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Review

Abdominal Bloating: Pathophysiology and Treatment

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Abdominal bloating is a very common and troublesome symptom of all ages, but it has not been fully understood to date. Bloating is usually associated with functional gastrointestinal disorders or organic diseases, but it may also appear alone. The pathophysiology of bloating remains ambiguous, although some evidences support the potential mechanisms, including gut hypersensitivity, impaired gas handling, altered gut microbiota, and abnormal abdominal-phrenic reflexes. Owing to the insufficient understanding of these mechanisms, the available therapeutic options are limited. However, medical treatment with some prokinetics, rifaximin, lubiprostone and linaclotide could be considered in the treatment of bloating. In addition, dietary intervention is important in relieving symptom in patients with bloating.
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Key Words
Bloating; Pathophysiology; Rifaximin; Therapy

Introduction

Bloating is one of the most common gastrointestinal (GI) symptoms, which is a frequent complaint in the patients of all ages. This symptom is very common in patients with irritable bowel syndrome (IBS) and other functional gastrointestinal disorders (FGIDs) as well as in patients with organic disorders. Many clinicians encounter the patients' complaints such as "too much gas in abdomen," "heavy and uncomfortable feeling in abdomen" and "full belly." The severity of bloating is varied from mild discomfort to severe, and it is one of the bothersome symptoms of the patients, affecting their quality of life. Despite being one of the frequent and bothersome complaints, bloating remains incompletely understood of all the symptoms. Therefore clinicians need to be more considerate when evaluating patients with abdominal bloating.

The possible causes of bloating are various and complicated, thus intestinal gas production and transit, gut microflora and hypersensitivity of the patient's gut might be the factors for the symptom generation. As the underlying mechanism of bloating remains elusive to date, there are few evidences for diagnostic and

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therapeutic options available. In addition, patients who complain of bloating tend to have IBS or functional dyspepsia (FD), thus most of the therapeutic approaches of abdominal bloating are based on the treatments of IBS and FD.[1-4] However bloating could occur alone without associated diseases and there has been not enough data of randomized controlled trials for treatment of bloating alone. The treatments for bloating have not been standardized and there is no evidence-based algorithm. Although there have been several comprehensive reviews for pathophysiology or treatment of abdominal bloating in FGID (Table 1),[5-10] both clinical trials and systematic reviews regarding functional bloating (FB) alone are scarce so far. Only one available pilot study was from Spain, which indicated that sugar intolerance was frequently observed in patients with FB and associated with bloating symptom. Additionally, a malabsorbed sugar-free diet gave rise to clinical improvement in high percentage of patients.[11] Thus, in the clinical setting, rational treatment for bloating is hard and the result of treatment is frequently unsatisfactory. Most treatment options for bloating are similar to treatments for IBS, but as previously mentioned, FB and IBS are in different disease entities.

Aims and Methods

Our aim was to explain the clinical importance, pathophysiologic mechanisms, and management of abdominal bloating, thus to provide a better understanding of this specific problem. We reviewed the literature of mechanisms and treatment interventions for abdominal bloating based on a PubMed search on the following terms; "abdominal bloating," "intestinal gas and IBS," "distension and IBS" and "FGID." We also quoted important knowledge from a standard textbook, the chapter "intestinal gas."[12]

Definition

Bloating is defined as subjective discomfort by patient's sensation of intestinal gas; otherwise, abdominal distension is a visible increase in abdominal girth. In the past, bloating had been considered to be related to abdominal distension directly, but recent studies have suggested that it is not always accompanied by abdominal distension.[13] There have been many studies to evaluate the relationship between bloating and abdominal distension. One study has shown that actual abdominal distension only occurred in about half of the patients suffering from bloating.[14] In addition, some patients with both visceral hypersensitivity and FGID complained of bloating in the absence of visible distension.[15,16] Briefly, abdominal bloating is the subjective symptom and distension is the objective sign, so bloating and distension should be considered as separate disorders with different mechanisms. Although bloating has been considered as a supportive symptom for IBS or FD according to Rome classification, FB is also included as an independent entity in Rome criteria.[17-19] The diagnosis of FB is made in patients who do not meet the diagnostic criteria of IBS or other FGIDs, but have recurrent symptoms of bloating. According to Rome III, the diagnostic criteria include recurrent feeling of bloating or visible distension at least 3 days a month in the last 3 months with symptom onset at least 6 months prior to diagnosis. Also it should exclude FD, IBS or other FGIDs. The name has been changed from functional abdominal bloating in Rome I and II criteria to functional bloating in Rome III criteria.[17-19]

Epidemiology

'Bloating' has been first described by Alvarez of the Mayo Clinic in 1949, in a woman patient with psychological problem.[20] In USA, 15-30% of general population has been reported to experience bloating.[16,21,22] Also in Asia, similar result has been shown (15-23%), suggesting that the prevalence of bloating is not interracially different.[23] Though the data for FB alone are relatively little, women typically have higher rates of bloating than men according to the reports of IBS.[16,21,22] This relevance between female gender and bloating has long been suggested and the hormonal effect in connection with menstrual cycle is regarded as one of the possible explanation.[24,25] Besides, there are some reports of obese people experiencing more GI symptoms such as abdominal pain or bloating.[26,27]

