting from organic diseases, such as neoplastic and inflammatory diseases, must be considered [88–90]. In addition, "risk factors" for chronic constipation include onset at age 50 or older and a personal or family history of organic colorectal disease [90]. Colonoscopy (or barium enema) is required if any of the following is observed: "warning symptoms and signs," "risk factors," or "abnormal findings on routine clinical tests."

CQ4-2. Is external ultrasound examination useful in the pathophysiological and functional evaluation of chronic constipation?

Although there are few studies on the clinical application of external ultrasonography to the pathophysiological and functional evaluation of chronic constipation, it may be useful and we recommend its use.

Strength of recommendation: Weak

Evidence level: B

Agreement rate: 96%

Comment: Due to recent improvements in equipment performance, the clinical application of external ultrasound testing to gastrointestinal diseases is attracting attention for being noninvasive, low-cost, simple, and repeatable. Several studies exist on the clinical application of external ultrasound examination to the treatment of chronic constipation [93–95]. Chronic constipation therapy involves physicians and multidisciplinary staff, including co-medical staff. Furthermore, since many patients with chronic constipation are older adults, we expect treatment for chronic constipation will come to be based on pathophysiological and functional evaluations using the noninvasive, simple, and repeatable testing method of external ultrasound.

CQ4-3. Is the radiopaque marker technique useful in the pathophysiological and functional evaluation of chronic constipation?

The radiopaque marker technique is useful in the pathophysiological and functional evaluation of chronic constipation, and its use is recommended.

Strength of recommendation: Strong

Evidence level: B

Agreemnet rate: 74%

Comment: The radiopaque marker technique is established as a clinical significant colonic transit time testing method and is the most widely used technique

worldwide [96], with SITZMARKS® being the representative marker technique. Strictly speaking, the radiopaque marker technique is a total gastrointestinal transit time test, because it evaluates the time from oral ingestion of the marker to expulsion from the anus. The instruction manual for SITZMARKS® states that "It is normal for 80% or more of the markers to be excreted on the 5th day after ingestion." A study on Japanese participants demonstrated the safety, tolerability, and efficacy of the radiopaque marker technique [97]. However, as of August 2022, the use of SITZMARKS® in the marker technique has not been approved in Japan.

CQ4-4. Is MRI/CT useful in the pathological and functional evaluation of chronic constipation?

Although few studies have evaluated the use of MRI/CT in the pathophysiological and functional evaluation of chronic constipation, these tests are used in general clinical practice to evaluate intestinal dilatation and the presence of stool; therefore, we believe they can be useful when implemented in an appropriate manner.

Strength of recommendation: Weak

Evidence level: B

Agreement rate: 96%

Comment: In general clinical practice, MRI and CT are often used in clinical practice of constipation [98]. Morphological abnormalities of the sigmoid colon were frequently observed in colorectal CT scans of IBS patients [99]. MRI has shown that increased lumen diameter is associated with indicators of constipation [100]. Colonic contents measured by MRI were significantly higher in the constipated group even after psyllium stimulation [101]. Cine MRI of the fed state enabled dynamic evaluation of small intestinal motility [102] and total colonic transit time [103]. MRI defecography has been useful in the diagnosis of anatomical abnormalities of the pelvic floor and for dynamic findings of anatomical abnormalities and motor dysfunction, such as rectocele, rectal intussusception, atrophic external anal sphincter, and pelvic dysfunction [104]. Standardization of test methods, definition of true abnormalities, and optimal cutoffs (from the viewpoint of anatomy and discharge disorders) must be determined internationally, and standardized data on languages used, techniques, evaluation methods must be gathered.

BQ4-4. Is defecography useful in the pathophysiological and functional evaluation of chronic constipation?

While defecography is useful in the pathophysiological and functional evaluation of chronic constipation, it should be implemented together with other functional tests.

Comment: X-ray defecography is a test that uses pseudo-stool to video record and analyze anorectal movement of the rectum and anus under X-ray fluoroscopy, and it can be used to obtain information about anatomical abnormalities, such as rectoceles and rectal intussusceptions, and dynamic changes, such as changes in anorectal angle and coordination dysfunction during defecation, and it can be used to measure the presence and the size of a rectocele. This information is needed to determine whether surgery is appropriate, and it is generally performed when the anorectal manometry results do not match the results of other tests, i.e., clinical findings or balloon evacuation tests, or when rectocele is strongly suspected [105]. MRI defecography is another noninvasive test that does not involve radiation exposure.

BQ4-5. Is anorectal manometry (including balloon expulsion test) useful in the pathophysiological and functional evaluation of chronic constipation?

Anorectal manometry (including balloon expulsion test) is useful in the pathological and functional evaluation of chronic constipation.

Comment: Anorectal manometry is useful for evaluating anal sphincter function and defecation ability. Additionally, a balloon can be placed in the rectum to evaluate rectoanal reflexes, rectal sensation, and fecal storage capacity. Often in defecation disorders, when resting pressure is above the normal range, then rectal sensation is decreased, and maximum tolerated capacity is increased [106–108]. Methods for evaluating test values have not been standardized, limiting the diagnostic capacity of manometry alone [107, 109]. Balloon expulsion test is a useful test method that uses a water-filled balloon placed in the rectum to evaluate anorectal defecation function [106, 107, 110], and it is a simple test for objectively diagnosing functional defecation disorders, such as pelvic floor dysfunction. However, the test methods and evaluation methods have not been standardized [107].

Treatments

BQ5-1. What is the objective of chronic constipation therapy?

The objective of chronic constipation therapy is to achieve and maintain a state of complete spontaneous bowel movements, thereby improving QOL.

Comment: Chronic constipation is a pathophysiology where continued constipation interferes with daily life

Table 2. Classification of osmotic laxatives

Saline laxatives	Magnesium oxide Magnesium citrate Magnesium hydroxide Magnesium sulfate
Sugar laxatives	Lactulose D-Sorbitol Lactitol
Stool softener	Docusate sodium
High molecular weight compounds	Polyethylene glycol

and potentially causes various health problems. Therefore, constipation-related quantitative signs (stool form, frequency of bowel movements) and defecation-related subjective symptoms (feeling of straining, sensations of incomplete evacuation, sensation of anorectal obstruction/blockage, and manual assistance required) are taken into account [11]. Moreover, in addition to significantly reducing physical and mental health-related QOL, chronic constipation symptoms reduce labor productivity [111]. Hence, the objective of therapy is to achieve a condition where constipation-related quantitative signs and defecation-related subjective symptoms are under control (complete spontaneous bowel movements) and to maintain that condition, thereby improving QOL.

BQ5-2. Are improvements to lifestyle habits, dietary guidance, and diet therapy effective for chronic constipation?

Improvements to lifestyle habits, dietary guidance, and dietary therapy are effective for chronic constipation.

Comment: Among fermentable dietary fibers, partially hydrolyzed guar gum has been well studied in Japan. Moreover, it significantly increases the frequency of bowel movements in chronic constipation [112–114] and reduces the amount of laxatives used [115]. A RCT in which patients with chronic constipation ingested kiwifruit, prunes, and psyllium was observed that all foods increased both the spontaneous bowel movement rate and frequency of bowel movements to the same degree, indicating their effectiveness against chronic constipation [116]. A meta-analysis of the effectiveness of exercise therapy for chronic constipation reported that aerobic exercise is particularly effective in improving symptoms [117]. However, four reports comparing water intake between chronic constipation and control groups observed no difference between the two groups [118]; thus, the efficacy of water intake for chronic constipation has not been demonstrated [119].

BQ5-3. Are probiotics effective for chronic constipation?

Certain probiotics are effective in increasing the frequency of bowel movements and improving abdominal symptoms in patients with chronic constipation.

Comment: In clinical trials on probiotics for chronic constipation conducted in Japan and abroad, the following were shown to significantly increase the frequency of bowel movements in patients with chronic constipation: *Lactobacillus casei* strain Shirota [120, 121], *Bifidobacterium lactis* [122], *Bifidobacterium animalis* [123], *Lactobacillus reuteri* [124], *Lactococcus lactis* [125], *Lactobacillus plantarum* [126], and *Bifidobacterium bifidum* G9-1 [127]. Additionally, multiple meta-analyses of RCTs on chronic constipation have shown that probiotics can be used safely, increase frequency of bowel movements, improve abdominal symptoms associated with constipation, and contribute to shortening colonic transit time [128–133].

BQ5-4. Are bulk-forming laxatives effective for chronic constipation?

Bulk-forming laxatives are effective for chronic constipation.

Comment: Bulk-forming laxatives, such as carboxymethyl cellulose and calcium polycarbophil, act similarly to dietary fiber. They are not digested and absorbed in the gastrointestinal tract but instead facilitate increase in water volume, enhancing stool form and increasing stool volume, thereby promoting spontaneous bowel movements. In 2011, the World Gastroenterology Organization (WGO) assigned these compounds a low therapeutic drug evidence grade and recommendation level, categorized as evidence grade III and recommendation level C [134]. While there is a scarcity of high-quality studies examining the effects of either compound on chronic constipation, numerous reports highlight their efficacy for IBS-C [135]. Moreover, a few recent studies suggest their usefulness for chronic constipation [136, 137].

CQ5-1. Are osmotic laxatives effective for chronic constipation?

Osmotic laxatives are effective for chronic constipation and are recommended for use. However, when administering salt laxatives containing magnesium, periodic serum magnesium measurements are recommended.

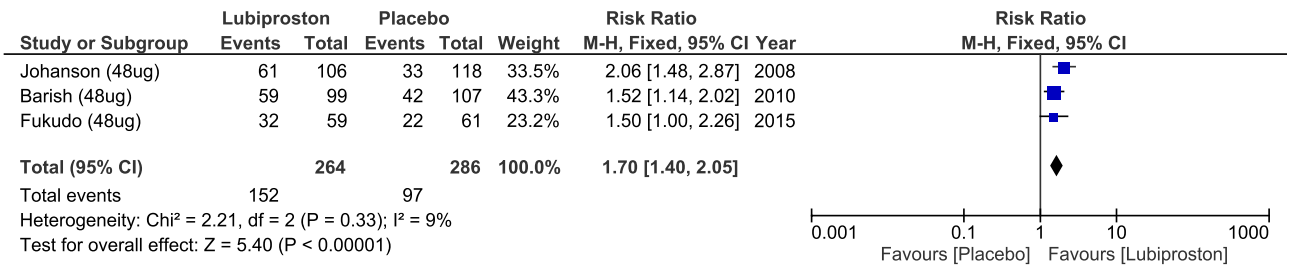

Fig. 2. Therapeutic response rate of lubiprostone for chronic constipation. A meta-analysis showing that the therapeutic response rate of lubiprostone for chronic constipation by targeting RCTs lasting 4 weeks or longer is shown. Responders were analyzed using complete spontaneous bowel movements as an index.

Strength of recommendation: Strong
Evidence level: A
Agreement rate: 100%

Comment: The classification is shown in Table 2. These drugs secrete water into the intestines using osmotic pressure [138].

1. Saline laxatives: magnesium oxide has been shown to be effective in RCTs [139–141]. Care must be taken when administering this drug to the older adults and people with impaired renal function. Serum magnesium measurements and the development of hypermagnesemia symptoms should be monitored as appropriate [142–144]. Additionally, appropriate caution should be exercised with concomitant drugs such as proton pump inhibitors [145].
2. Sugar laxatives: monosaccharide and disaccharide are osmotic agents effective for promoting spontaneous bowel movements [146, 147].
3. Stool softener: dioctyl sodium sulfosuccinate works by reducing the surface tension via surfactant action. While it has few side effects and no tolerance, its action is weak and it is typically used in combination with bulk-forming and stimulant laxatives.
4. High molecular weight compounds: polyethylene glycol, which has been available for prescription since 2018 in Japan [148], maintains osmotic pressure in a dose-dependent manner [149] and can be administered to children (2 years and older) [150].

As described above, osmotic laxatives are effective [151], and their position as drugs with novel mechanisms of action is likely to become clearer in the future.

BQ5-5. Are stimulant laxatives effective for chronic constipation?

Stimulant laxatives are effective for chronic constipation. To avoid tolerance and habituation, limit use to the minimum necessary, a single dose if possible, or over as a short period of time as possible.

Comment: Stimulant laxatives include anthraquinones and diphenyls [152, 153]. The efficacy of diphenyl drugs has been demonstrated by a small number of RCTs conducted overseas [154, 155]. Meanwhile, a Japanese RCT showed that 4 weeks of therapy with senna, an anthraquinone drug, significantly improved spontaneous bowel movements frequency, stool form, and Patient Assessment of Constipation Quality of Life (PAC-QOL) compared to those in placebo [141]. Stimulant laxatives are effective within a few hours, but caution is required as they may cause electrolyte abnormalities, such as watery diarrhea, and abdominal pain and dehydration [156]. In addition, long-term use may lead to tolerance and habituation; therefore, they should be prescribed with caution [157].

CQ5-2. Are intestinal secretagogues effective for chronic constipation?

Intestinal secretagogues are effective for chronic constipation, and their administration is recommended.

