Chapter

The Management of Constipation: Current Status and Future Prospects

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Abstract

Chronic constipation, a common condition, can have remarkably negative effects on a patient's quality of life. Recent research has identified factors that may influence the prognosis of chronic constipation and suggests the need for adequate therapy. However, the major obstacles in this field were: (1) a small number of therapeutic options, (2) no clear diagnostic criteria, and (3) no effective method to collect information form the patients. These were due to the fact that bowel movement patterns vary widely among individuals, and also the functional constipation, including irritable bowel syndrome, is difficult to be distinguished from the chronic constipation. Recently, it has been demonstrated that the Rome IV diagnostic criteria of functional constipation and the Bristol stool form scale are useful for the objective evaluation and recording of stool. Based on these developments, and the increase of newly developed medicines the therapy for the constipation is significantly changing and therefore, if conventional therapy for chronic constipation is ineffective, switching of medicines is possible. Therefore, clinicians should update the information of these newly developed drugs available in clinics and diagnostic criteria. For this purpose, in this chapter, we have summarized the perspective on the current paradigm of treatment for chronic constipation focusing on recently introduced therapeutic drugs.

Keywords: chronic constipation, Rome IV diagnostic criteria, secretagogues, lubiprostone

1. Introduction

Many reports describe a high prevalence of constipation worldwide. For example, a survey conducted in North America by Higgins et al. reported prevalence rates of 12–19%, particularly among older populations [1]. Generally, research suggests that constipation reduces the patient's quality of life (QOL) to a level comparable with the negative effects of allergy or inflammatory bowel disease [2]. Despite these negative characteristics, however, a clear overview of chronic constipation has not yet been established.

The Rome IV diagnostic criteria, which were revised in 2016, are often used to evaluate functional constipation. However, these diagnostic criteria exclude irritable bowel syndrome (IBS), a prevalent condition (7–21%) that exists on a continuous spectrum with functional constipation. Notably, IBS and functional constipation may be associated with predominant symptoms such as abdominal pain or bloating, which are not necessarily predominant in all cases of constipation [3]. This suggests that IBS and functional constipation often overlap in real-world scenarios [4]. Furthermore, the diagnosis of chronic constipation, which often involves the appraisal of symptoms (including QOL measures), and associated therapies appear to be incomplete.

In addition to the lack of diagnostic and treatment methodology, the Japan Collaborative Cohort Study found evidence suggesting that a low bowel movement frequency increases the risks of cardiovascular disease (CVD), such as stroke and ischemic myocardial infarction, and of related mortality. The same study also found a high incidence of CVD among laxative users in Japan [5, 6]. Therefore, the effect of constipation indicates an increasingly poor prognosis. In this chapter, we review the present clinical practices targeting constipation and discuss newly introduced therapeutic drugs for constipation, such as secretagogues, which have recently yielded medical advances. With this review, we aim to prevent a perspective on the future treatment of chronic constipation.

2. Definition of constipation

Individual bowel movement patterns (including constipation) vary widely and are easily affected by many factors, including changes in the diet, living environment, mental status, and time course [7, 8]. Additionally, physicians and patients may hold different understandings of constipation. Consequently, the term "constipation" may encompass a broad spectrum of symptoms and situations. Despite these differences, constipation can be adequately defined as a status in which comfortable defecation is impossible, in accordance with many international clinical practice guidelines and review articles, as well as the Rome IV criteria [4, 9, 10].

3. Chronic constipation, including chronic functional constipation and IBS

Constipation can be roughly classified as acute or chronic, each of which can be further divided according to an organized or functional pathogenic mechanism. However, this chapter will discuss specifically chronic functional constipation in adult patients and its deleterious effects on the long-term QOL. Previously, the Rome III criteria were used to diagnose chronic functional constipation when a stringent definition is required for research purposes. In May 2016, however, the revised Rome IV criteria were published [10] (**Table 1**). Notably, these updated criteria include the requirement of other symptoms associated with difficulty of defecation and incompleteness of evacuation, as well as symptoms associated with constipation, and do not diagnose chronic functional constipation based on the frequency of bowel movements alone. Of note, these criteria require the exclusion of IBS prior to a diagnosis of chronic functional constipation (**Table 2**). However, this condition overlaps with IBS in many clinical cases. Accordingly, we recommend that in actual clinical settings, cases in which a patient's continued inability to defecate comfortably that has deleterious effects on daily life should be managed

Diagnostic criteria[a] for functional constipation (FC)
1. Must include 2 or more of the following:[b] a. Straining during more than one-fourth (25%) of defecations b. Lumpy or hard stools (Bristol Stool Form Scale: BSFS 1-2) more than one-fourth (25%) of defecations c. Sensation of incomplete evacuation more than one-fourth (25%) of defecations d. Sensation of anorectal obstruction/blockage more than one-fourth (25%) of defecations e. Manual maneuvers to facilitate more than one fourth (25%) of defecations (e.g., digital evacuation, support of the pelvic floor) f. Fewer than 3 spontaneous bowel movements per week 2. Loose stools are rarely present without the use of laxatives 3. Insufficient criteria for irritable bowel syndrome
[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. *[b]For research studies, patients meeting criteria for Opioid-Induced Constipation (OIC) should not be given a diagnosis of FC because it is difficult to distinguish between opioid side effects and other causes of constipation. However, clinicians recognize that these 2 conditions might overlap.*

Table 1.
The diagnostic criteria for functional constipation: This criteria is cited from "Mearin et al. [10]".