Strength of recommendation: Strong
Evidence level: A
Agreement rate: 100%

Comment: In Japan, the intestinal secretagogue lubiprostone was introduced in 2012, followed by linaclotide in 2017 for chronic constipation therapy. In small intestinal mucosal epithelial cells, lubiprostone activates chloride channels while linaclotide activates guanylyl cyclase C-receptors, thereby promoting water secretion and demonstrating a laxative effect. To date, three RCTs on the therapeutic effects of lubiprostone for chronic constipation [158–160] along with a meta-analysis (targeting RCTs lasting 4 weeks or longer and analyzing responders using complete spontaneous bowel movements as an index)

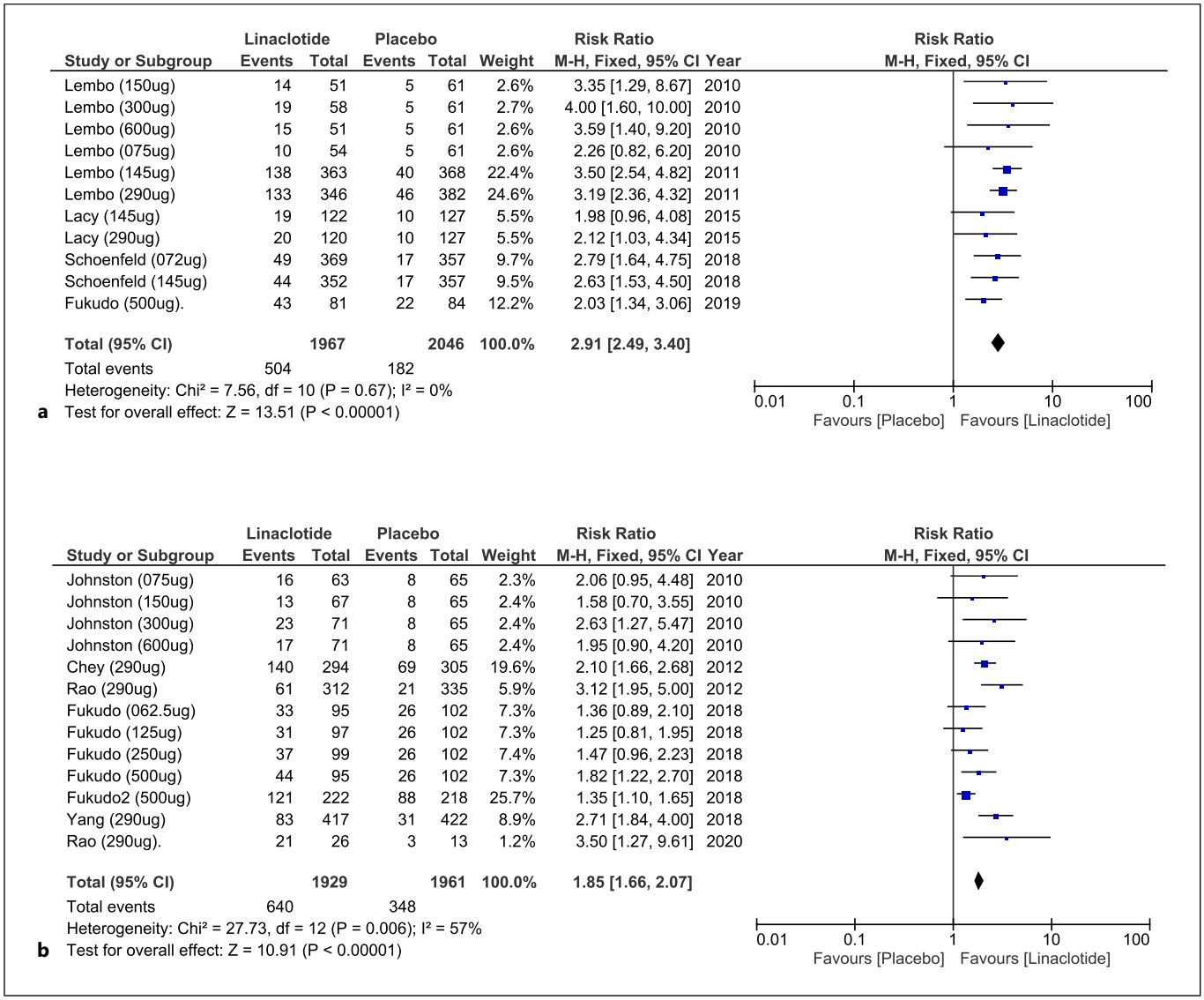

Fig. 3. Therapeutic response rate of linaclotide for chronic constipation and constipation-predominant irritable bowel syndrome (IBS-C). A meta-analysis showing that the therapeutic response rate of linaclotide for chronic constipation (**a**) and IBS-C (**b**) by targeting RCTs lasting 4 weeks or longer is shown. Responders were analyzed using complete spontaneous bowel movements as an index.

have shown that the therapeutic response rate and 95% CI of lubiprostone was 1.70 (95% CI: 1.40–2.05), indicating that lubiprostone is significantly more effective than placebo (Fig. 2). Additionally, five RCTs on linaclotide for chronic constipation [161–165], seven RCTs on IBS-C [166–172], and a meta-analysis (targeting RCTs of 4 weeks or longer, responder analysis using complete spontaneous bowel movements as an index) showed that the therapeutic response rate and 95% CI of linaclotide were 2.91 (95% CI: 2.49–3.40) and 1.85 (95% CI: 1.66–2.07), respectively. This indicates that linaclotide is significantly more effective than placebo (Fig. 3). As described, intestinal secretagogues are considered effective for chronic constipation.

CQ5-3. Are IBAT inhibitors effective for chronic constipation?

IBAT inhibitors are effective for chronic constipation, and their administration is recommended.

Strength of recommendation: Strong
Evidence level: A
Agreement rate: 100%

Comment: Elobixibat blocks IBAT in the terminal ileum and partially suppress bile acid reabsorption, thereby increasing the amount of bile acids entering the colon and rectum. This action promotes water secretion and peristalsis in the intestinal tract, which increases the frequency of bowel movements and improves stool form and improves patient QOL [173, 174]. In a Japanese phase III trial of elobixibat [174], the time to onset (median)] of first spontaneous bowel movement was 5.2 h in the elobixibat group, significantly lower than that in the placebo group at 25.5 h. To date, the efficacy of elobixibat has been investigated in the older adults [175] and patients with comorbid chronic constipation, such as those with cancer [176] and chronic renal failure, including patients on dialysis [177, 178]. Its usefulness has been recognized [179–185].

BQ5-6. Are prokinetic agents effective for chronic constipation?

Although there is little evidence for the agents available in Japan, prokinetics are effective for chronic constipation.

Comment: For chronic constipation or constipation-dominant IBS, several prokinetics have demonstrated usefulness: cisapride [186, 187], tegaserod [188, 189], renzapride [190], prucalopride [191], velusetrag [192], naronapride [193], YKP10811 [194], YH12852 [195], minesapride (DSP-6952) [196, 197], and mosapride [198]. However, among these agents, only tegaserod and prucalopride are currently available for clinical use in Europe and the USA. Only mosapride is available in Japan, but it is not covered by insurance for chronic constipation or IBS-C. Additionally, certain Kampo medicines have been shown to be useful in improving gastrointestinal motility (BQ5-7).

BQ5-7. Is Kampo medicine effective for chronic constipation?

Certain Kampo medicines are effective as treatments for chronic constipation.

Comment: Many Kampo medicines are indicated for chronic constipation. These medicines comprise various herbal ingredients, such as rhubarb and Japanese pepper, known for increasing intestinal motility; sodium sulfate, which softens stools through osmotic pressure; and hemp seed, which acts to moisturize the intestines. Studies examining the usefulness of Daio-kanzo-to, Mashiningan, Juncho-to, and Choi-joki-to for chronic constipation reported that all these Kampo medicines were effective in improving constipation symptoms. However, while there are many pre- and post-comparison trials, there is a scarcity of high-level evidence studies, such as RCTs. Despite Dai-kenchu-to not being specifically indicated for constipation, it is often used in clinical practice, with multiple studies indicating its effectiveness for chronic constipation. Although both studies had small sample sizes, Dai-kenchu-to was effective in improving symptoms in patients with chronic constipation [199, 200].

BQ5-8. Are enemas, suppositories, disimpaction, and retrograde irrigation effective for chronic constipation?

Enemas, suppositories, disimpaction, and retrograde irrigation are effective for chronic constipation. However, they should be used as appropriate and continuous use should be avoided as much as possible.

Comment: As an enema, glycerin promotes defecation by promoting catharsis and increasing the contractile force of the distal colon and rectum. However, its effectiveness diminishes due to increased tolerance with repeated use, making long-term use inadvisable [153]. Suppositories such as sodium bicarbonate and anhydrous sodium dihydrogen phosphate combination tablets generate carbon dioxide to physically stimulate the distal colon and rectum to promote defecation [201]. Disimpaction is a method of manually expelling stool for patients who are unable to spontaneously defecate, or who have paralysis or anorectal dysfunction and cannot apply abdominal pressure [202]. Retrograde bowel irrigation, also known as transanal irrigation, is a treatment method that involves injecting lukewarm water transanally into the rectum to empty the rectum and left side of the colon as much as possible to prevent fecal incontinence and improve the symptoms of constipation [203].

BQ5-9. Is psychotherapy effective for chronic constipation?

Psychotherapy may be effective for chronic constipation.

Comment: Regarding chronic constipation, although there have been few studies of the effectiveness of psychotherapy for functional constipation, many reports abound on the effectiveness of psychotherapy for IBS. Cognitive behavioral therapy, relaxation, hypnotherapy, and psychodynamic therapy for IBS (including IBS-C) have all been observed to have significant symptom-improving effects compared to that in control treatments [204]. These findings suggest that psychotherapy is useful for certain types of chronic constipation, especially conditions where psychosocial factors are strongly associated with gastrointestinal symptoms.

Table 3. Exclusion criteria for colectomy in intractable colonic type motility disorder-associated constipation

Unproven prolongation of colonic transit time
Fecal incontinence and anal sphincter dysfunction
Upper gastrointestinal motility disorders
Irritable bowel syndrome
Untreated defecation disorders
Mental disorders
Chronic use of opioids
Neurological disorders

CQ5-4. What is the treatment for OIC?

Osmotic laxatives, stimulant laxatives, naldemedine, and lubiprostone are effective for patients suspected of having OIC. However, laxatives should be considered with respect to the individual pathophysiology, taking into account safety, cost, and type of opioid being administered.

Recommendation: n.a.

Evidence level: C

Comment: OIC has been observed to occur in 60–90% of cancer patients using opioids [205]. Osmotic and stimulant laxatives are considered preferred drugs for OIC, but care must be taken to avoid renal dysfunction with magnesium oxide and long-term use of stimulant laxatives. Naldemedine is a peripheral μ-opioid receptor antagonist available for use in Japan, and in a Japanese clinical trial, naldemedine significantly improved the frequency of spontaneous bowl movements per week compared to that in placebo [206]. Furthermore, a meta-analysis of naldemedine for the treatment of OIC from 6 RCTs demonstrated that the proportion of spontaneous bowel movement responders was significantly higher in the naldemedine group versus the placebo group [207]. For the palliative patients, simultaneous administration of opioid and prophylactic treatments for OIC can be considered. It has been shown that simultaneous administration of opioid and naldemedine significantly prevented deterioration in the QOL [208]. Lubiprostone also has been reported to significantly improve constipation symptoms compared to that in placebo [209] in OIC patients, but because there are reports that it did not improve constipation symptoms in patients taking methadone, attention should be paid to differences in the type of opioid being administered [210]. Although peripheral μ-opioid receptor antagonists, including naldemedine, have strong evidence in treating OIC, the evidence is still insufficient to determine what treatment should be selected as first-line among naldemedine, lubiprostone, other laxatives due to considerations of cost-effectiveness and the fact that OIC often overlaps with chronic constipation caused by multiple factors other than opioids.

FRQ5-1. What are the clinical characteristics for which lubiprostone, linaclotide, and elobixibat should be used?

Clinical characteristics for the use of lubiprostone, linaclotide, and elobixibat have not been clarified, and further studies are required.

Comment: Lubiprostone, linaclotide, and elobixibat each have different mechanisms of action, yet there is currently no established strategy regarding which drug should be used for cases with specific clinical characteristics. A meta-analysis of lubiprostone, linaclotide, and elobixibat reported that these drugs elicited similar effects in altering the frequency of spontaneous bowel movements and achieving complete spontaneous bowel movements [211]. Additionally, a network meta-analysis demonstrated comparable outcomes in increasing the frequency of complete spontaneous defecation (three or more times per week) across the three drugs [212]. These findings underscore the lack of clarity regarding the appropriate clinical strategies for prescribing lubiprostone, linaclotide, and elobixibat should be used are not clear, and further studies for this issue are demanded.

BQ5-10. Is biofeedback therapy (BT) effective for chronic constipation?

BT is effective for chronic constipation caused by pelvic floor dysfunction. However, because a high level of expertise is required, treatment at specialized facilities is recommended.

Comment: BT in chronic constipation therapy is "a general term for techniques and phenomena that make it possible to consciously adjust internal states by using engineering means to intentionally feedback biological information that does not rise to consciousness" [213, 214]. Specifically, it is a type of rehabilitation therapy aimed at improving pelvic floor dysfunction by visually making patients aware of their own anal movements using anal manometers, electromyography, rectal balloons [215]. Studies have reported that the rate of improvement of constipation symptoms with BT is approximately 70% [216], electromyographic BT is significantly more effective therapy than various laxatives [217], and that BT is effective in 71% of patients with pelvic floor dysfunction [218].

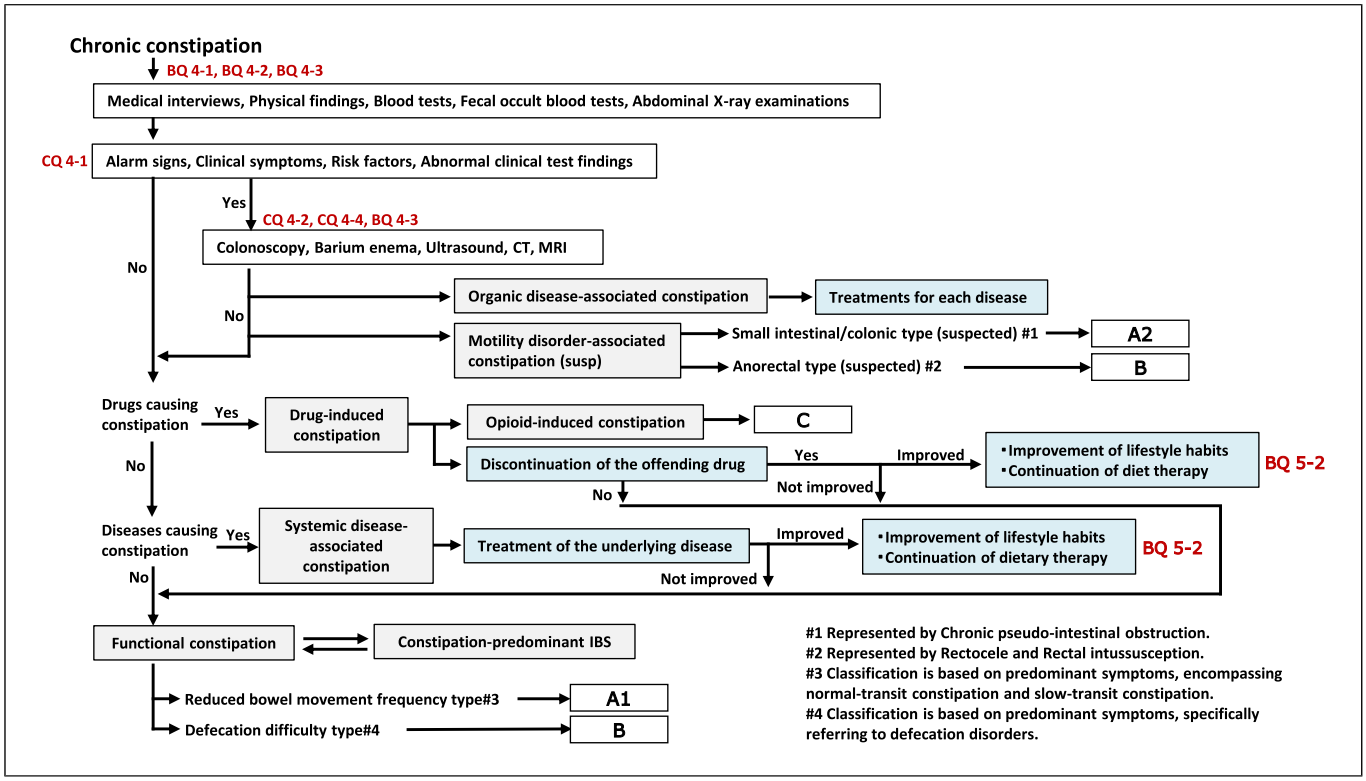

Fig. 4. Initial medical treatment strategy of chronic constipation. First, the patients with chronic constipation are assessed through a medical interview, physical findings, blood tests, fecal occult blood tests, abdominal X-ray examinations. If patients exhibit alarm signs and risk factors, or abnormal test findings, further studies including colonoscopy, barium enema, ultrasound, CT, and MRI were conducted to rule out organic disease-associated constipation and motility disorder-associated constipation. Subsequently, drug-induced constipation and systemic disease-associated constipation are excluded. The remaining patients are likely diagnosed with functional constipation or constipation-predominant IBS. These patients should then be classified into either reduced bowel movement frequency type or defecation difficulty type for targeted treatment. CT, computed tomography; IBS, irritable bowel syndrome; MRI, magnetic resonance imaging.