Diagnostic criteria[a] for irritable bowel syndrome
Recurrent abdominal pain, on average, at least a day per week in the last 3 months, associated with 2 or more of the following criteria: 1. Related to defecation 2. Associated with a change in frequency of stool 3. Associated with a change in form (appearance) of stool
[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Table 2.
The diagnostic criteria for irritable bowel syndrome: This criteria is cited from "Mearin, et al. [10]".

as chronic constipation, even if the Rome IV criteria are not fulfilled [4]. Later, we discuss the diagnosis and management of chronic constipation, including chronic functional constipation and IBS.

3.1 Alarming symptoms associated with chronic constipation

Particular attention should be given to the management of constipation associated with alarming symptoms, which may correlate with a poor outcome due to the required therapy for an underlying disease or surgically treated condition. Patients with alarming symptoms should be further scrutinized and subjected to additional diagnostic testing before treatment is administered for constipation. Potentially alarming symptoms may include a change in stool caliber, heme-positive stool, iron-deficiency anemia, obstructive symptoms, an age of >50 years with no history of colon cancer screening, recent onset of constipation, rectal bleeding, rectal prolapse, and weight loss [9–11]. Such symptoms should be considered an indication for colonoscopy.

3.2 Secondary constipation

Secondary constipation should be excluded prior to a diagnosis of functional or chronic constipation due to IBS, as underlying high-risk diseases and etiologies must be identified [4, 10, 11]. Secondary constipation can be subdivided coarsely into drug-induced and symptomatic cases. Consequently, a diagnostic interview for chronic constipation should inquire about the time of onset, duration of disease, frequency of bowel movements, consistency of stool, symptoms associated with

constipation, and the presence of concrete situations of dyschezia (e.g., abdominal pain and/or bloating, sensation of incomplete evacuation, need for manual maneuvers to facilitate defecation, and evacuation time). A clinical history, including lifestyle factors and dietary fiber and fluid intake, should also be taken. A systemic physical examination that includes a digital rectal examination (palpation for gastrointestinal mass, anorectal inspection to assess fecal impaction, stricture, rectal prolapse, rectocele, paradoxical or nonrelaxing puborectalis activity, and rectal mass), laboratory analyses (complete blood counts, biochemical profile, calcium and glucose levels, and thyroid function tests) and colonoscopy is also required to exclude secondary constipation. In summary, underlying diseases and drug-affected constipation should be considered in an evaluation of chronic constipation.

3.2.1 Underlying diseases

The diagnosis and treatment of underlying diseases is very important in the management of chronic constipation. Underlying diseases that may cause chronic constipation are listed below [9]:

Mechanical obstruction: colorectal tumor, diverticulosis, stricture, external compression from tumor/other structures, large rectocele, megacolon, postoperative abnormalities, and anal fissure.

Neurological disorders/neuropathy: autonomic neuropathy, cerebrovascular disease, cognitive impairment/dementia, depression, multiple sclerosis, Parkinson's disease, and spinal cord pathology.

Endocrine/metabolic conditions: chronic kidney disease (CKD), dehydration, diabetes mellitus, heavy metal poisoning, hypercalcemia, hypermagnesemia, hyperparathyroidism, hypokalemia, hypomagnesemia, hypothyroidism, multiple endocrine neoplasia II, and porphyria.

Gastrointestinal disorders and local painful conditions: IBS, abscess, anal fissure, fistula, hemorrhoids, levator ani syndrome, megacolon, proctalgia fugax, rectal prolapse, rectocele, and volvulus.

Myopathies: amyloidosis, dermatomyositis, scleroderma, and systemic sclerosis.

Dietary causes: dieting, fluid depletion, low fiber intake, anorexia, dementia, and depression.

Other causes: cardiac disease, degenerative joint disease, and immobility.

3.2.2 Drug-induced constipation

When evaluating a case of chronic constipation, the patient's current profile of medicine use must be understood precisely and considered during further treatment. A list of drugs that may cause chronic constipation is provided below [9].

Prescription drugs: antidepressants, antiepileptics, antihistamines, antiparkinson drugs, antipsychotics, antispasmodics, calcium channel blockers, diuretics, monoamine oxidase inhibitors, opiates, sympathomimetics, tricyclic antidepressants, and statins.

Self-medication (i.e., over-the-counter drugs): antacids (containing aluminum and calcium), antidiarrheal agents, calcium and iron supplements, and nonsteroidal anti-inflammatory drugs.

4. Diagnostic approaches to the treatment of chronic constipation

An interview based on the diagnostic criteria (**Table 1**) for functional constipation is useful when planning treatment for chronic constipation. The simple

and objective Bristol stool form scale, which is used worldwide, is particularly useful for enabling an evaluation and record of the stool form and thus elucidating an individual patient's defecation status [12, 13]. When possible, the patient should maintain a stool diary that includes the number of bowel movements per day and stool consistency (Bristol stool form types 1–7, **Figure 1**) for approximately 1 week. This record is also useful for evaluating symptoms and sensations (e.g., sensation of incomplete evacuation, abdominal pain, and/or bloating) after evacuation [4].

The Bristol scale can also be used to estimate the colonic transit time. Currently, cases of functional constipation are categorized as normal-transit, slow-transit, or defecatory rectal evacuation disorder [10]. A previous histological analysis reported that slow-transit constipation results from a reduction in Cajal cells [14], suggesting that this type is caused by a decrease in the statuses of lower postprandial phasic responses (e.g., the disappearance of bowel peristalsis) [15]. Other research indicates that defecatory rectal evacuation disorders are caused by functional failures (e.g., pelvic floor line coordination disturbance) [16]. Although Bristol stool form types 1 and 2 can be attributed to slower transit constipation and types 6 and 7 are characteristic of rapid transit constipation [17], patients who meet the diagnostic criteria for functional constipation often exhibit characteristics of slow colonic transit constipation [18]. Still, the diagnosis of defecatory rectal evacuation disorders does not require diagnostic colonic and anorectal testing [19].

An improved QOL is among the most important goals of treatment for chronic constipation. Accordingly, various questionnaires are useful during the processes of diagnosis and treatment (see Section 5). If initial conservative medical management does not cure chronic constipation, additional measures such as the balloon expulsion test [8, 20, 21], manometric assessment [20], defecography [22], and radiopaque marker testing of the whole-gut transit time should be considered [23]. Additional tests may also be performed, although the availability may be limited to certain medical centers or countries. Accordingly, interinstitutional cooperation is important.

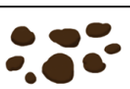
Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage, but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces (entirely liquid)

Figure 1.
The Bristol Stool Form Scale: This scale is a useful tool to evaluate stool and can evaluate colonic transit time

5. Self-reported questionnaires for diagnostic purposes

Questionnaire-based self-report measures can be classified by the type of QOL evaluation and type of constipation severity quantitation. Various methods are currently advocated, although further progress in this area is needed [24]. The questionnaires most frequently mentioned in a literature search via the PubMed database are shown below.

5.1 Evaluation of severity of constipation

Constipation scoring system (CSS) [25]. The CSS comprises eight questionnaire items to assess the frequency of bowel movements, difficult or painful evacuation, completeness of evacuation, abdominal pain, time per attempt, type of assistance (including laxatives, digitation, or enemas), number of unsuccessful attempts at evacuation in a 24-h period, and duration of constipation. All but one item are scored on a 5-point Likert scale (range: 0–4); the type of assistance, including laxatives, is scored on a 3-point scale (range: 0–2). A cutoff score of 15 is used to indicate constipation.

Patient assessment of constipation symptoms (PAC-SYM) [26]. The PAC-SYM was validated for the assessment of chronic functional constipation in 216 adult patients in the USA. This tool includes 12 items to assess abdominal, rectal, and stool factors. The items are scored on a 5-point Likert scale (range: 0–4), with a score of 4 indicating the worst symptom severity. The total possible scores for the PAC-SYM range from 0 to 48, and no diagnostic cutoff score has been reported. This questionnaire has a 7-point Likert scale for four items of abdominal symptoms and three items of rectal symptoms (e.g., abdominal pain, bloating, and rectal burning) from no discomfort to very severe discomfort.

5.2 QOL evaluation tool

Gastrointestinal symptom rating scale (GSRS) [27]. The GSRS is a questionnaire comprising 15 items intended to address common gastrointestinal symptoms. The scale can be completed by the patient within approximately 5 min, and the items are scored on a 7-point Likert scale ranging from no discomfort to very severe discomfort. For evaluation purposes, a mean scale score is calculated for the equivalent of items (e.g., heart burn, nausea, and abdominal pain), and a high score indicates more severe symptoms.

Patient assessment of constipation quality of life (PAC-QOL) [28]. The PAC-QOL is a simple self-reported questionnaire used to measure the patient's QOL associated with constipation, including daily behavioral and therapeutic aspects relevant to constipation during the previous 2 week period. The PAC-QOL comprises 28 items divided into four subscales that address the patient's worries/concerns relevant to constipation, physical discomfort, psychosocial discomfort, and satisfaction. The items are scored on a 5-point scale, and a higher score indicates a lower QOL. The original edition was developed in English and has since been translated into many languages.

6. Practical treatment

In this section, we aim to provide an overview of the various available treatments for chronic constipation for which the details have been published. Patient education is a very important first step in the therapeutic management of chronic

constipation [3]. Patients should be instructed to consume an adequate quantity of dietary fiber (total fiber intake: 20–30 g/day), set a routine of regular toilet time after mealtimes, and take an on-defecation position involving elevation of the lower limbs. If such measures are ineffective, an oral fiber supplement, such as psyllium (up to 30 mg/day in divided doses) may be attempted [29].

Drug therapy should be initiated if the above-described lifestyle modifications fail to treat chronic constipation, and this should be accompanied by an assessment of bowel movements every 2–4 weeks to determine the therapeutic effects. Generally, osmotic laxatives (e.g., lactulose, lactitol, mannitol, and sorbitol) are administered initially as these are cost-effective and have few adverse effects [18, 30]. Although saline laxatives (e.g., magnesium sulfate) are frequently administered in Japan, these drugs are not widely accepted worldwide and have only been evaluated clinically in small-scale randomized controlled trials (RCTs) [31]. Furthermore, patients with renal failure face the risk of serious hypermagnesemia consequent to the use of magnesium sulfate [32]. However, this drug should be considered, given its low cost and abundant use in Japan. Polyethylene glycol laxatives (17–34 g/day) should also be considered, as many RCTs have indicated that these agents are more effective than lactulose [33, 34].

If chronic constipation remains unresolved by the above therapies, newer medicines should be considered. Recent years have seen the rapid development of novel agents such as secretagogues (e.g., lubiprostone and linaclotide). However, as the availability and indications of these new drugs for chronic constipation vary among countries, all medical treatment for chronic constipation should comply with national clinical practice guidelines or guiding principle. Finally, surgical or biofeedback treatment should be considered for cases of chronic constipation that cannot be resolved with medication and patients with defecatory rectal evacuation disorders [35, 36].