BQ5-11. Is antegrade continence enema (ACE) effective for chronic constipation?

ACE is an effective surgical treatment for avoiding colostomy or colon resection surgery for constipation where conservative treatment is ineffective or difficult to continue. However, because a high level of expertise is required, treatment at specialized facilities is recommended.

Comment: ACE is a treatment that involves creating an appendicostomy or cecostomy through laparotomy, laparoscopic surgery, or colonoscopy, and it aims to alleviate defecation disorders caused by constipation by periodically emptying the colon through cyclic intestinal washouts [219]. ACE is a surgical treatment for constipation cases where conservative treatments, including retrograde irrigation, are ineffective or difficult to continue and to circumvent mentally or physically invasive surgeries, such as colostomy. Additionally, it is indicated for severe STC and defecation disorders. Although it is not covered by insurance in Japan, cecostomy using a colonoscope and gastrostomy kit is simple, minimally invasive, and has few complications [220].

BQ5-12. Is colectomy effective for STC (colonic-type motility disorder-associated constipation) that does not improve with conservative treatment?

Colectomy for STC (colonic-type motility disorder-associated constipation) that does not improve with conservative treatment can be effective, if the patient is selected according to certain criteria.

Comment: First, it is important to perform a colon transit time test using an X-ray opaque marker or scintigraphy to physiologically evaluate the prolongation of the transit time. Because colectomy will not solve any problems for patients with defecation disorder-associated constipation, such as pelvic floor dysfunction or

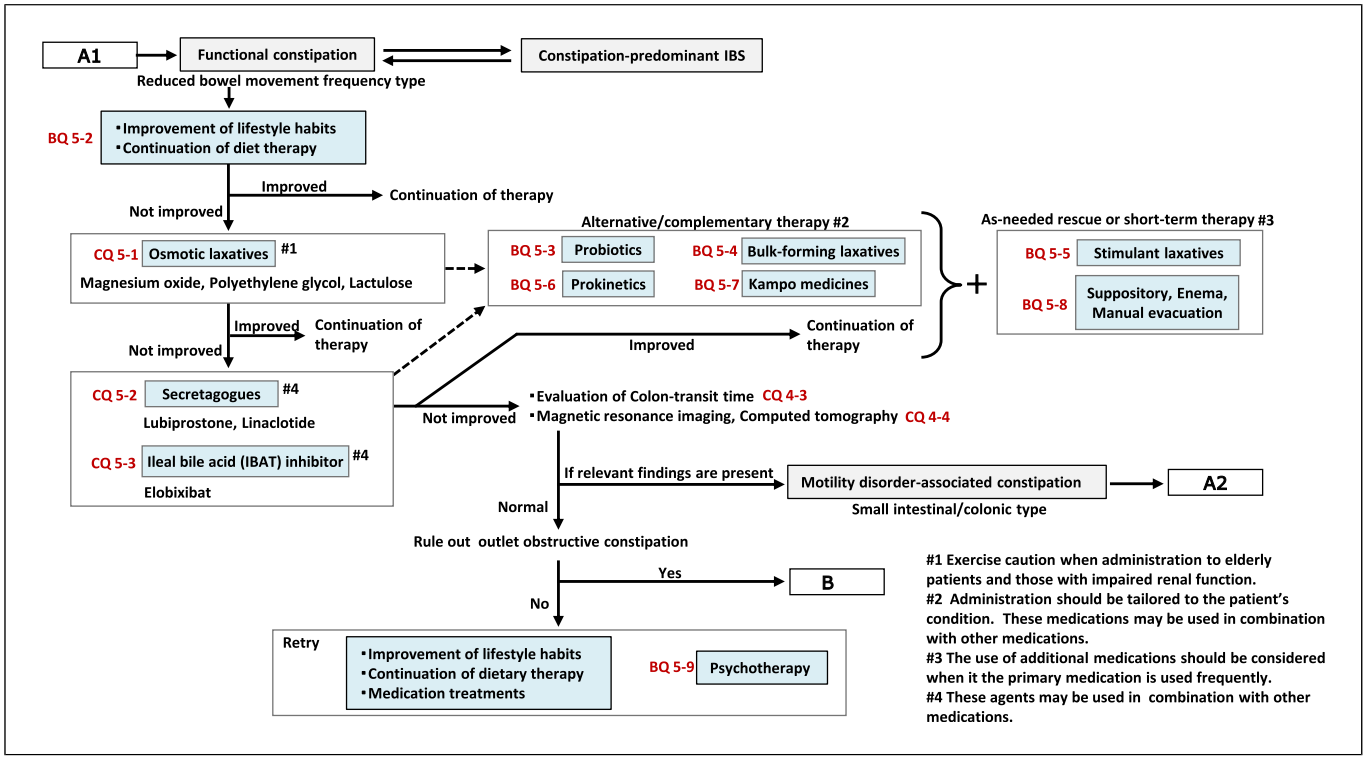

Fig. 5. Medical treatment strategy for functional constipation or constipation-predominant IBS with reduced bowel movement frequency type. Initially, improvements in lifestyle habits, dietary guidance, and dietary therapy are recommended. If these are ineffective, osmotic laxatives are applied. Should these have a poor response, the use of secretagogues and IBAT inhibitors should be considered. Stimulant laxatives are recommended for as-needed rescue or short-term therapy. Probiotics, bulk-forming laxatives, prokinetics, Kampo medicines may be used as alternative or complementary therapies. If these medications prove ineffective, motility disorder-associated constipation or outlet obstructive constipation should be ruled out. IBS, irritable bowel syndrome.

rectoceles, they must be excluded by anorectal function tests, such as anorectal manometry, defecography, and balloon expulsion test. Table 3 shows the exclusion items for colectomy for STC (colonic type motility disorder-associated constipation).

BQ5-13. Is surgical treatment effective for defecation disorder-associated constipation that does not improve with conservative treatment?

Although there are differences depending on the surgical method, surgical treatment is effective for defecation disorder-associated constipation that does not improve with conservative treatment.

Comment: Chronic constipation with defecation disorders is divided into two types: functional defecation disorders and anorectal type motility disorders, and main causes of anorectal type motility disorders are rectocele, rectal intussusception, and anal prolapse. Surgical treatment is useful in cases that do not respond to conservative treatment. Laparoscopic ventral rectopexy, transvaginal mesh repair, and stapled transanal rectal resection are effective for improving anorectal type motility disorders (rectocele, rectal intussusception, and anal prolapse) and have been evaluated to be postoperatively effective. Comparative studies conducted on surgical methods, surgical devices, approach methods (transperineal, transvaginal), and drug therapy have shown the effectiveness of surgery. However, surgery requires a high level of expertise; therefore, it is recommended to be performed at specialized facilities [221–225].

CQ5-5. What tests should be considered when selecting the surgical methods in surgery for intractable colonic-type motility disorder-associated constipation?

Total colectomy is effective for intractable colonic type motility disorder-associated constipation, but it is difficult to obtain sufficient efficacy even when performed in cases involving gastric emptying disorder or defecation disorder. Thus, it is important to evaluate the state of dysfunction

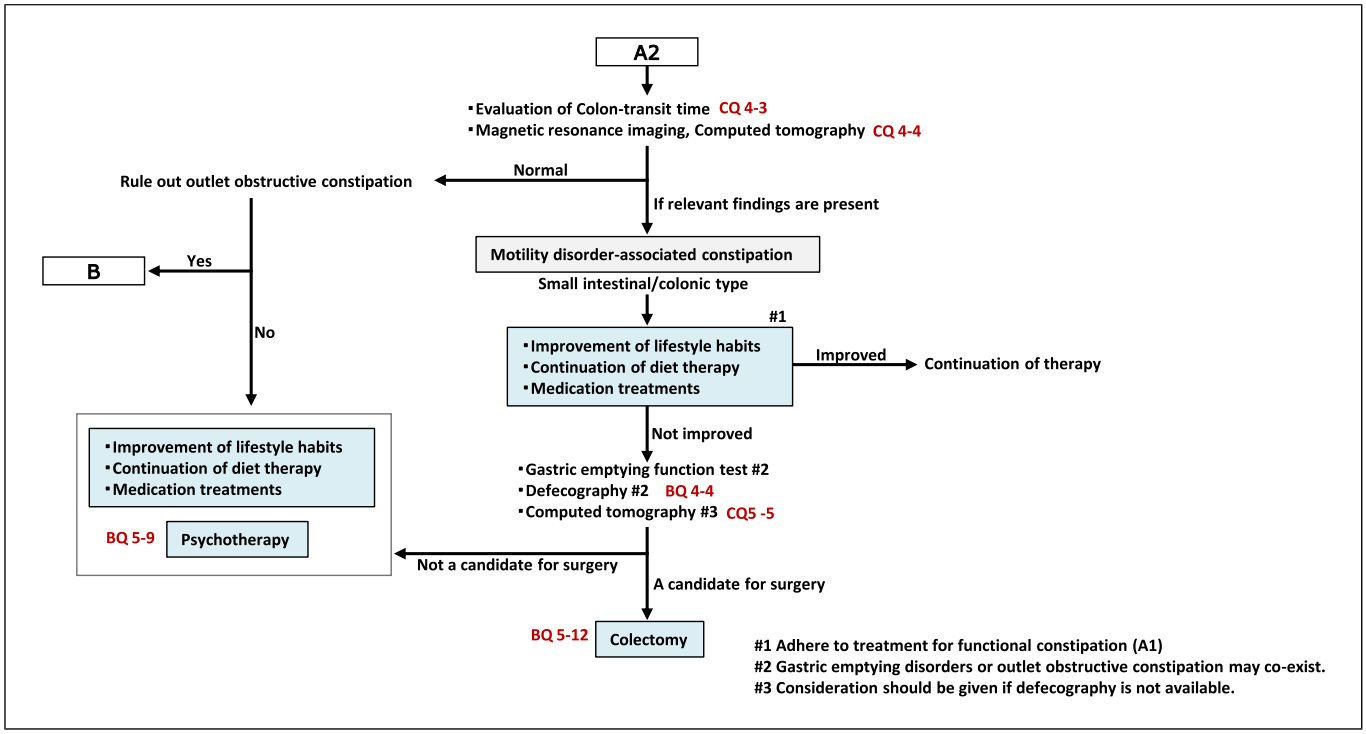

Fig. 6. Medical treatment strategy for motility disorder-associated constipation of small intestinal/colonic type. If improvement of lifestyle habits, dietary guidance, dietary therapy, and all forms of medication treatments prove ineffective, assess whether the patient is a candidate for colectomy. Before deciding on colectomy, it is essential to rule out gastroparesis and outlet obstructive constipation. Colectomy is often ineffective in the patients who also suffer from gastroparesis or outlet obstructive constipation.

before surgery. As an evaluation method for gastric emptying disorder, gastric emptying tracking contrast testing is simple and recommended. As an evaluation method for defecation disorder, CT examination is recommended when defecography is not possible.

Strength of recommendation: Strong

Evidence level: B,

Agreement rate: 73%

Comment: Methods for evaluating gastric emptying disorders include the RI method, ^{13}C breath test, and gastric emptying tracking contrast imaging. The RI method and ^{13}C breath test method are testing methods that can only be performed in special facilities and lack insurance coverage in Japan. The easiest test method is gastric emptying tracking contrast test. This test evaluates changes in the remaining amount of contrast agent in the stomach using X-ray examinations immediately following internal administration of Gastrografin. This is repeated 1–2 h after initial result. Defecography has been considered an effective method for evaluating defecation disorders, but in many cases, it has been difficult to perform the test because of refractory constipation, which often prevents sufficient pretreatment. CT examination is effective in determining the pros and cons of ileorectal anastomosis in such cases [226].

CQ5-6. Is treatment according to the pathophysiology of chronic constipation effective?

Treatment according to the pathophysiology is effective, and it is recommended that chronic constipation be treated based on evidence in line with the pathophysiology.

Strength of recommendation: Strong

Evidence level: B

Agreement rate: 73%

Comment: First, it is important to improve lifestyle habits. However, if this approach proves ineffective, the disease is classified using colonic transit time tests and anorectal manometry. For constipation with normal-transit constipation and STC, use bulk-forming laxatives, osmotic laxatives (magnesium preparations and polyethylene glycol), and stimulant laxatives if necessary. If their responses are poor, consider using secretagogues and IBAT inhibitors [227]. For defecation disorders, BT should be considered, and surgical treatment should be

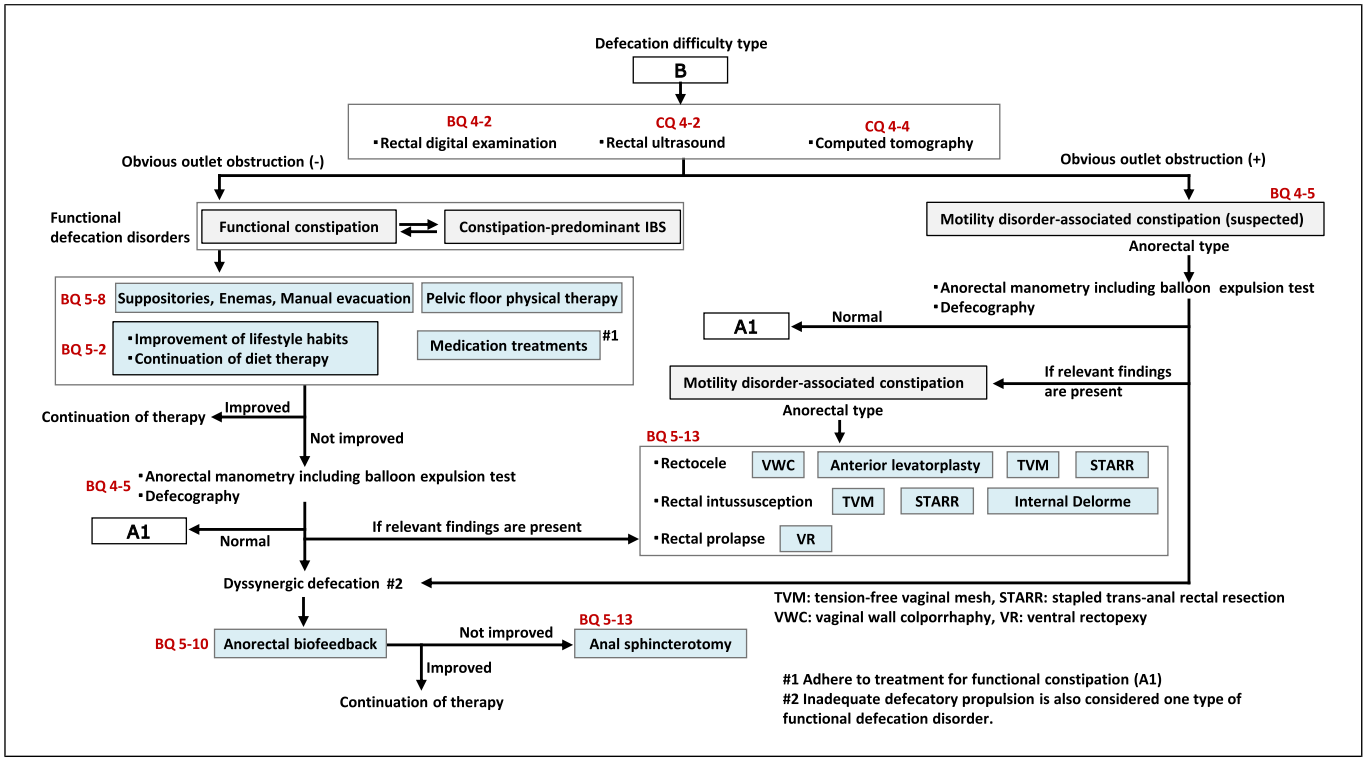

Fig. 7. Medical treatment strategy for chronic constipation of the defecation difficulty type. Rectal digital examination, rectal ultrasound, and computed tomography help determine whether the patient has obvious outlet obstruction. If on obvious outlet obstruction is present, treatments such as suppositories, enemas, manual evacuation, pelvic floor physical therapy, improvements of lifestyle habits, diet guidance, and medication treatments are conducted. If these treatments are ineffective, anorectal manometry with balloon expulsion test and defecography should be conducted to assess functional defecation disorders. If obvious outlet obstruction is present, anorectal manometry with balloon expulsion test and defecography should initially be conducted to determine whether the patient suffers from motility disorder-associated constipation of the anorectal type or from functional defecation disorders.

considered if defecography reveals anatomical abnormalities. In contrast, in Japan, the tests required to classify the pathophysiology are not as widespread as in Europe and the USA. Medication treatment is typically performed after distinguishing between "reduced bowel movement frequency type" and "defecation difficulty type" based on symptoms.