7. New therapeutic drugs for chronic constipation

The extensive development of novel drugs for chronic constipation has led to variability in the potential applications among countries. For example, neither secretagogues (e.g., plecanatide) nor serotonergic enterokinetic agents (e.g., prucalopride and selective 5-hydroxytryptamine receptor agonists) have been approved for use in Japan. Below, we comment mainly on the new therapeutic drugs for chronic constipation that have been authorized for use in Japan.

7.1 Lubiprostone

Various studies have analyzed lubiprostone, the most well-developed one of the newer class of drugs. The mechanism of action of this constipation-targeting drug is interesting. Lubiprostone is a selective type-2 chloride channel (ClC-2 channel) activator. This biogenic bicyclic fatty acid was developed by Cuppoletti and Ueno for the treatment of chronic constipation and has been approved for use worldwide after the initial authorization for manufacturing and marketing in the US and Japan. [37, 38] Lubiprostone is the first clinically applied secretagogue, and accordingly, a broad range of clinical experience is associated with this drug. Moreover, the mechanism of action of this drug has been analyzed in much greater detail relative to secretagogues introduced subsequently. Specifically, this drug activates ClC-2 channels expressed in the apical membranes of intestinal epithelial cells and exerts its laxative function by inducing the secretion of intestinal fluids. The ability of lubiprostone to improve constipation symptoms has been validated through RCTs

[39], which reported the maintenance of efficacy throughout a 48-week administration period with no significant side effects [40].

Lubiprostone promotes the secretion of intestinal fluid by activating ClC-2 channels. Upon absorption from the small intestine, lubiprostone is degraded immediately to an inactive metabolite. Therefore, the effects of this drug are tissue selective, and few side effects have been observed. In the small intestine, lubiprostone activates the ClC-2 channels expressed on mucosal epithelial cells to promote the transport of chloride ions from the visceral lumen and concomitant countertransport of cations into the lumen. This activity induces a difference in the local osmotic pressure across the epithelial cell membrane, and the resulting secretion of intestinal fluid expedites defecation [41, 42]. As the expression of the ClC-2 channel is not expected to vary according to age, sex, or race, lubiprostone may be effective in elderly patients with constipation.

Clinical usefulness of lubiprostone for chronic constipation. As mentioned above, multiple RCTs have validated the effectiveness of lubiprostone for chronic constipation [39] and demonstrated a both sustained efficacy and a lack of serious adverse effects during a 48-week period of administration. The most common side effects of this drug include nausea (frequency: 19.8%), diarrhea (9.7%), abdominal distension (6.9%), headache (6.9%), and abdominal pain (5.2%) [40]. Recently, the mechanism of action of lubiprostone as a therapeutic drug for constipation was investigated in detail (see below.) Notably, a study based on a questionnaire regarding QOL, work productivity, and lifestyle impairment found that lubiprostone improved both symptoms related to chronic constipation and the patients' QOL [43]. In a phase 3 trial, Fukudo et al. found that long-term lubiprostone administration was associated with an average increase in the average spontaneous bowel movement (SBM) number per week and an improved QOL among Japanese patients with chronic idiopathic constipation [44]. In a randomized, double-blind, placebo-controlled trial of the effects of lubiprostone on chronic idiopathic constipation in diabetic patients, Christie et al. found that this drug reduced the colon transit time and increased the SBM number safely and effectively [45].

Parkinson's disease: Parkinson's disease is a very common neurodegenerative disorder characterized by motility disturbances. Constipation occurs very frequently in affected patients and is a predictor of the onset of movement disorder. Constipation appears as a symptom prior to more obvious signs of parkinsonism before disappearance of dopamine cells in substantia nigra. Accordingly, clinicians should consider the early detection of a movement disorder when evaluating cases of constipation. In a double-blind RCT of the efficacy and tolerability of lubiprostone in patients with Parkinson's disease with constipation, Ondo et al. concluded that the drug was well tolerated and effective when administered for a short duration [46].

Efficacy of lubiprostone for CKD: Mishima et al. demonstrated clearly that lubiprostone could inhibit an exacerbation of adenine-induced CKD by altering the intestinal environment or intestinal flora. That study suggested that in a patient with CKD, the intestinal tract acts as a conduit for uremic toxin excretion that is comparable with hemodialysis and urine. Lubiprostone may, therefore, be a novel therapeutic drug for CKD [47].

Protective effects on the small intestine and "leaky gut syndrome." The small intestine serves as a barrier for the selective transport of molecules in and out of the gastrointestinal tract. Failure of this barrier function renders the patient unable to absorb the nutrient for use as energy and can enable the transport of microbial pathogens and harmful chemical substances into the interior of the body. This state is known as the "leaky gut syndrome" and is thought to induce various diseases, including gastrointestinal diseases (e.g., inflammatory bowel disease), allergies,

diabetes, connective tissue diseases, and liver diseases [48]. Therefore, the prevention of leaky gut syndrome would be therapeutically valuable.

No currently available therapeutic drug can improve abnormal intestinal tract permeability in humans. However, Moeser et al. revealed that lubiprostone not only promotes the secretion of intestinal fluid by activating ClC-2 channels but also protects and restores injured small intestinal mucosa [49]. The mechanism underlying the restoration of tight junctions in the mucosa remains unknown, although the ClC-2 channel was found to play an important role in restoring the tight-junction structure and barrier function in a mouse model of colitis [48]. Furthermore, Kato et al. demonstrated that lubiprostone could improve intestinal permeability in humans [50]. Although these research findings require validation, lubiprostone appears to be a promising treatment for leaky gut syndrome.