Flowcharts of Clinical Practice for Chronic Constipation

Based on the 15 CQs, 2 FRQs, and 30 BQs outlined in the guideline, we have constructed flowcharts for clinical practice in managing chronic constipation. These include the initial medical treatment strategy of chronic constipation (Fig. 4), the medical treatment strategy for functional constipation or constipation-predominant IBS with reduced bowel movement frequency type (Fig. 5), the medical treatment strategy for motility disorder-associated constipation of small intestinal/colonic type (Fig. 6), the medical treatment strategy for chronic constipation of the defecation difficulty type (Fig. 7), and the medical treatment strategy for OIC (Fig. 8).

Appendix

The members of the Guidelines Committee who created and evaluated the Japanese Gastroenterological Association "Evidence-Based Clinical Guidelines for Chronic Constipation 2023" are listed below.

Creation Committee

Chair: Eikichi Ihara (Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University). Vice-Chair: Noriaki Manabe (Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School). Members:

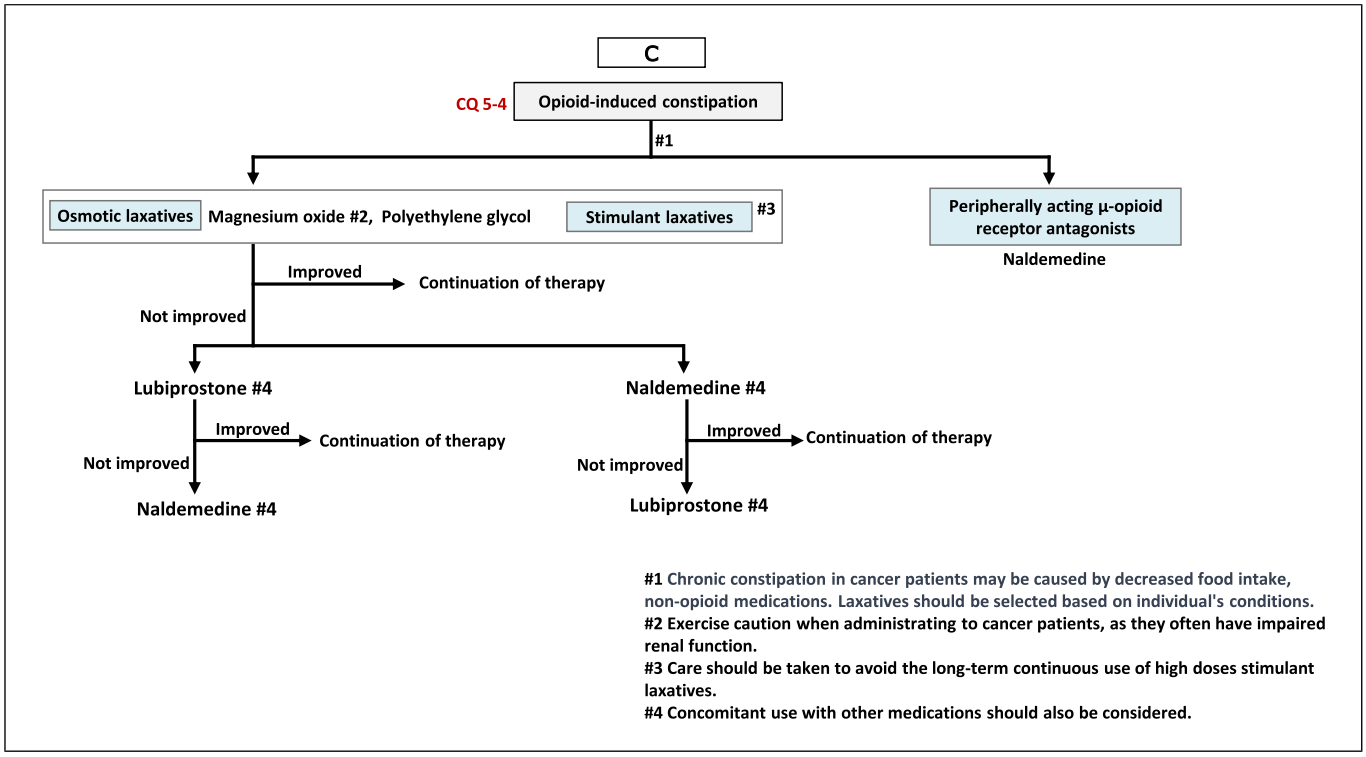

Fig. 8. Medical treatment strategy for OIC. Chronic constipation in cancer patients may be caused by decreased food intake and non-opioid medications. Laxatives should be selected based on individual's conditions. If chronic constipation is exclusively caused by opioid use, peripherally acting μ-opioid receptor antagonists are recommended. Lubiprostone has been shown to be effective for OIC.

Hidenori Ohkubo (Department of Gastroenterology, Sagami Rinkan Hospital), Naotaka Ogasawara (Department of Gastroenterology, Aichi Medical University School of Medicine), Haruei Ogino (Department of Gastroenterology and Metabolism, Graduate School of Medical Sciences, Kyushu University), Kazuki Kakimoto (2nd Department of Internal Medicine, Osaka Medical and Pharmaceutical University), Motoyori Kanazawa (Department of Behavioral Medicine, Tohoku University Graduate School of Medicine), Hidejiro Kawahara (Department of Surgery, National Hospital Organization Nishisaitama-Chuo National Hospital), Chika Kusano (Department of Gastroenterology, Kitasato University School of Medicine), Shiko Kuribayashi (Department of Gastroenterology and Hepatology, Gunma University Graduate School of Medicine), Akinari Sawada (Department of Gastroenterology, Osaka Metropolitan University Graduate School of Medicine), Tomohisa Takagi (Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine), Shota Takano (Department of Colorectal Surgery, Coloproctology Center Takano Hospital), Toshihiko Tomita (Division of Gastroenterology, Department of Internal Medicine, Hyogo Medical University), Toshihiro Noake (Department of Surgery, Kurume Coloproctology Center), Mariko Hojo (Department of Gastroenterology, Juntendo University Faculty of Medicine), Ryota Hokari (Department of Internal Medicine, National Defense Medical College), Tatsuhiro Masaoka (Center for Endoscopy, Kawasaki Municipal Hospital), Tomohiko Machida (Department of Surgery, Saiseikai Hyogo Prefectural Hospital), Noboru Misawa (Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine), Yoshiyuki Mishima (Department of Internal Medicine II, Shimane University Faculty of Medicine), Hiroshi Yajima (Yashio Hospital), Sayuri Yamamoto (Department of General Medicine and Gastroenterology, Aichi Medical University), and Hiroshi Yamawaki (Department of Gastroenterology, Nippon Medical School Tama Nagayama Hospital).

Evaluation Committee

Members: Tatsuya Abe (Department of Proctology, Kunimoto Hospital), Yasumi Araki (Department of Surgery, Kurume Coloproctology Center), Kunio Kasugai (Department of Gastroenterology, Aichi Medical University School of Medicine), Takeshi Kamiya (Department of Medical Innovation, Nagoya City University Graduate School of Medical Sciences), Akira Torii (Torii Medical Clinic), Atsushi Nakajima (Department of Gastroenterology and Hepatology, Yokohama City University Graduate School of Medicine), Koji Nakada (Kawamura Hospital), Shin Fukudo (Department of Psychosomatic Medicine, Japanese Red Cross Ishinomaki Hospital), Yasuhiro Fujiwara (Department of Gastroenterology, Osaka Metropolitan University Graduate School of Medicine), and Hiroto Miwa (Kawanishi City Medical Center).

Japanese Gastroenterological Association

President: Akihito Nagahara (Department of Gastroenterology, Juntendo University Faculty of Medicine). Past President: Kazuhide Higuchi (Osaka Medical and Pharmaceutical University). Director Responsible: Hiromi Kataoka (Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences).

Acknowledgments

The authors thank Kazuhiro Kamada (Department of Gastroenterology, Matsushita Memorial Hospital), Yoshimasa Tanaka (Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University), and Hiroko Hosaka (Department of Gastroenterology and Hepatology Gunma University, Graduate School of Medicine, Gunma) for assistance with data collection, data analysis, and manuscript preparation. The authors thank Japan Medical Library Association for assistance with professional bibliographic search.

Conflict of Interest Statement

Competing interests of guideline development committee members, guideline committee members, and guideline evaluation committee members were in the following. Any financial relationship with enterprises, businesses, or academic institutions in the subject matter or materials discussed in the manuscript are as follows: (1) those from which the authors, the spouse, partner, or immediate relatives of the authors have received individually any income, honoraria, or any other type of remuneration; Otsuka Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company, EA Pharma Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., AstraZeneca K.K., Olympus Corporation, JIMRO Co., Ltd., AbbVie GK, KYORIN Pharmaceutical Co., Ltd., Viatris Inc., Astellas Pharma Inc., Gilead Sciences, Inc., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., Mochida Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Tsumura & Co., Towa Pharmaceutical Co., Ltd., Bristol-Myers Squibb K.K., Kowa Pharmaceutical Co., Ltd., Taisho Pharmaceutical Holdings Co., Ltd., Biofermin Pharmaceutical Co., Ltd., Mylan EPD G.K., Daiichi Sankyo Inc., Zeria Pharmaceutical Co., Ltd., and (2) those from which the authors have received research grant; AbbVie GK, GlaxoSmithKline K.K., Janssen Pharmaceutical K.K., EA Pharma Co., Ltd., Fujifilm Corporation, Mochida Pharmaceutical Co., Ltd., ASKA Pharmaceutical Co., Ltd., Astellas Pharma Inc., Gilead Sciences, Inc., Biofermin Pharmaceutical Co., Ltd., Mylan EPD G.K., Tsumura & Co., Zespri International Limited, and (3) those from which the authors have received scholarship; Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Tobishima Kodomo Clinic, Takeda Pharmaceutical Company, Daiichi Sankyo Inc., AbbVie GK, KYORIN Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Bristol-Myers Squibb K.K., EA Pharma Co., Ltd., Mochida Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., and (4) those from which the authors have received individually endowed chair; Ono Pharmaceutical Co., Ltd., Miyarisan Pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Otsuka Pharmaceutical Factory, Inc., Fujifilm Medical Co., Ltd., Terumo Corporation, FANCL Corporation, Ohga Pharmacy, Abbott Japan LLC, and Muta Hospital.

Funding Sources

The members of Guidelines Development Group are relevant professionals from the JGA. The funding body per se did not influence the content of the guidelines.

Author Contributions

Writing – original draft: Eikichi Ihara, Noriaki Manabe, Hidenori Ohkubo, Naotaka Ogasawara, Haruei Ogino, Kazuki Kakimoto, Motoyori Kanazawa, Hidejiro Kawahara, Chika Kusano, Shiko Kuribayashi, Akinari Sawada, Tomohisa Takagi, Shota Takano, Toshihiko Tomita, Toshihiro Noake, Mariko Hojo, Ryota Hokari, Tatsuhiro Masaoka, Tomohiko Machida, Noboru Misawa, Yoshiyuki Mishima, Hiroshi Yajima, Sayuri Yamamoto, and Hiroshi Yamawaki. Writing – review and editing: Eikichi Ihara and Noriaki Manabe. Supervision: Tatsuya Abe, Yasumi Araki, Kunio Kasugai, Takeshi Kamiya, Akira Torii, Atsushi Nakajima, Koji Nakada, Shin Fukudo, Yasuhiro Fujiwara, Hiroto Miwa, Hiromi Kataoka, Akihito Nagahara, and Kazuhide Higuchi.

References

1 Chang JY, Locke GR 3rd, McNally MA, Halder SL, Schleck CD, Zinsmeister AR, et al. Impact of functional gastrointestinal disorders on survival in the community. Am J Gastroenterol. 2010;105(4):822–32. https://doi.org/10.1038/ajg.2010.40

2 Sumida K, Molnar MZ, Potukuchi PK, Thomas F, Lu JL, Yamagata K, et al. Constipation and risk of death and cardiovascular events. Atherosclerosis. 2019;281:114–20. https://doi.org/10.1016/j.atherosclerosis.2018.12.021

3 Li H, Xing X, Yao L, Li M, Xun Y, Yan P, et al. Assessment of the quality and content of clinical practice guidelines on irritable bowel syndrome using the agree ii instrument. Digestion. 2020;101(4):355–65. https://doi.org/10.1159/000499838

4 Yoshida M, Kinoshita Y, Watanabe M, Sugano K. Jsge clinical practice guidelines 2014: standards, methods, and process of developing the guidelines. J Gastroenterol. 2015;50(1):4–10. https://doi.org/10.1007/s00535-014-1016-1

5 Qaseem A, Kansagara D, Lin JS, Mustafa RA, Wilt TJ; Clinical Guidelines Committee of the American College of Physicians, et al. The development of clinical guidelines and guidance statements by the clinical guidelines committee of the American college of physicians: update of methods. Ann Intern Med. 2019;170(12):863–70. https://doi.org/10.7326/M18-3290

6 Qaseem A, Snow V, Owens DK, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med. 2010;153(3):194–9. https://doi.org/10.7326/0003-4819-153-3-201008030-00010
7 Lembo A, Camilleri M. Chronic constipation. N Engl J Med. 2003;349(14):1360–8. https://doi.org/10.1056/NEJMra020995
8 Serra J, Pohl D, Azpiroz F, Chiarioni G, Ducrotte P, Gourcerol G, et al. European society of neurogastroenterology and motility guidelines on functional constipation in adults. Neurogastroenterol Motil. 2020;32(2):e13762. https://doi.org/10.1111/nmo.13762
9 Tack J, Muller-Lissner S, Stanghellini V, Boeckxstaens G, Kamm MA, Simren M, et al. Diagnosis and treatment of chronic constipation--a European perspective. Neurogastroenterol Motil. 2011;23(8):697–710. https://doi.org/10.1111/j.1365-2982.2011.01709.x
10 Adams-Carr KL, Bestwick JP, Shribman S, Lees A, Schrag A, Noyce AJ. Constipation preceding Parkinson's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2016;87(7):710–6. https://doi.org/10.1136/jnnp-2015-311680
11 Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. Gastroenterology. 2016;150(6):1393–407.e5. https://doi.org/10.1053/j.gastro.2016.02.031
12 Wilkinson-Smith V, Bharucha AE, Emmanuel A, Knowles C, Yiannakou Y, Corsetti M. When all seems lost: management of refractory constipation-surgery, rectal irrigation, percutaneous endoscopic colostomy, and more. Neurogastroenterol Motil. 2018;30(5):e13352. https://doi.org/10.1111/nmo.13352
13 Soh AYS, Kang JY, Siah KTH, Scarpignato C, Gwee KA. Searching for a definition for pharmacologically refractory constipation: a systematic review. J Gastroenterol Hepatol. 2018;33(3):564–75. https://doi.org/10.1111/jgh.13998
14 Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from espghan and naspghan. J Pediatr Gastroenterol Nutr. 2014;58(2):258–74. https://doi.org/10.1097/MPG.0000000000000266
15 Ogasawara N, Funaki Y, Kasugai K, Ebi M, Tamura Y, Izawa S, et al. Overlap between constipation and gastroesophageal reflux disease in Japan: results from an internet survey. J Neurogastroenterol Motil. 2022;28(2):291–302. https://doi.org/10.5056/jnm21065
16 Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome foundation global study. Gastroenterology. 2021;160(1):99–114.e3. https://doi.org/10.1053/j.gastro.2020.04.014
17 Barberio B, Judge C, Savarino EV, Ford AC. Global prevalence of functional constipation according to the Rome criteria: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2021;6(8):638–48. https://doi.org/10.1016/S2468-1253(21)00111-4
18 Suares NC, Ford AC. Prevalence of, and risk factors for chronic idiopathic constipation in the community: systematic review and meta-analysis. Am J Gastroenterol. 2011;106(9):1582–92; quiz 1581, 1592. https://doi.org/10.1038/ajg.2011.164
19 Moezi P, Salehi A, Molavi H, Poustchi H, Gandomkar A, Imanieh MH, et al. Prevalence of chronic constipation and its associated factors in pars cohort study: a study of 9000 adults in southern Iran. Middle East J Dig Dis. 2018;10(2):75–83. https://doi.org/10.15171/mejdd.2018.94
20 Choung RS, Locke GR 3rd, Schleck CD, Zinsmeister AR, Talley NJ. Cumulative incidence of chronic constipation: a population-based study 1988–2003. Aliment Pharmacol Ther. 2007;26(11–12):1521–8. https://doi.org/10.1111/j.1365-2036.2007.03540.x
21 Choung RS, Rey E, Locke GR 3rd, Schleck CD, Baum C, Zinsmeister AR, et al. Chronic constipation and co-morbidities: a prospective population-based nested case-control study. United Eur Gastroenterol J. 2016;4(1):142–51. https://doi.org/10.1177/2050640614558476
22 Schmidt FM, de Gouveia Santos VL, de Cassia Domansky R, Neves JM. Constipation: prevalence and associated factors in adults living in Londrina, southern Brazil. Gastroenterol Nurs. 2016;39(3):204–11. https://doi.org/10.1097/SGA.0000000000000224
23 Sorouri M, Pourhoseingholi MA, Vahedi M, Safaee A, Moghimi-Dehkordi B, Pourhoseingholi A, et al. Functional bowel disorders in Iranian population using Rome iii criteria. Saudi J Gastroenterol. 2010;16(3):154–60. https://doi.org/10.4103/1319-3767.65183
24 Werth BL, Christopher SA. Potential risk factors for constipation in the community. World J Gastroenterol. 2021;27(21):2795–817. https://doi.org/10.3748/wjg.v27.i21.2795
25 Ruszkowski J, Heleniak Z, Krol E, Tarasewicz A, Galgowska J, Witkowski JM, et al. Constipation and the quality of life in conservatively treated chronic kidney disease patients: a cross-sectional study. Int J Med Sci. 2020;17(18):2954–63. https://doi.org/10.7150/ijms.49648
26 Tomita T, Kazumori K, Baba K, Zhao X, Chen Y, Miwa H. Impact of chronic constipation on health-related quality of life and work productivity in Japan. J Gastroenterol Hepatol. 2021;36(6):1529–37. https://doi.org/10.1111/jgh.15295
27 Nomura H, Agatsuma T, Mimura T. Validity and reliability of the Japanese version of the patient assessment of constipation quality of life questionnaire. J Gastroenterol. 2014;49(4):667–73. https://doi.org/10.1007/s00535-013-0825-y
28 Ohkubo H, Yoshihara T, Misawa N, Ashikari K, Fuyuki A, Matsuura T, et al. Relationship between stool form and quality of life in patients with chronic constipation: an internet questionnaire survey. Digestion. 2021;102(2):147–54. https://doi.org/10.1159/000502815
29 Kapoor WN, Peterson JR, Karpf M. Micturition syncope: a reappraisal. JAMA. 1985;253(6):796–8. https://doi.org/10.1001/jama.1985.03350300084025
30 Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011;472(7341):57–63. https://doi.org/10.1038/nature09922
31 Honkura K, Tomata Y, Sugiyama K, Kaiho Y, Watanabe T, Zhang S, et al. Defecation frequency and cardiovascular disease mortality in Japan: the Ohsaki cohort study. Atherosclerosis. 2016;246:251–6. https://doi.org/10.1016/j.atherosclerosis.2016.01.007
32 Kubota Y, Iso H, Tamakoshi A. Bowel movement frequency, laxative use, and mortality from coronary heart disease and stroke among Japanese men and women: the Japan collaborative cohort (JACC) study. J Epidemiol. 2016;26(5):242–8. https://doi.org/10.2188/jea.JE20150123
33 Ma W, Li Y, Heianza Y, Staller KD, Chan AT, Rimm EB, et al. Associations of bowel movement frequency with risk of cardiovascular disease and mortality among US women. Sci Rep. 2016;6:33005. https://doi.org/10.1038/srep33005
34 Sumida K, Molnar MZ, Potukuchi PK, Thomas F, Lu JL, Matsushita K, et al. Constipation and incident ckd. J Am Soc Nephrol. 2017;28(4):1248–58. https://doi.org/10.1681/ASN.2016060656
35 Cummings JH, Bingham SA, Heaton KW, Eastwood MA. Fecal weight, colon cancer risk, and dietary intake of nonstarch polysaccharides (dietary fiber). Gastroenterology. 1992;103(6):1783–9. https://doi.org/10.1016/0016-5085(92)91435-7
36 Power AM, Talley NJ, Ford AC. Association between constipation and colorectal cancer: systematic review and meta-analysis of observational studies. Am J Gastroenterol. 2013;108(6):894–904. quiz 904. https://doi.org/10.1038/ajg.2013.52
37 Bassotti G, Stanghellini V, Chiarioni G, Germani U, De Giorgio R, Vantini I, et al. Upper gastrointestinal motor activity in patients with slow-transit constipation: further evidence for an enteric neuropathy. Dig Dis Sci. 1996;41(10):1999–2005. https://doi.org/10.1007/BF02093603
38 Panagamuwa B, Kumar D, Ortiz J, Keighley MR. Motor abnormalities in the terminal ileum of patients with chronic idiopathic constipation. Br J Surg. 1994;81(11):1685–8. https://doi.org/10.1002/bjs.1800811142

39 Scott SM, Picon L, Knowles CH, Fourquet F, Yazaki E, Williams NS, et al. Automated quantitative analysis of nocturnal jejunal motor activity identifies abnormalities in individuals and subgroups of patients with slow transit constipation. Am J Gastroenterol. 2003;98(5):1123–34. https://doi.org/10.1111/j.1572-0241.2003.07419.x
40 Seidl H, Gundling F, Pehl C, Pfeiffer A, Schepp W, Schmidt T. Small bowel motility in functional chronic constipation. Neurogastroenterol Motil. 2009;21(12):1278–e122. https://doi.org/10.1111/j.1365-2982.2009.01364.x
41 Rao SS, Kuo B, McCallum RW, Chey WD, DiBaise JK, Hasler WL, et al. Investigation of colonic and whole-gut transit with wireless motility capsule and radiopaque markers in constipation. Clin Gastroenterol Hepatol. 2009;7(5):537–44. https://doi.org/10.1016/j.cgh.2009.01.017
42 van der Sijp JR, Kamm MA, Nightingale JM, Britton KE, Granowska M, Mather SJ, et al. Disturbed gastric and small bowel transit in severe idiopathic constipation. Dig Dis Sci. 1993;38(5):837–44. https://doi.org/10.1007/BF01295909
43 Sadik R, Stotzer PO, Simren M, Abrahamsson H. Gastrointestinal transit abnormalities are frequently detected in patients with unexplained gi symptoms at a tertiary centre. Neurogastroenterol Motil. 2008;20(3):197–205. https://doi.org/10.1111/j.1365-2982.2007.01025.x
44 Rao SS, Singh S. Clinical utility of colonic and anorectal manometry in chronic constipation. J Clin Gastroenterol. 2010;44(9):597–609. https://doi.org/10.1097/MCG.0b013e3181e88532
45 Pucciani F, Trafeli M. Sampling reflex: pathogenic role in functional defecation disorder. Tech Coloproctol. 2021;25(5):521–30. https://doi.org/10.1007/s10151-020-02393-5
46 Ohkubo H, Takatsu T, Yoshihara T, Misawa N, Ashikari K, Fuyuki A, et al. Difference in defecation desire between patients with and without chronic constipation: a large-scale internet survey. Clin Transl Gastroenterol. 2020;11(9):e00230. https://doi.org/10.14309/ctg.0000000000000230
47 Vollebregt PF, Burgell RE, Hooper RL, Knowles CH, Scott SM. Clinical impact of rectal hyposensitivity: a cross-sectional study of 2,876 patients with refractory functional constipation. Am J Gastroenterol. 2021;116(4):758–68. https://doi.org/10.14309/ajg.0000000000001039
48 Palit S, Lunniss PJ, Scott SM. The physiology of human defecation. Dig Dis Sci. 2012;57(6):1445–64. https://doi.org/10.1007/s10620-012-2071-1
49 Locke GR 3rd, Pemberton JH, Phillips SF. AGA technical review on constipation. American gastroenterological association. Gastroenterology. 2000;119(6):1766–78. https://doi.org/10.1053/gast.2000.20392
50 Jessurun JG, van Harten PN, Egberts TC, Pijl YJ, Wilting I, Tenback DE. The relation between psychiatric diagnoses and constipation in hospitalized patients: a cross-sectional study. Psychiatry J. 2016;2016:2459693. https://doi.org/10.1155/2016/2459693
51 Sakakibara R, Odaka T, Uchiyama T, Asahina M, Yamaguchi K, Yamaguchi T, et al. Colonic transit time and rectoanal videomanometry in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2003;74(2):268–72. https://doi.org/10.1136/jnnp.74.2.268
52 Yasuda G, Shibata K, Takizawa T, Ikeda Y, Tokita Y, Umemura S, et al. Prevalence of constipation in continuous ambulatory peritoneal dialysis patients and comparison with hemodialysis patients. Am J Kidney Dis. 2002;39(6):1292–9. https://doi.org/10.1053/ajkd.2002.33407
53 Bitar K, Greenwood-Van Meerveld B, Saad R, Wiley JW. Aging and gastrointestinal neuromuscular function: insights from within and outside the gut. Neurogastroenterol Motil. 2011;23(6):490–501. https://doi.org/10.1111/j.1365-2982.2011.01678.x
54 Hanani M, Fellig Y, Udassin R, Freund HR. Age-related changes in the morphology of the myenteric plexus of the human colon. Auton Neurosci. 2004;113(1–2):71–8. https://doi.org/10.1016/j.autneu.2004.05.007
55 Every-Palmer S, Newton-Howes G, Clarke MJ. Pharmacological treatment for antipsychotic-related constipation. Cochrane Database Syst Rev. 2017;1:CD011128. https://doi.org/10.1002/14651858.CD011128.pub2
56 Leroi AM, Lalaude O, Antonietti M, Touchais JY, Ducrotte P, Menard JF, et al. Prolonged stationary colonic motility recording in seven patients with severe constipation secondary to antidepressants. Neurogastroenterol Motil. 2000;12(2):149–54. https://doi.org/10.1046/j.1365-2982.2000.00189.x
57 Valladales-Restrepo LF, Paredes-Mendoza M, Machado-Alba JE. Potentially inappropriate prescriptions for anticholinergic medications for patients with constipation. Dig Dis. 2020;38:500–6. https://doi.org/10.1159/000506981
58 Yuan CS, Foss JF, O'Connor M, Moss J, Roizen MF. Gut motility and transit changes in patients receiving long-term methadone maintenance. J Clin Pharmacol. 1998;38(10):931–5. https://doi.org/10.1002/j.1552-4604.1998.tb04389.x
59 Pagano G, Tan EE, Haider JM, Bautista A, Tagliati M. Constipation is reduced by beta-blockers and increased by dopaminergic medications in Parkinson's disease. Parkinsonism Relat Disord. 2015;21(2):120–5. https://doi.org/10.1016/j.parkreldis.2014.11.015
60 Xiao-Ling Q, Gang C, Bo L, Zai-Li L, Xue-Kui L, Xue L, et al. Depression is associated with constipation in patients with Parkinson's disease. Front Neurol. 2020;11:567574. https://doi.org/10.3389/fneur.2020.567574
61 Bharucha AE, Lacy BE. Mechanisms, evaluation, and management of chronic constipation. Gastroenterology. 2020;158(5):1232–49.e3. https://doi.org/10.1053/j.gastro.2019.12.034
62 Gibson RJ, Keefe DM. Cancer chemotherapy-induced diarrhoea and constipation: mechanisms of damage and prevention strategies. Support Care Cancer. 2006;14(9):890–900. https://doi.org/10.1007/s00520-006-0040-y
63 He D, Pan Q, Chen Z, Sun C, Zhang P, Mao A, et al. Treatment of hypertension by increasing impaired endothelial trpv4-kca2.3 interaction. EMBO Mol Med. 2017;9(11):1491–503. https://doi.org/10.15252/emmm.201707725
64 Talley NJ, Jones M, Nuyts G, Dubois D. Risk factors for chronic constipation based on a general practice sample. Am J Gastroenterol. 2003;98(5):1107–11. https://doi.org/10.1111/j.1572-0241.2003.07465.x
65 Dykes S, Smilgin-Humphreys S, Bass C. Chronic idiopathic constipation: a psychological enquiry. Eur J Gastroenterol Hepatol. 2001;13(1):39–44. https://doi.org/10.1097/00042737-200101000-00007
66 Nehra V, Bruce BK, Rath-Harvey DM, Pemberton JH, Camilleri M. Psychological disorders in patients with evacuation disorders and constipation in a tertiary practice. Am J Gastroenterol. 2000;95(7):1755–8. https://doi.org/10.1111/j.1572-0241.2000.02184.x
67 Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther. 2010;31(9):938–49. https://doi.org/10.1111/j.1365-2036.2010.04273.x
68 Zhou L, Lin Z, Lin L, Wang M, Zhang H. Functional constipation: implications for nursing interventions. J Clin Nurs. 2010;19(13–14):1838–43. https://doi.org/10.1111/j.1365-2702.2010.03246.x
69 Albiani JJ, Hart SL, Katz L, Berian J, Del Rosario A, Lee J, et al. Impact of depression and anxiety on the quality of life of constipated patients. J Clin Psychol Med Settings. 2013;20(1):123–32. https://doi.org/10.1007/s10880-012-9306-3
70 Ohkusa T, Koido S, Nishikawa Y, Sato N. Gut microbiota and chronic constipation: a review and update. Front Med. 2019;6:19. https://doi.org/10.3389/fmed.2019.00019
71 Vandeputte D, Falony G, Vieira-Silva S, Tito RY, Joossens M, Raes J. Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. Gut. 2016;65(1):57–62. https://doi.org/10.1136/gutjnl-2015-309618
72 Cherbut C, Ferrier L, Roze C, Anini Y, Blottiere H, Lecannu G, et al. Short-chain fatty acids modify colonic motility through nerves and polypeptide yy release in the rat. Am J Physiol. 1998;275(6):G1415–22. https://doi.org/10.1152/ajpgi.1998.275.6.G1415
73 Fukumoto S, Tatewaki M, Yamada T, Fujimiya M, Mantyh C, Voss M, et al. Short-chain fatty acids stimulate colonic transit via intraluminal 5-ht release in rats. Am J Physiol Regul Integr Comp Physiol. 2003;284(5):R1269–76. https://doi.org/10.1152/ajpregu.00442.2002