Anti-inflammatory effect. Experimentally, lubiprostone was shown to prevent indomethacin-induced intestinal disease through a mechanism dependent on the prostaglandin EP4 receptor subtype in male Sprague-Dawley rats. This effect might suppress excessive intestinal motility and promote intestinal fluid secretion, while controlling bacterial invasion and inducible nitric-oxide synthase/tumor necrosis factor alpha expression, the main pathological events of intestinal disease. However, it is difficult to understand how the protective effect of lubiprostone would rely on the direct activation of the cystic fibrosis transmembrane regulator/ClC-2 channel [51].

Promotion of mucin secretion. Lubiprostone has been shown to promote mucin secretion in the small intestinal mucosa via a prostaglandin-like action and thus maintain digestive function [51]. Lubiprostone might also promote the intestinal transit of feces by providing lubrication and could thus improve the likelihood of comfortable defecation [52, 53].

Lubiprostone in clinic. A previous report indicated a correlation of Munchausen syndrome with the overuse of stimulant laxatives [54], which presents a challenge regarding dependence on these drugs. We, therefore, investigated whether lubiprostone administration would facilitate a reduction in the dose of a continuously administered stimulant laxative. In real clinics, we have shown the successful reduction or cessation of the stimulant laxative (e.g., sodium picosulfate, senna) in more than 50% of cases (n = 21) within 6 months of administering lubiprostone (manuscript in preparation). Notably, no further medications were needed in these cases. These clinical experiences suggested us that the lubiprostone may be useful not only for the symptom itself but also for the reduction of stimulant laxatives leading to the safe and cost effective treatment of constipation.

7.2 Linaclotide

Linaclotide is a newly developed therapeutic drug for chronic constipation and constipation-predominant IBS. This drug is absorbed at low levels and has few adverse effects, of which the main complaint is diarrhea [55]. This peptide drug comprises 14 amino acids and acts by binding to the guanylate cyclase C (GC-C) receptor expressed on intestinal epithelial cells, which promotes the secretion of fluids into the intestinal lumen. The GC-C receptor is associated with bodily fluid and ionic homeostasis, bowel movements, and relief from afferent pain signaling and is thus considered a therapeutic target for chronic constipation and constipation-predominant IBS [56].

When compared with placebo, linaclotide yielded excellent results in terms of the reduction in abdominal pain and increase in complete SBMs at 12 weeks after the initial first administration [57]. Furthermore, linaclotide was associated with a significant increase in the average QOL score relative to placebo in a questionnaire-based survey [58]. A cost-effectiveness analysis study revealed that

the less expensive linaclotide yielded equivalent patient satisfaction to that achieved with lubiprostone [59]. As chronic constipation overlaps partially with constipation-predominant IBS, linaclotide may greatly expand the treatment options for constipation. Although linaclotide has been prescribed widely at our hospital at an appropriate once-daily dosage of 0.5 mg, we presume that many physicians may initiate this drug at a daily dosage of 0.25 mg to avoid adverse effects.

7.3 Elobixibat

Bile acids are synthesized from cholesterol in the liver and secreted to the duodenum, where they play an essential role in lipid digestion and absorption. Upon reaching the terminal ileum, bile acids are absorbed solely by the ileal bile acid transporter (IBAT) expressed only in the terminal ileum [60]. Here, 95% of the bile acids are reabsorbed through the portal system and are reconjugated and reexcreted into bile by hepatocytes in an enterohepatic cycle that occurs 2–15 times daily. Unabsorbed bile acids are transported to the colon, where they encourage the secretion of water into the large bowel lumen and thus promote large bowel movement [61, 62]. Accordingly, the administration of ursodeoxycholic acid or the occurrence of ileal diseases that enable the transport of excess amounts of bile acids to the large bowel can cause diarrhea [60].

The drug elobixibat specifically inhibits the IBAT required for bile acid reabsorption and is thus commercially available as the first IBAT inhibitor. Through its inhibitory actions, elobixibat increases the entry of bile acids into the large bowel and thus promotes evacuation. When administered orally, this drug is absorbed at low levels; accordingly, it has few adverse effects and is considered safe [63]. In Japan, elobixibat is administered orally at a once-daily dosage of 10 mg before a meal. However, the usage of this drug may vary among countries and should be confirmed carefully. To date, elobixibat has been used in only seven cases at our hospital in the short time since it has been licensed. Although only two patients have used this drug continuously for at least 2 months, all treated patients have achieved complete SBM. Elobixbat appears to act simultaneously as a stool softener and laxative stimulant. We expect that the use of this drug will increase.

7.4 Naldemedine

Naldemedine, a peripherally acting μ-opioid receptor antagonist, was developed as a therapeutic drug for opioid-induced constipation and is approved in the US and Japan [64]. This new class medication showed important therapeutic effect in improving opioid-induced constipation without reducing the efficacy of opioid drugs because it selectively targets the peripheral μ-opioid receptor as demonstrated in two-phase 3 trials [65, 66]. Therefore, although opioid-induced constipation has been initially treated with conventional laxatives, however, based on these evidences, naldemedine is expected to become a leading therapy for cases using opioids. Recently, we are switching to naldemedine to manage the constipation in cases using opioid, and approximately one-third of patients using opioids have been treated with naldemedine and showed the safe and effective bowel movement (manuscript in preparation).

8. Conclusion

To improve the QOL in the cases suffered with chronic constipation, the appropriate therapeutic intervention is essential. With the rise in the therapeutic options

and its real world data, and the objective assessment methods, its treatment is dramatically changing. It is obvious that the correct diagnosis excluding the emergent situation is essential; however, the physicians need to update the information for these newly developed medicines useful for constipation and switch from the conventional agents for better QOL.