74 Bunnett NW. Neuro-humoral signalling by bile acids and the TGR5 receptor in the gastrointestinal tract. J Physiol. 2014; 592(14):2943–50. https://doi.org/10.1113/jphysiol.2014.271155
75 Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell. 2015; 161(2):264–76. https://doi.org/10.1016/j.cell.2015.02.047
76 Khalif IL, Quigley EM, Konovitch EA, Maximova ID. Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. Dig Liver Dis. 2005;37(11): 838–49. https://doi.org/10.1016/j.dld.2005.06.008
77 Sahakian AB, Jee SR, Pimentel M. Methane and the gastrointestinal tract. Dig Dis Sci. 2010;55(8):2135–43. https://doi.org/10.1007/s10620-009-1012-0
78 van der Schoot A, Helander C, Whelan K, Dimidi E. Probiotics and synbiotics in chronic constipation in adults: a systematic review and meta-analysis of randomized controlled trials. Clin Nutr. 2022;41(12):2759–77. https://doi.org/10.1016/j.clnu.2022.10.015
79 Tian H, Ge X, Nie Y, Yang L, Ding C, McFarland LV, et al. Fecal microbiota transplantation in patients with slow-transit constipation: a randomized, clinical trial. PLoS One. 2017;12(2):e0171308. https://doi.org/10.1371/journal.pone.0171308
80 Palsson OS, Whitehead WE, van Tilburg MA, Chang L, Chey W, Crowell MD, et al. Rome iv diagnostic questionnaires and tables for investigators and clinicians. Gastroenterology. 2016;3:S0016–5085. https://doi.org/10.1053/j.gastro.2016.02.014
81 Nakajima S, Takahashi K, Sato J, Fukuda M, Yamamoto K, Inoue T, et al. Spectra of functional gastrointestinal disorders diagnosed by Rome iii integrative questionnaire in a Japanese outpatient office and the impact of overlapping. J Gastroenterol Hepatol. 2010;25(Suppl 1):S138–143. https://doi.org/10.1111/j.1440-1746.2010.06244.x
82 Le Pluart D, Sabate JM, Bouchoucha M, Hercberg S, Benamouzig R, Julia C. Functional gastrointestinal disorders in 35,447 adults and their association with body mass index. Aliment Pharmacol Ther. 2015;41(8):758–67. https://doi.org/10.1111/apt.13143
83 Park KS, Jee SR, Lee BE, Hong KS, Shin JE, Na SY, et al. Motility: nationwide multicenter study for overlaps of common functional gastrointestinal disorders in Korean patients with constipation. J Neurogastroenterol Motil. 2017;23(4): 569–77. https://doi.org/10.5056/jnm17033
84 Vakil N, Stelwagon M, Shea EP, Miller S. Symptom burden and consulting behavior in patients with overlapping functional disorders in the US population. United Eur Gastroenterol J. 2016;4(3):413–22. https://doi.org/10.1177/2050640615600114
85 Knowles CH, Scott SM, Legg PE, Allison ME, Lunniss PJ. Level of classification performance of kess (symptom scoring system for constipation) validated in a prospective series of 105 patients. Dis Colon Rectum. 2002;45(6):842–3. https://doi.org/10.1007/s10350-004-6309-7
86 Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci. 1998;43(2):400–11. https://doi.org/10.1023/a:1018831127942
87 Kanazawa M, Drossman DA, Shinozaki M, Sagami Y, Endo Y, Palsson OS, et al. Translation and validation of a Japanese version of the irritable bowel syndrome-quality of life measure (ibs-qol-j). Biopsychosoc Med. 2007;1:6. https://doi.org/10.1186/1751-0759-1-6
88 American College of Gastroenterology Chronic Constipation Task Force. An evidence-based approach to the management of chronic constipation in North America. Am J Gastroenterol. 2005; 100(Suppl 1):S1–4. https://doi.org/10.1111/j.1572-0241.2005.50613_1.x
89 American Gastroenterological Association; Bharucha AE, Dorn SD, Lembo A, Pressman A. American gastroenterological association medical position statement on constipation. Gastroenterology. 2013;144(1):211–7. https://doi.org/10.1053/j.gastro.2012.10.029
90 Remes-Troche JM, Coss-Adame E, Lopez-Colombo A, Amieva-Balmori M, Carmona Sanchez R, Charua Guindic L, et al. The Mexican consensus on chronic constipation. Rev Gastroenterol Mex. 2018; 83(2):168–89. https://doi.org/10.1016/j.rgmx.2017.12.005
91 Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas A, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med. 2012; 366(8):697–706. https://doi.org/10.1056/NEJMoa1108895
92 Pepin C, Ladabaum U. The yield of lower endoscopy in patients with constipation: survey of a university hospital, a public county hospital, and a veterans administration medical center. Gastrointest Endosc. 2002;56(3):325–32. https://doi.org/10.1016/s0016-5107(02)70033-3
93 Manabe N, Kamada T, Hata J, Haruma K. New ultrasonographic evaluation of stool and/or gas distribution for treatment of chronic constipation. Int J Colorectal Dis. 2018;33(3):345–8. https://doi.org/10.1007/s00384-018-2964-3
94 Manabe N, Kamada T, Kusunoki H, Hata J, Haruma K. Usefulness of ultrasonographic evaluation of stool and/or gas distribution for the treatment strategy of chronic constipation. JGH Open. 2019;3(4):310–5. https://doi.org/10.1002/jgh3.12162
95 Matsumoto M, Misawa N, Tsuda M, Manabe N, Kessoku T, Tamai N, et al. Expert consensus document: diagnosis for chronic constipation with faecal retention in the rectum using ultrasonography. Diagnostics. 2022;12(2):300. https://doi.org/10.3390/diagnostics12020300
96 Metcalf AM, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW, Wolff BG. Simplified assessment of segmental colonic transit. Gastroenterology. 1987;92(1):40–7. https://doi.org/10.1016/0016-5085(87)90837-7
97 Abe T, Kunimoto M, Hachiro Y, Ohara K, Inagaki M, Murakami M. Rectosigmoid localization of radiopaque markers for identifying defecation disorders in patients with chronic constipation: a retrospective cohort study. J Neurogastroenterol Motil. 2021;27(3):419–25. https://doi.org/10.5056/jnm20204
98 Spiller RC, Thompson WG. Bowel disorders. Am J Gastroenterol. 2010;105(4): 775–85. https://doi.org/10.1038/ajg.2010.69
99 Mizukami T, Sugimoto S, Masaoka T, Suzuki H, Kanai T. Colonic dysmotility and morphological abnormality frequently detected in Japanese patients with irritable bowel syndrome. Intest Res. 2017;15(2): 236–43. https://doi.org/10.5217/ir.2017.15.2.236
100 Inoh Y, Kanoshima K, Ohkuma K, Fuyuki A, Uchiyama S, Ohkubo H, et al. Assessment of colonic contents in patients with chronic constipation using MRI. J Clin Biochem Nutr. 2018;62(3):277–80. https://doi.org/10.3164/jcbn.17-104
101 Major G, Murray K, Singh G, Nowak A, Hoad CL, Marciani L, et al. Demonstration of differences in colonic volumes, transit, chyme consistency, and response to psyllium between healthy and constipated subjects using magnetic resonance imaging. Neurogastroenterol Motil. 2018;30(9):e13400. https://doi.org/10.1111/nmo.13400
102 Khalaf A, Nowak A, Menys A, Marciani L, Taylor SA, Spiller RC, et al. Cine mri assessment of motility in the unprepared small bowel in the fasting and fed state: beyond the breath-hold. Neurogastroenterol Motil. 2019;31(1):e13466. https://doi.org/10.1111/nmo.13466
103 Khalaf A, Hoad CL, Menys A, Nowak A, Taylor SA, Paparo S, et al. Mri assessment of the postprandial gastrointestinal motility and peptide response in healthy humans. Neurogastroenterol Motil. 2018;30(1). https://doi.org/10.1111/nmo.13182
104 Kanmaniraja D, Arif-Tiwari H, Palmer SL, Kamath A, Lewis SC, Flusberg M, et al. MR defecography review. Abdom Radiol. 2021; 46(4):1334–50. https://doi.org/10.1007/s00261-019-02228-4
105 Bharucha AE, Wald A. Chronic constipation. Mayo Clin Proc. 2019;94(11): 2340–57. https://doi.org/10.1016/j.mayocp.2019.01.031