As the appropriate use of these new agents under various conditions remains uncertain, therefore, the accumulation of the clinical information, real-world data are necessary. For this purpose, this review overviewed the symptoms, diagnosis, and medicines available to date. We hope that these informations are useful for physicians treating patients and that various pathophysiological studies will elucidate the correct use of these new anticonstipation agents.

Furthermore, we hope that the development of a more ideal questionnaire will enable effective decisions regarding the most effective treatment for chronic constipation.

Conflict of interest

The authors declare that they have no current financial arrangement or affiliation with any organization that may have a direct influence on their work.

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References

[1] Higgins PD, Johanson JF. Epidemiology of constipation in North America: A systematic review. The American Journal of Gastroenterology. 2004;**99**:750-759. DOI: 10.1111/j.1572-0241.2004.04114.x

[2] Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: Impact of constipation on quality of life in adults and children. Alimentary Pharmacology & Therapeutics. 2010;**31**:938-949. DOI: 10.1111/j.1365-2036.2010.04273.x

[3] Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: A clinical review. Journal of the American Medical Association. 2015;**313**:949-958. DOI: 10.1001/jama.2015.0954

[4] Rao SS, Rattanakovit K, Patcharatrakul T. Diagnosis and management of chronic constipation in adults. Nature Reviews. Gastroenterology & Hepatology. 2016;**13**:295-305. DOI: 10.1038/nrgastro.2016.53

[5] 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. Journal of Epidemiology. 2016;**26**:242-248. DOI: 10.2188/jea.JE20150123

[6] 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**:251-256. DOI: 10.1016/j.atherosclerosis.2016.01.007

[7] Herz MJ, Kahan E, Zalevski S, Aframian R, Kuznitz D, Reichman S. Constipation: A different entity for patients and doctors. Family Practice. 1996;**13**:156-159

[8] Bharucha AE, Pemberton JH, Locke GR 3rd. American Gastroenterological Association technical review on constipation. Gastroenterology. 2013;**144**:218-238. DOI: 10.1053/j.gastro.2012.10.028

[9] Lindberg G, Hamid SS, Malfertheiner P, Thomsen OO, Fernandez LB, Garisch J, et al. World gastroenterology organisation global guideline: Constipation–a global perspective. Journal of Clinical Gastroenterology. 2011;**45**:483-487. DOI: 10.1097/MCG.0b013e31820fb914

[10] Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel disorders. Gastroenterology. 2016. DOI: 10.1053/j.gastro.2016.02.031

[11] Wald A. Constipation: Advances in diagnosis and treatment. Journal of the American Medical Association. 2016;**315**:185-191. DOI: 10.1001/jama.2015.16994

[12] O'Donnell LJ, Virjee J, Heaton KW. Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. BMJ. 1990;**300**:439-440. DOI: 10.1136/bmj.300.6722.439

[13] Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology. 2006;**130**:1480-1491. DOI: 10.1053/j.gastro.2005.11.061

[14] He CL, Burgart L, Wang L, Pemberton J, Young-Fadok T, Szurszewski J, et al. Decreased interstitial cell of cajal volume in patients with slow-transit constipation. Gastroenterology. 2000;**118**:14-21. DOI: 10.1016/S0016-5085(00)70409-4

[15] O'Brien MD, Camilleri M, von der Ohe MR, Phillips SF, Pemberton JH, Prather CM, et al. Motility and tone of the left colon in constipation: A role in

clinical practice? The American Journal of Gastroenterology. 1996;**91**:2532-2538

[16] Rao SS, Welcher KD, Leistikow JS. Obstructive defecation: A failure of rectoanal coordination. The American Journal of Gastroenterology. 1998;**93**:1042-1050. DOI: 10.1111/j.1572-0241.1998.00326.x

[17] Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scandinavian Journal of Gastroenterology. 1997;**32**:920-924. DOI: 10.3109/00365529709011203

[18] Ford AC, Moayyedi P, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. The American Journal of Gastroenterology. 2014;**109**(Suppl 1):S2-S26; quiz S27. DOI: 10.1038/ajg.2014.187

[19] Rao SS, Bharucha AE, Chiarioni G, Felt-Bersma R, Knowles C, Malcolm A, et al. Functional anorectal disorders. Gastroenterology. 2016. DOI: 10.1053/j.gastro.2016.02.009

[20] 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 Journal of Gastroenterology. 2012;**18**:1555-1564. DOI: 10.3748/wjg.v18.i14.1555

[21] Ratuapli S, Bharucha AE, Harvey D, Zinsmeister AR. Comparison of rectal balloon expulsion test in seated and left lateral positions. Neurogastroenterology and Motility. 2013;**25**:e813-e820. DOI: 10.1111/nmo.12208

[22] Pelsang RE, Rao SS, Welcher K. FECOM: A new artificial stool for evaluating defecation. The American Journal of Gastroenterology. 1999;**94**:183-186. DOI: 10.1111/j.1572-0241.1999.00793.x

[23] Remes-Troche JM, Rao SS. Diagnostic testing in patients with chronic constipation. Current Gastroenterology Reports. 2006;**8**:416-424

[24] McCrea GL, Miaskowski C, Stotts NA, Macera L, Hart SA, Varma MG. Review article: Self-report measures to evaluate constipation. Alimentary Pharmacology & Therapeutics. 2008;**27**:638-648. DOI: 10.1111/j.1365-2036.2008.03626