106 Bharucha AE, Pemberton JH, Locke GR 3rd. American gastroenterological association technical review on constipation. Gastroenterology. 2013;144(1):218–38. https://doi.org/10.1053/j.gastro.2012.10.028
107 Bove A, Pucciani F, Bellini M, Battaglia E, Bocchini R, Altomare DF, et al. Consensus statement aigo/siccr: diagnosis and treatment of chronic constipation and obstructed defecation (part i: diagnosis). World J Gastroenterol. 2012;18(14):1555–64. https://doi.org/10.3748/wjg.v18.i14.1555
108 Grossi U, Carrington EV, Bharucha AE, Horrocks EJ, Scott SM, Knowles CH. Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defecation. Gut. 2016;65(3):447–55. https://doi.org/10.1136/gutjnl-2014-308835
109 Rao SS. Constipation: evaluation and treatment of colonic and anorectal motility disorders. Gastrointest Endosc Clin N Am. 2009;19(1):117–39. vii. https://doi.org/10.1016/j.giec.2008.12.006
110 Ratuapli S, Bharucha AE, Harvey D, Zinsmeister AR. Comparison of rectal balloon expulsion test in seated and left lateral positions. Neurogastroenterol Motil. 2013;25(12):e813–820. https://doi.org/10.1111/nmo.12208
111 Kinoshita Y, Shoji S, Hayashi T, Okumura H. A cross-sectional analysis of the health-related quality of life and work productivity in Japanese subjects with self-reported chronic constipation using the national health and wellness survey 2017. Nihon Shokakibyo Gakkai Zasshi. 2020;117(6):504–13. https://doi.org/10.11405/nisshoshi.117.504
112 Inoue R, Sakaue Y, Kawada Y, Tamaki R, Yasukawa Z, Ozeki M, et al. Dietary supplementation with partially hydrolyzed guar gum helps improve constipation and gut dysbiosis symptoms and behavioral irritability in children with autism spectrum disorder. J Clin Biochem Nutr. 2019;64(3):217–23. https://doi.org/10.3164/jcbn.18-105
113 Polymeros D, Beintaris I, Gaglia A, Karamanolis G, Papanikolaou IS, Dimitriadis G, et al. Partially hydrolyzed guar gum accelerates colonic transit time and improves symptoms in adults with chronic constipation. Dig Dis Sci. 2014;59(9):2207–14. https://doi.org/10.1007/s10620-014-3135-1
114 Russo L, Andreozzi P, Zito FP, Vozzella L, Savino IG, Sarnelli G, et al. Partially hydrolyzed guar gum in the treatment of irritable bowel syndrome with constipation: effects of gender, age, and body mass index. Saudi J Gastroenterol. 2015;21(2):104–10. https://doi.org/10.4103/1319-3767.153835
115 Chan TC, Yu VMW, Luk JKH, Chu LW, Yuen JKY, Chan FHW. Effectiveness of partially hydrolyzed guar gum in reducing constipation in long term care facility residents: a randomized single-blinded placebo-controlled trial. J Nutr Health Aging. 2022;26(3):247–51. https://doi.org/10.1007/s12603-022-1747-2
116 Chey SW, Chey WD, Jackson K, Eswaran S. Exploratory comparative effectiveness trial of green kiwifruit, psyllium, or prunes in US patients with chronic constipation. Am J Gastroenterol. 2021;116(6):1304–12. https://doi.org/10.14309/ajg.0000000000001149
117 Gao R, Tao Y, Zhou C, Li J, Wang X, Chen L, et al. Exercise therapy in patients with constipation: a systematic review and meta-analysis of randomized controlled trials. Scand J Gastroenterol. 2019;54(2):169–77. https://doi.org/10.1080/00365521.2019.1568544
118 Murakami K, Sasakii S, Okubo H, Takahashi Y, Hoso Y, Itabashi M, et al. Food intake and functional constipation: a cross-sectional study of 3,835 Japanese women aged 18–20 years. J Nutr Sci Vitaminol. 2007;53(1):30–6. https://doi.org/10.3177/jnsv.53.30
119 Muller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. Am J Gastroenterol. 2005;100(1):232–42. https://doi.org/10.1111/j.1572-0241.2005.40885.x
120 Koebnick C, Wagner I, Leitzmann P, Stern U, Zunft HJ. Probiotic beverage containing lactobacillus casei shirota improves gastrointestinal symptoms in patients with chronic constipation. Can J Gastroenterol. 2003;17(11):655–9. https://doi.org/10.1155/2003/654907
121 Sakai T, Makino H, Ishikawa E, Oishi K, Kushiro A. Fermented milk containing lactobacillus casei strain shirota reduces incidence of hard or lumpy stools in healthy population. Int J Food Sci Nutr. 2011;62(4):423–30. https://doi.org/10.3109/09637486.2010.542408
122 Yang YX, He M, Hu G, Wei J, Pages P, Yang XH, et al. Effect of a fermented milk containing bifidobacterium lactis dn-173010 on Chinese constipated women. World J Gastroenterol. 2008;14(40):6237–43. https://doi.org/10.3748/wjg.14.6237
123 Ibarra A, Latreille-Barbier M, Donazzolo Y, Pelletier X, Ouwehand AC. Effects of 28-day bifidobacterium animalis subsp. lactis hn019 supplementation on colonic transit time and gastrointestinal symptoms in adults with functional constipation: a double-blind, randomized, placebo-controlled, and dose-ranging trial. Gut Microbes. 2018;9(3):236–51. https://doi.org/10.1080/19490976.2017.1412908
124 Ojetti V, Ianiro G, Tortora A, D'Angelo G, Di Rienzo TA, Bibbo S, et al. The effect of lactobacillus reuteri supplementation in adults with chronic functional constipation: a randomized, double-blind, placebo-controlled trial. J Gastrointestin Liver Dis. 2014;23(4):387–91. https://doi.org/10.15403/jgld.2014.1121.234.elr
125 Ozaki K, Maruo T, Kosaka H, Mori M, Mori H, Yamori Y, et al. The effects of fermented milk containing lactococcus lactis subsp. cremoris fc on defaecation in healthy young Japanese women: a double-blind, placebo-controlled study. Int J Food Sci Nutr. 2018;69(6):762–9. https://doi.org/10.1080/09637486.2017.1417977
126 Higashikawa F, Noda M, Awaya T, Nomura K, Oku H, Sugiyama M. Improvement of constipation and liver function by plant-derived lactic acid bacteria: a double-blind, randomized trial. Nutrition. 2010;26(4):367–74. https://doi.org/10.1016/j.nut.2009.05.008
127 Fuyuki A, Higurashi T, Kessoku T, Ashikari K, Yoshihara T, Misawa N, et al. Efficacy of bifidobacterium bifidum g9-1 in improving quality of life in patients with chronic constipation: a prospective intervention study. Biosci Microbiota Food Health. 2021;40(2):105–14. https://doi.org/10.12938/bmfh.2020-073
128 Dimidi E, Christodoulides S, Fragkos KC, Scott SM, Whelan K. The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2014;100(4):1075–84. https://doi.org/10.3945/ajcn.114.089151
129 Ford AC, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. Am J Gastroenterol. 2014;109(10):1547–62; quiz 1546, 1562. https://doi.org/10.1038/ajg.2014.202
130 Miller LE, Ouwehand AC. Probiotic supplementation decreases intestinal transit time: meta-analysis of randomized controlled trials. World J Gastroenterol. 2013;19(29):4718–25. https://doi.org/10.3748/wjg.v19.i29.4718
131 Miller LE, Zimmermann AK, Ouwehand AC. Contemporary meta-analysis of short-term probiotic consumption on gastrointestinal transit. World J Gastroenterol. 2016;22(21):5122–31. https://doi.org/10.3748/wjg.v22.i21.5122
132 Wen Y, Li J, Long Q, Yue CC, He B, Tang XG. The efficacy and safety of probiotics for patients with constipation-predominant irritable bowel syndrome: a systematic review and meta-analysis based on seventeen randomized controlled trials. Int J Surg. 2020;79:111–9. https://doi.org/10.1016/j.ijsu.2020.04.063
133 Zhang C, Jiang J, Tian F, Zhao J, Zhang H, Zhai Q, et al. Meta-analysis of randomized controlled trials of the effects of probiotics on functional constipation in adults. Clin Nutr. 2020;39(10):2960–9. https://doi.org/10.1016/j.clnu.2020.01.005
134 Lindberg G, Hamid SS, Malfertheiner P, Thomsen OO, Fernandez LB, Garisch J, et al. World gastroenterology organisation global guideline: constipation--a global perspective. J Clin Gastroenterol. 2011;45(6):483–7. https://doi.org/10.1097/MCG.0b013e31820fb914
135 Toskes PP, Connery KL, Ritchey TW. Calcium polycarbophil compared with placebo in irritable bowel syndrome. Aliment Pharmacol Ther. 1993;7(1):87–92. https://doi.org/10.1111/j.1365-2036.1993.tb00074.x

136 Fleming V, Wade WE. A review of laxative therapies for treatment of chronic constipation in older adults. Am J Geriatr Pharmacother. 2010;8(6):514–50. https://doi.org/10.1016/S1543-5946(10)80003-0

137 Sakakibara R, Yamaguchi T, Uchiyama T, Liu Z, Yamamoto T, Ito T, et al. Calcium polycarbophil improves constipation in non-traumatic spinal cord disorders. Clin Auton Res. 2006;16(4):289–92. https://doi.org/10.1007/s10286-006-0356-1

138 Luthra P, Camilleri M, Burr NE, Quigley EMM, Black CJ, Ford AC. Efficacy of drugs in chronic idiopathic constipation: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2019;4(11):831–44. https://doi.org/10.1016/S2468-1253(19)30246-8

139 Goodoory VC, Black CJ, Ford AC. Efficacy of senna and magnesium oxide for the treatment of chronic idiopathic constipation. Am J Gastroenterol. 2021;116(6):1352–3. https://doi.org/10.14309/ajg.0000000000001041

140 Mori S, Tomita T, Fujimura K, Asano H, Ogawa T, Yamasaki T, et al. A randomized double-blind placebo-controlled trial on the effect of magnesium oxide in patients with chronic constipation. J Neurogastroenterol Motil. 2019;25(4):563–75. https://doi.org/10.5056/jnm18194

141 Morishita D, Tomita T, Mori S, Kimura T, Oshima T, Fukui H, et al. Senna versus magnesium oxide for the treatment of chronic constipation: a randomized, placebo-controlled trial. Am J Gastroenterol. 2021;116(1):152–61. https://doi.org/10.14309/ajg.0000000000000942

142 Bokhari SR, Siriki R, Teran FJ, Batuman V. Fatal hypermagnesemia due to laxative use. Am J Med Sci. 2018;355(4):390–5. https://doi.org/10.1016/j.amjms.2017.08.013

143 Horibata K, Tanoue A, Ito M, Takemura Y. Relationship between renal function and serum magnesium concentration in elderly outpatients treated with magnesium oxide. Geriatr Gerontol Int. 2016;16:600–5. https://doi.org/10.1111/ggi.12530

144 Yamaguchi H, Shimada H, Yoshita K, Tsubata Y, Ikarashi K, Morioka T, et al. Severe hypermagnesemia induced by magnesium oxide ingestion: a case series. CEN Case Rep. 2019;8(1):31–7. https://doi.org/10.1007/s13730-018-0359-5

145 Yamasaki M, Funakoshi S, Matsuda S, Imazu T, Takeda Y, Murakami T, et al. Interaction of magnesium oxide with gastric acid secretion inhibitors in clinical pharmacotherapy. Eur J Clin Pharmacol. 2014;70(8):921–4. https://doi.org/10.1007/s00228-014-1694-x

146 Kasugai K, Iwai H, Kuboyama N, Yoshikawa A, Fukudo S. Efficacy and safety of a crystalline lactulose preparation (sk-1202) in Japanese patients with chronic constipation: a randomized, double-blind, placebo-controlled, dose-finding study. J Gastroenterol. 2019;54(6):530–40. https://doi.org/10.1007/s00535-018-01545-7

147 Sanders JF. Lactulose syrup assessed in a double-blind study of elderly constipated patients. J Am Geriatr Soc. 1978;26(5):236–9. https://doi.org/10.1111/j.1532-5415.1978.tb01967.x

148 Nakajima A, Shinbo K, Oota A, Kinoshita Y. Polyethylene glycol 3350 plus electrolytes for chronic constipation: a 2-week, randomized, double-blind, placebo-controlled study with a 52-week open-label extension. J Gastroenterol. 2019;54(9):792–803. https://doi.org/10.1007/s00535-019-01581-x

149 Hammer HF, Santa Ana CA, Schiller LR, Fordtran JS. Studies of osmotic diarrhea induced in normal subjects by ingestion of polyethylene glycol and lactulose. J Clin Invest. 1989;84(4):1056–62. https://doi.org/10.1172/JCI114267

150 DiPalma JA, DeRidder PH, Orlando RC, Kolts BE, Cleveland MB. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol laxative. Am J Gastroenterol. 2000;95(2):446–50. https://doi.org/10.1111/j.1572-0241.2000.01765.x

151 Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut. 2011;60(2):209–18. https://doi.org/10.1136/gut.2010.227132

152 Bassotti G, Chiarioni G, Germani U, Battaglia E, Vantini I, Morelli A. Endoluminal instillation of bisacodyl in patients with severe (slow transit type) constipation is useful to test residual colonic propulsive activity. Digestion. 1999;60(1):69–73. https://doi.org/10.1159/000007591

153 Portalatin M, Winstead N. Medical management of constipation. Clin Colon Rectal Surg. 2012;25(1):12–9. https://doi.org/10.1055/s-0032-1301754

154 Kamm MA, Mueller-Lissner S, Wald A, Richter E, Swallow R, Gessner U. Oral bisacodyl is effective and well-tolerated in patients with chronic constipation. Clin Gastroenterol Hepatol. 2011;9(7):577–83. https://doi.org/10.1016/j.cgh.2011.03.026

155 Mueller-Lissner S, Kamm MA, Wald A, Hinkel U, Koehler U, Richter E, et al. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of sodium picosulfate in patients with chronic constipation. Am J Gastroenterol. 2010;105(4):897–903. https://doi.org/10.1038/ajg.2010.41

156 MacLennan WJ, Pooler A. A comparison of sodium picosulphate ("laxoberal") with standardised senna ("senokot") in geriatric patients. Curr Med Res Opin. 1975;2(10):641–7. https://doi.org/10.1185/03007997409111877

157 Wald A. Is chronic use of stimulant laxatives harmful to the colon? J Clin Gastroenterol. 2003;36(5):386–9. https://doi.org/10.1097/00004836-200305000-00004

158 Barish CF, Drossman D, Johanson JF, Ueno R. Efficacy and safety of lubiprostone in patients with chronic constipation. Dig Dis Sci. 2010;55(4):1090–7. https://doi.org/10.1007/s10620-009-1068-x

159 Fukudo S, Hongo M, Kaneko H, Takano M, Ueno R. Lubiprostone increases spontaneous bowel movement frequency and quality of life in patients with chronic idiopathic constipation. Clin Gastroenterol Hepatol. 2015;13(2):294–301.e5. https://doi.org/10.1016/j.cgh.2014.08.026

160 Johanson JF, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol. 2008;103(1):170–7. https://doi.org/10.1111/j.1572-0241.2007.01524.x

161 Fukudo S, Miwa H, Nakajima A, Kinoshita Y, Kosako M, Hayashi K, et al. High-dose linaclotide is effective and safe in patients with chronic constipation: a phase iii randomized, double-blind, placebo-controlled study with a long-term open-label extension study in Japan. Neurogastroenterol Motil. 2019;31(1):e13487. https://doi.org/10.1111/nmo.13487

162 Lacy BE, Schey R, Shiff SJ, Lavins BJ, Fox SM, Jia XD, et al. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. PLoS One. 2015;10(7):e0134349. https://doi.org/10.1371/journal.pone.0134349

163 Lembo AJ, Kurtz CB, Macdougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology. 2010;138(3):886–95.e1. https://doi.org/10.1053/j.gastro.2009.12.050

164 Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011;365(6):527–36. https://doi.org/10.1056/NEJMoa1010863

165 Schoenfeld P, Lacy BE, Chey WD, Lembo AJ, Kurtz CB, Reasner DS, et al. Low-dose linaclotide (72 μg) for chronic idiopathic constipation: a 12-week, randomized, double-blind, placebo-controlled trial. Am J Gastroenterol. 2018;113(1):105–14. https://doi.org/10.1038/ajg.2017.230

166 Yang Y, Fang J, Guo X, Dai N, Shen X, Yang Y, et al. Linaclotide in irritable bowel syndrome with constipation: a phase 3 randomized trial in China and other regions. J Gastroenterol Hepatol. 2018;33(5):980–9. https://doi.org/10.1111/jgh.14086

167 Rao SSC, Xiang X, Yan Y, Rattanakovit K, Patcharatrakul T, Parr R, et al. Randomised clinical trial: linaclotide vs placebo-a study of bi-directional gut and brain axis. Aliment Pharmacol Ther. 2020;51(12):1332–41. https://doi.org/10.1111/apt.15772

168 Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012;107(11):1714–p.1725. quiz p. 1725. https://doi.org/10.1038/ajg.2012.255

169 Johnston JM, Kurtz CB, Macdougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Linaclotide improves abdominal pain and bowel habits in a phase iib study of patients with irritable bowel syndrome with constipation. Gastroenterology. 2010;139(6):1877–86.e2. https://doi.org/10.1053/j.gastro.2010.08.041
170 Fukudo S, Nakajima A, Fujiyama Y, Kosako M, Nakagawa A, Akiho H, et al. Determining an optimal dose of linaclotide for use in Japanese patients with irritable bowel syndrome with constipation: a phase ii randomized, double-blind, placebo-controlled study. Neurogastroenterol Motil. 2018;30(5):e13275. https://doi.org/10.1111/nmo.13275
171 Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012;107(11):1702–12. https://doi.org/10.1038/ajg.2012.254
172 Fukudo S, Miwa H, Nakajima A, Haruma K, Kosako M, Nakagawa A, et al. A randomized controlled and long-term linaclotide study of irritable bowel syndrome with constipation patients in Japan. Neurogastroenterol Motil. 2018;30(12):e13444. https://doi.org/10.1111/nmo.13444
173 Nakajima A, Ishizaki S, Matsuda K, Kurosu S, Taniguchi S, Gillberg PG, et al. Impact of elobixibat on serum and fecal bile acid levels and constipation symptoms in patients with chronic constipation. J Gastroenterol Hepatol. 2022;37(5):883–90. https://doi.org/10.1111/jgh.15800
174 Nakajima A, Seki M, Taniguchi S, Ohta A, Gillberg PG, Mattsson JP, et al. Safety and efficacy of elobixibat for chronic constipation: results from a randomised, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial. Lancet Gastroenterol Hepatol. 2018;3(8):537–47. https://doi.org/10.1016/S2468-1253(18)30123-7
175 Abe T, Kunimoto M, Hachiro Y, Ohara K, Inagaki M, Murakami M. Efficacy and safety of elobixibat in elderly patients with chronic constipation: a single-center, observational study. J Anus Rectum Colon. 2020;4(3):122–7. https://doi.org/10.23922/jarc.2020-006
176 Ozaki A, Kessoku T, Kasai Y, Takeda Y, Okubo N, Iwaki M, et al. Elobixibat effectively relieves chronic constipation in patients with cancer regardless of the amount of food intake. Oncologist. 2021;26(10):e1862–9. https://doi.org/10.1002/onco.13879
177 Kamei D, Kamei Y, Nagano M, Mineshima M, Nitta K, Tsuchiya K. Elobixibat alleviates chronic constipation in hemodialysis patients: a questionnaire-based study. BMC Gastroenterol. 2020;20(1):26. https://doi.org/10.1186/s12876-020-1179-6
178 Matsuyama M, Hirai K, Nonaka H, Ueda M, Morino J, Kaneko S, et al. Effects of elobixibat on constipation and lipid metabolism in patients with moderate to end-stage chronic kidney disease. Front Med. 2021;8:780127. https://doi.org/10.3389/fmed.2021.780127
179 Chey WD, Camilleri M, Chang L, Rikner L, Graffner H. A randomized placebo-controlled phase iib trial of a3309, a bile acid transporter inhibitor, for chronic idiopathic constipation. Am J Gastroenterol. 2011;106(10):1803–12. https://doi.org/10.1038/ajg.2011.162
180 Eguchi T, Yoshizaki T, Ikeoka S, Takagi M, Fujinami M, Matsuda T, et al. Real-world comparison of elobixibat and lubiprostone treatment in patients with chronic constipation: a propensity score-matched analysis. Dig Dis. 2021;39(4):341–50. https://doi.org/10.1159/000512745
181 Kumagai Y, Amano H, Sasaki Y, Nakagawa C, Maeda M, Oikawa I, et al. Effect of single and multiple doses of elobixibat, an ileal bile acid transporter inhibitor, on chronic constipation: a randomized controlled trial. Br J Clin Pharmacol. 2018;84(10):2393–404. https://doi.org/10.1111/bcp.13698
182 Odaka T, Tominaga K. Uncontrolled, open-label pre-dinner administration of elobixibat in Japanese adults with chronic constipation: a retrospective chart review. Curr Ther Res Clin Exp. 2020;93:100616. https://doi.org/10.1016/j.curtheres.2020.100616
183 Simren M, Bajor A, Gillberg PG, Rudling M, Abrahamsson H. Randomised clinical trial: the ileal bile acid transporter inhibitor a3309 vs. placebo in patients with chronic idiopathic constipation--a double-blind study. Aliment Pharmacol Ther. 2011;34(1):41–50. https://doi.org/10.1111/j.1365-2036.2011.04675.x
184 Tomie A, Yoshida N, Kugai M, Hirose R, Dohi O, Inoue K, et al. The efficacy and safety of elobixibat for the elderly with chronic constipation: a multicenter retrospective cohort study. Gastroenterol Res Pract. 2020;2020:9656040. https://doi.org/10.1155/2020/9656040
185 Wong BS, Camilleri M, McKinzie S, Burton D, Graffner H, Zinsmeister AR. Effects of a3309, an ileal bile acid transporter inhibitor, on colonic transit and symptoms in females with functional constipation. Am J Gastroenterol. 2011;106(12):2154–64. https://doi.org/10.1038/ajg.2011.285
186 Aboumarzouk OM, Agarwal T, Antakia R, Shariff U, Nelson RL. Cisapride for intestinal constipation. Cochrane Database Syst Rev. 2011(1):CD007780. https://doi.org/10.1002/14651858.CD007780.pub2
187 Muller-Lissner SA. Treatment of chronic constipation with cisapride and placebo. Gut. 1987;28:1033–8. https://doi.org/10.1136/gut.28.8.1033
188 Evans BW, Clark WK, Moore DJ, Whorwell PJ. Tegaserod for the treatment of irritable bowel syndrome and chronic constipation. Cochrane Database Syst Rev. 2007(4):CD003960. https://doi.org/10.1002/14651858.CD003960.pub3
189 Kamm MA, Muller-Lissner S, Talley NJ, Tack J, Boeckxstaens G, Minushkin ON, et al. Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study. Am J Gastroenterol. 2005;100(2):362–72. https://doi.org/10.1111/j.1572-0241.2005.40749.x
190 Mozaffari S, Nikfar S, Abdollahi M. Efficacy and tolerability of renzapride in irritable bowel syndrome: a meta-analysis of randomized, controlled clinical trials including 2528 patients. Arch Med Sci. 2014;10(1):10–8. https://doi.org/10.5114/aoms.2014.40729
191 Sajid MS, Hebbar M, Baig MK, Li A, Philipose Z. Use of prucalopride for chronic constipation: a systematic review and meta-analysis of published randomized, controlled trials. J Neurogastroenterol Motil. 2016;22(3):412–22. https://doi.org/10.5056/jnm16004
192 Goldberg M, Li YP, Johanson JF, Mangel AW, Kitt M, Beattie DT, et al. Clinical trial: the efficacy and tolerability of velusetrag, a selective 5-ht4 agonist with high intrinsic activity, in chronic idiopathic constipation: a 4-week, randomized, double-blind, placebo-controlled, dose-response study. Aliment Pharmacol Ther. 2010;32(9):1102–112. https://doi.org/10.1111/j.1365-2036.2010.04456.x
193 Camilleri M, Vazquez-Roque MI, Burton D, Ford T, McKinzie S, Zinsmeister AR, et al. Pharmacodynamic effects of a novel prokinetic 5-ht receptor agonist, ati-7505, in humans. Neurogastroenterol Motil. 2007;19(1):30–8. https://doi.org/10.1111/j.1365-2982.2006.00865.x
194 Shin A, Acosta A, Camilleri M, Boldingh A, Burton D, Ryks M, et al. A randomized trial of 5-hydroxytryptamine4-receptor agonist, ykp10811, on colonic transit and bowel function in functional constipation. Clin Gastroenterol Hepatol. 2015;13(4):701–8.e1. https://doi.org/10.1016/j.cgh.2014.08.012
195 Lee HA, Ju Moon S, Yoo H, Kyung Kim M, Bok Jang S, Lee S, et al. Yh12852, a potent and selective receptor agonist of 5-hydroxytryptamine, increased gastrointestinal motility in healthy volunteers and patients with functional constipation. Clin Transl Sci. 2021;14(2):625–34. https://doi.org/10.1111/cts.12924
196 Fukudo S, Nakamura M, Hamatani T, Kazumori K, Miwa H. Efficacy and safety of 5-ht4 receptor agonist minesapride for irritable bowel syndrome with constipation in a randomized controlled trial. Clin Gastroenterol Hepatol. 2021;19(3):538–46.e8. https://doi.org/10.1016/j.cgh.2020.03.019

197 Hamatani T, Fukudo S, Nakada Y, Inada H, Kazumori K, Miwa H. Randomised clinical trial: minesapride vs placebo for irritable bowel syndrome with predominant constipation. Aliment Pharmacol Ther. 2020; 52(3):430–41. https://doi.org/10.1111/apt.15907
198 Kanazawa M, Watanabe S, Tana C, Komuro H, Aoki M, Fukudo S. Effect of 5-ht4 receptor agonist mosapride citrate on rectosigmoid sensorimotor function in patients with irritable bowel syndrome. Neurogastroenterol Motil. 2011;23(8):754–e332. https://doi.org/10.1111/j.1365-2982.2011.01732.x
199 Hirose T, Shinoda Y, Kuroda A, Yoshida A, Mitsuoka M, Mori K, et al. Efficacy and safety of daikenchuto for constipation and dose-dependent differences in clinical effects. Int J Chronic Dis. 2018;2018:1296717. https://doi.org/10.1155/2018/1296717
200 Numata T, Takayama S, Tobita M, Ishida S, Katayose D, Shinkawa M, et al. Traditional Japanese medicine daikenchuto improves functional constipation in poststroke patients. Evid Based Complement Alternat Med. 2014;2014:231258. https://doi.org/10.1155/2014/231258
201 Lazzaroni M, Casini V, Bianchi PG. Role of carbon dioxide-releasing suppositories in the treatment of chronic functional constipation: a double-blind, randomised, placebo-controlled trial. Clin Drug Investig. 2005;25:499–505.
202 Obokhare I. Fecal impaction: a cause for concern? Clin Colon Rectal Surg. 2012; 25(1):53–8. https://doi.org/10.1055/s-0032-1301760
203 Gosselink MP, Darby M, Zimmerman DD, Smits AA, van Kessel I, Hop WC, et al. Long-term follow-up of retrograde colonic irrigation for defaecation disturbances. Colorectal Dis. 2005;7(1):65–9. https://doi.org/10.1111/j.1463-1318.2004.00696.x
204 Ford AC, Lacy BE, Harris LA, Quigley EMM, Moayyedi P. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. Am J Gastroenterol. 2019;114(1):21–39. https://doi.org/10.1038/s41395-018-0222-5
205 Yang P, Wang Y, Xiao Y, Ma Q, Ma R, Mi J, et al. Acupuncture for opioid-induced constipation: protocol for a systematic review and meta-analysis. Medicine. 2020; 99(49):e23352. https://doi.org/10.1097/MD.0000000000023352
206 Katakami N, Oda K, Tauchi K, Nakata K, Shinozaki K, Yokota T, et al. Phase iib, randomized, double-blind, placebo-controlled study of naldemedine for the treatment of opioid-induced constipation in patients with cancer. J Clin Oncol. 2017;35(17):1921–8. https://doi.org/10.1200/JCO.2016.70.8453
207 Esmadi M, Ahmad D, Hewlett A. Efficacy of naldemedine for the treatment of opioid-induced constipation: a meta-analysis. J Gastrointestin Liver Dis. 2019; 28(1):41–6. https://doi.org/10.15403/jgld.2014.1121.281.any
208 Ozaki A, Kessoku T, Tanaka K, Yamamoto A, Takahashi K, Takeda Y, et al. Effectiveness of naldemedine compared with magnesium oxide in preventing opioid-induced constipation: a randomized controlled trial. Cancers. 2022;14(9):2112. https://doi.org/10.3390/cancers14092112
209 Cryer B, Katz S, Vallejo R, Popescu A, Ueno R. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med. 2014;15(11):1825–34. https://doi.org/10.1111/pme.12437
210 Spierings ELH, Drossman DA, Cryer B, Mazen Jamal M, Losch-Beridon T, Mareya SM, et al. Efficacy and safety of lubiprostone in patients with opioid-induced constipation: phase 3 study results and pooled analysis of the effect of concomitant methadone use on clinical outcomes. Pain Med. 2018;19(6):1184–94. https://doi.org/10.1093/pm/pnx156
211 Zhang Y, Yin F, Xu L, Li YF, Chen JC, Liu HX, et al. Comparative efficacy of drugs for the treatment of chronic constipation: quantitative information for medication guidelines. J Clin Gastroenterol. 2020; 54(10):e93–e102. https://doi.org/10.1097/MCG.0000000000001303
212 Nelson AD, Camilleri M, Chirapongsathorn S, Vijayvargiya P, Valentin N, Shin A, et al. Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: a systematic review and network meta-analysis. Gut. 2017; 66(9):1611–22. https://doi.org/10.1136/gutjnl-2016-311835
213 Bleijenberg G, Kuijpers HC. Treatment of the spastic pelvic floor syndrome with biofeedback. Dis Colon Rectum. 1987; 30(2):108–11. https://doi.org/10.1007/BF02554946
214 Weber J, Ducrotte P, Touchais JY, Roussignol C, Denis P. Biofeedback training for constipation in adults and children. Dis Colon Rectum. 1987;30(11):844–6. https://doi.org/10.1007/BF02555421
215 Cadeddu F, Salis F, De Luca E, Ciangola I, Milito G. Efficacy of biofeedback plus transanal stimulation in the management of pelvic floor dyssynergia: a randomized trial. Tech Coloproctol. 2015;19(6): 333–8. https://doi.org/10.1007/s10151-015-1292-7
216 Heymen S, Jones KR, Scarlett Y, Whitehead WE. Biofeedback treatment of constipation: a critical review. Dis Colon Rectum. 2003;46(9): 1208–17. https://doi.org/10.1007/s10350-004-6717-8
217 Chiarioni G, Whitehead WE, Pezza V, Morelli A, Bassotti G. Biofeedback is superior to laxatives for normal transit constipation due to pelvic floor dyssynergia. Gastroenterology. 2006;130(3):657–64. https://doi.org/10.1053/j.gastro.2005.11.014
218 Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. Gastroenterology. 2005;129(1):86–97. https://doi.org/10.1053/j.gastro.2005.05.015
219 Abildgaard HA, Borgager M, Ellebaek MB, Qvist N. Ileal neoappendicostomy for antegrade colonic enema (ace) in the treatment of fecal incontinence and chronic constipation: a systematic review. Tech Coloproctol. 2021;25(8):915–21. https://doi.org/10.1007/s10151-021-02434-7
220 Uno Y. Introducer method of percutaneous endoscopic cecostomy and antegrade continence enema by use of the chait trapdoor cecostomy catheter in patients with adult neurogenic bowel. Gastrointest Endosc. 2006;63(4):666–73. https://doi.org/10.1016/j.gie.2005.12.035
221 Balata M, Elgendy H, Emile SH, Youssef M, Omar W, Khafagy W. Functional outcome and sexual-related quality of life after transperineal versus transvaginal repair of anterior rectocele: a randomized clinical trial. Dis Colon Rectum. 2020;63(4):527–37. https://doi.org/10.1097/DCR.0000000000001595
222 Boccasanta P, Agradi S, Vergani C, Calabro G, Bordoni L, Missaglia C, et al. The evolution of transanal surgery for obstructed defecation syndrome: mid-term results from a randomized study comparing double tst 36 hv and contour transtar staplers. Am J Surg. 2018;216(5):893–9. https://doi.org/10.1016/j.amjsurg.2018.01.074
223 Formijne Jonkers HA, Poierrie N, Draaisma WA, Broeders IA, Consten EC. Laparoscopic ventral rectopexy for rectal prolapse and symptomatic rectocele: an analysis of 245 consecutive patients. Colorectal Dis. 2013;15(6):695–9. https://doi.org/10.1111/codi.12113
224 Renzi A, Brillantino A, Di Sarno G, D'Aniello F, Ferulano G, Falato A, et al. Evaluating the surgeons' perception of difficulties of two techniques to perform starr for obstructed defecation syndrome: a multicenter randomized trial. Surg Innov. 2016;23(6):563–71. https://doi.org/10.1177/1553350616656281
225 Shi Y, Yu Y, Zhang X, Li Y. Transvaginal mesh and transanal resection to treat outlet obstruction constipation caused by rectocele. Med Sci Monit. 2017;23:598–605. https://doi.org/10.12659/msm.898790
226 Kawahara H, Omura N, Akiba T. The usefulness of preoperative evaluation for intractable slow transit constipation by computed tomography. J Anus Rectum Colon. 2021;5(2):144–7. https://doi.org/10.23922/jarc.2020-065
227 Aziz I, Whitehead WE, Palsson OS, Tornblom H, Simren M. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. Expert Rev Gastroenterol Hepatol. 2020;14(1):39–46. https://doi.org/10.1080/17474124.2020.1708718