[25] Agachan F, Chen T, Pfeifer J, Reissman P, Wexner SD. A constipation scoring system to simplify evaluation and management of constipated patients. Diseases of the Colon and Rectum. 1996;**39**:681-685. DOI: 10.1007/BF02056950

[26] Frank L, Kleinman L, Farup C, Taylor L, Miner P Jr. Psychometric validation of a constipation symptom assessment questionnaire. Scandinavian Journal of Gastroenterology. 1999;**34**:870-877. DOI: 10.1080/003655299750025327

[27] Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the gastrointestinal symptom rating scale in patients with gastroesophageal reflux disease. Quality of Life Research. 1998;**7**:75-83

[28] Marquis P, De La Loge C, Dubois D, McDermott A, Chassany O. Development and validation of the patient assessment of constipation quality of life questionnaire. Scandinavian Journal of Gastroenterology. 2005;**40**:540-551. DOI: 10.1080/00365520510012208

[29] Moayyedi P, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. The effect of fiber supplementation on irritable bowel syndrome: A systematic

review and meta-analysis. The American Journal of Gastroenterology. 2014;**109**:1367-1374. DOI: 10.1038/ajg.2014.195

[30] Suares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: Systematic review and meta-analysis. The American Journal of Gastroenterology. 2011;**106**:1582-1591; quiz 1581, 1592. DOI: 10.1038/ajg.2011.164

[31] Dupont C, Campagne A, Constant F. Efficacy and safety of a magnesium sulfate-rich natural mineral water for patients with functional constipation. Clinical Gastroenterology and Hepatology. 2014;**12**(8):1280-1287. DOI: 10.1016/j.cgh.2013.12.005

[32] Nyberg C, Hendel J, Nielsen OH. The safety of osmotically acting cathartics in colonic cleansing. Nature Reviews. Gastroenterology & Hepatology. 2010;**7**:557-564. DOI: 10.1038/nrgastro.2010.136

[33] Dipalma JA, Cleveland MV, McGowan J, Herrera JL. A randomized, multicenter, placebo-controlled trial of polyethylene glycol laxative for chronic treatment of chronic constipation. The American Journal of Gastroenterology. 2007;**102**:1436-1441. DOI: 10.1111/j.1572-0241.2007.01199.x

[34] Attar A, Lémann M, Ferguson A, Halphen M, Boutron MC, Flourié B, et al. Comparison of a low dose polyethylene glycol electrolyte solution with lactulose for treatment of chronic constipation. Gut. 1999;**44**:226-230. DOI: 10.1136/gut.44.2.226

[35] Bleijenberg G, Kuijpers HC. Treatment of the spastic pelvic floor syndrome with biofeedback. Diseases of the Colon and Rectum. 1987;**30**:108-111. DOI: 10.1007/BF02554946

[36] Rao SS, Benninga MA, Bharucha AE, Chiarioni G, Di Lorenzo C, Whitehead WE. ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. Neurogastroenterology and Motility. 2015;**27**:594-609. DOI: 10.1111/nmo.12520

[37] Cuppoletti J, Malinowska DH, Tewari KP, Li QJ, Sherry AM, Patchen ML, et al. SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. American Journal of Physiology. Cell Physiology. 2004 Nov;**287**(5):C1173-C1183. Epub 2004 Jun 22

[38] Bao HF, Liu L, Self J, Duke BJ, Ueno R, Eaton DC. A synthetic prostone activates apical chloride channels in A6 epithelial cells. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2008;**295**(2):G234-G251. DOI: 10.1152/ajpgi.00366.2007 Epub 2008 May 29

[39] Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: Systematic review and meta-analysis. Gut. 2011;**60**:209-218. DOI: 10.1136/gut.2010.227132

[40] Lembo AJ, Johanson JF, Parkman HP, Rao SS, Miner PB Jr, Ueno R. Long-term safety and effectiveness of lubiprostone, a chloride channel (ClC-2) activator, in patients with chronic idiopathic constipation. Digestive Diseases and Sciences. 2011;**56**:2639-2645. DOI: 10.1007/s10620-011-1801-0

[41] Cuppoletti J, Malinowska DH, Tewari KP, Li QJ, Sherry AM, Patchen ML, et al. SPI-0211 activates T84 cell chloride transport and recombinant human ClC-2 chloride currents. American Journal of Physiology. Cell Physiology. 2004;**287**:C1173-C1183

[42] Bao HF, Liu L, Self J, Duke BJ, Ueno R, Eaton DC. A synthetic prostone activates apical chloride channels in A6

epithelial cells. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2008;**295**:G234-G251. DOI: 10.1152/ajpgi.00366.2007

[43] Abe T, Hachiro Y, Ebisawa Y, Hishiyama H, Murakami M, Kunimoto M. Efficacy of lubiprostone in chronic constipation: Clinical and work productivity outcomes. Journal of Gastrointestinal and Digestive System. 2014;**4**:5. DOI: 10.4172/2161-069X.1000223

[44] 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. Clinical Gastroenterology and Hepatology. 2015;**13**:294-301.e5. DOI: 10.1016/j.cgh.2014.08.026

[45] Christie J, Shroff S, Shahnavaz N, Carter LA, Harrison MS, Dietz-Lindo KA, et al. A randomized, double-blind, placebo-controlled trial to examine the effectiveness of lubiprostone on constipation symptoms and colon transit time in diabetic patients. The American Journal of Gastroenterology. 2017;**112**: 356-364. DOI: 10.1038/ajg.2016.531

[46] Ondo WG, Kenney C, Sullivan K, Davidson A, Hunter C, Jahan I, et al. Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease. Neurology. 2012;**78**:1650-1654. DOI: 10.1212/WNL.0b013e3182574f28

[47] Mishima E, Fukuda S, Shima H, Hirayama A, Akiyama Y, Takeuchi Y, et al. Alternation of the intestinal environment by Lubiprostone is associated with amelioration of adenine-induced CKD. Journal of the American Society of Nephrology. 2015;**26**: 1787-1794. DOI: 10.1681/ASN.2014060530

[48] Jin Y, Pridgen TA, Blikslager AT. Pharmaceutical activation or genetic absence of ClC-2 alters tight junctions during experimental colitis. Inflammatory Bowel Diseases. 2015;**21**:2747-2757. DOI: 10.1097/MIB.0000000000000550

[49] Moeser AJ, Nighot PK, Engelke KJ, Ueno R, Blikslager AT. Recovery of mucosal barrier function in ischemic porcine ileum and colon is stimulated by a novel agonist of the ClC-2 chloride channel, lubiprostone. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2007;**292**:G647-G656. DOI: 10.1152/ajpgi.00183.2006

[50] Kato T, Honda Y, Kurita Y, Iwasaki A, Sato T, Kessoku T, et al. Lubiprostone improves intestinal permeability in humans, a novel therapy for the leaky gut: A prospective randomized pilot study in healthy volunteers. PLoS One. 2017;**12**:e0175626. DOI: 10.1371/journal.pone.0175626

[51] Hayashi S, Kurata N, Yamaguchi A, Amagase K, Takeuchi K. Lubiprostone prevents nonsteroidal anti-inflammatory drug-induced small intestinal damage by suppressing the expression of inflammatory mediators via EP4 receptors. The Journal of Pharmacology and Experimental Therapeutics. 2014;**349**:470-479. DOI: 10.1124/jpet.114.213991

[52] Majewski M, Sarosiek I, Wallner G, Edlavitch SA, Sarosiek J. Stimulation of mucin, mucus, and viscosity during lubiprostone in patients with chronic constipation may potentially lead to increase of lubrication. Clinical and Translational Gastroenterology. 2014;**5**:e66. DOI: 10.1038/ctg.2014.19

[53] De Lisle RC. Lubiprostone stimulates small intestinal mucin release. BMC Gastroenterology. 2012;**12**:156. DOI: 10.1186/1471-230X-12-156

[54] Oster JR, Materson BJ, Rogers AI. Laxative abuse syndrome. The American Journal of Gastroenterology. 1980;**74**:451-458

[55] Andresen V, Camilleri M. Linaclotide acetate. Drugs of the Future. 2008;**33**:570-576. DOI: 10.1358/dof.2008.033.07.1214164

[56] Góngora-Benítez M, Tulla-Puche J, Albericio F. Constella™(EU)-Linzess™(USA): The last milestone in the long journey of the peptide linaclotide and its implications for the future of peptide drugs. Future Medicinal Chemistry. 2013;**5**:291-300. DOI: 10.4155/fmc.13.5

[57] Sood R, Ford AC. Linaclotide: New mechanisms and new promise for treatment in constipation and irritable bowel syndrome. Therapeutic Advances in Chronic Disease. 2013;**4**:268-276. DOI: 10.1177/2040622313500110

[58] O'Dell KM, Rummel AE, Fang NC, Nguyen NN. Linaclotide: A guanylate cyclase type-C agonist for the treatment of constipation-predominant irritable bowel syndrome and chronic constipation. Formulary. 2012;**47**:15-22. DOI: 10.4103/0972-4958.121571

[59] Huang H, Taylor DC, Carson RT, Sarocco P, Friedman M, Munsell M, et al. Economic evaluation of linaclotide for the treatment of adult patients with chronic idiopathic constipation in the United States. Managed Care. 2016;**25**:41-48. DOI: 10.3111/13696998.2014.979291

[60] Jiang C, Xu Q, Wen X, Sun H. Current developments in pharmacological therapeutics for chronic constipation. Acta Pharmaceutica Sinica B. 2015;**5**:300-309. DOI: 10.1016/j.apsb.2015.05.006

[61] Mekjian HS, Phillips SF, Hofmann AF. Colonic secretion of water and electrolytes induced by bile acids: Perfusion studies in man. The Journal of Clinical Investigation. 1971;**50**:1569-1577. DOI: 10.1172/JCI106644

[62] Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. The proximal colonic motor response to rectal mechanical and chemical stimulation. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2002;**282**:G443-G449. DOI: 10.1152/ajpgi.00194.2001

[63] Acosta A, Camilleri M. Elobixibat and its potential role in chronic idiopathic constipation. Therapeutic Advances in Gastroenterology. 2014;**7**:167-175. DOI: 10.1177/1756283X14528269

[64] Markham A. Naldemedine: First global approval. Drugs. 2017;**77**:923-927. DOI: 10.1007/s40265-017-0750-0

[65] Hale M, Wild J, Reddy J, Yamada T, Arjona Ferreira JC. Naldemedine versus placebo for opioid-induced constipation (COMPOSE-1 and COMPOSE-2): Two multicentre, phase 3, double-blind, randomised, parallel-group trials. The Lancet Gastroenterology & Hepatology. 2017;**2**:555-564. DOI: 10.1016/S2468-1253(17)30105-X

[66] Katakami N, Harada T, Murata T, Shinozaki K, Tsutsumi M, Yokota T, et al. Randomized phase III and extension studies of naldemedine in patients with opioid-induced constipation and cancer. Journal of Clinical Oncology. 2017;**35**:3859-3866. DOI: 10.1200/JCO.2017.73.0853