Bloating is the second most common reported symptom in patients with IBS following abdominal pain.[28] In a study from USA which assessed bloating in 542 IBS patients, 76% of the patients reported that they experienced bloating.[29] Other study revealed that more than 90% of patients with IBS suffered from bloating.[30] In addition, on comparing constipation dominant IBS (IBS-C) with diarrhea dominant IBS (IBS-D), the prevalence of bloating was higher in IBS-C.[31]

A survey from the USA suggested that more than 65% of patients with bloating rated their symptom as moderate to severe, and 54% of patients complained of decreased daily activity due to bloating. Furthermore, 43% of patients took medication for bloating or needed medication.[22]

Table 1. Summary of the Comprehensive Reviews for Abdominal Bloating

Author (yr)	Study aim (method)	Suggested mechanisms of bloating	Treatment strategy
Zar et al[5] (2002)	Pathophysiology and treatment for bloating in functional bowel disorders	1. Abnormal gas trapping 2. Fluid retension 3. Food intolerance 4. Altered gut microflora [c]altered abdominal muscle tone, altered mucosal sensitivity, colonic motor abnormalities	1. Limited efficacy; dietary intervention, activated charcoal, simethicone, hypnotherapy 2. No efficacy; antibiotics, probiotics, prokinetics
Houghton et al[6] (2005)	Pathophysiology and treatment for bloating in FGIDs	1. Gas accumulation 2. Visceral hypersensitivity 3. Fluid retension [a]motor dysfunction, abnormal gut flora, weak abdominal musculature	1. Some benefit; tegaserod, non-absorbable antibiotics, hypnotherapy, surfactant 2. No efficacy; probiotics, activated charcoal, exercise, weight loss, 5-HT_3 antagonist
Azpiroz et al[7] (2005)	Clinical importance, pathophysiology and management of abdominal bloating (literature review from January 1989 to September 2004, based on a PubMed search)	1. Altered abdominal wall activity 2. Abnormal perception 3. Intraluminal contents 4. Impaired gut and gas handling [b]Intraluminal gas volume	1. Some benefit; hypnosis, antidepressant 2. Undetermined; prokinetics, spasmolytics, peppermint oil, gas-reducing substances, exclusion diet, exercise
Agrawal et al[8] (2008)	Epidemiology and pathophysiology of abdominal bloating in FGIDs (literature review up to 2006, based on a Medline search)	1. Abnormal gas handling 2. Visceral hypersensitivity 3. Abnormal anterior wall muscular activity [a]carbohydrate intolerance, altered gut flora, small bowel bacterial overgrowth [b]gas excess, altered intestinal transit	1. Effective; prokinetics (tegaserod, neostigmine), antibiotcs (neomycin, rifiximin) 2. Worth trying; dietary intervention 3. Little evidence; simethicone, charcoal, antispasmodics, probiotics
Schmulson et al[9] (2011)	Treatmentfor abdominal bloating and distension (literature review up to February 2010 in Medline)	Not available	1. Some efficacy; 5-HT_4 agonist (cisapride, tegaserod), lubiprostone, rifaximin, some probiotics (*B. infantis* 35624 and *B. animalis*), antifoaming agents 2. New suggestion; low FODMAPs diet 3. Undetermined; antispasmodics, SSRIs, dopamine antagonist 4. No efficacy; bulking agents, laxatives
Lacy et al[10] (2011)	Pathophysiology, evaluation, and treatment of bloating and distension	1. Altered gut flora 2. Impaired gas transit 3. Impaired evacuation 4. Abnormal abdominal-diaphragmatic reflexes 5. Abnormal perception [a]psychosocial aspects	1. Some efficacy; exercise, rifaximin, cisapride, neostigmine, tegaserod, lubiprostone, linaclotide 2. New suggestion; diet (low FODMAPs) 3. Undetermined; simethicone, probiotics, TCAs, dopamine antagonist 4. No efficacy; antispasmodics

[a]possible mechanisms, [b]little or no evidence, [c]undetermined.
FGIDs, functional gastrointestinal disorders; 5-HT, 5-hydroxytryptamine; FODMAPs, fermentable oligo-, di- and mono-saccharides and polyols; SSRIs, selective serotonin reuptake inhibitors; TCAs, Tricyclic antidepressants.

Pathophysiology

Abnormal Gut Microbiota

The GI tract microbiota play an important role in host immune system, and there are more than 500 different species of GI microbiota in adult, which mostly are obligate anaerobes.[10] Only a fraction of these organisms can be cultured; therefore, the understanding of the functions of various microbes in the GI tract is still limited. However, researches over the past decades have shown that altered colonic flora were found in stool samples of patients with IBS.[32-34] Parkes et al[35] suggested that the GI microbiota can be divided into 2 ecosystems; the luminal bacteria and the mucosa-associated bacteria (Fig. 1). Luminal microbiota form the majority of the GI tract flora, and they play a key role in bloating and flatulence in IBS through carbohydrate fermentation and gas production.[35]

One comprehensive study of the luminal microbiota in IBS examined the fecal samples of IBS subgroups (diarrhea predominant, constipation predominant and mixed subtype) and the controls using 16S ribosomal RNA (rRNA) sequencing. It has been shown that fecal microbiota are significantly altered in IBS. That is, some patients with IBS seem to have different patterns of colonization with coliforms, such as *lactobacillus* and *bifidobacterium* compared to the controls.[36] Similar study from Korea using 16S rRNA gene signatures also has demonstrated significant differences in diversity and dominance between IBS and non-IBS fecal samples.[37] In addition, these microbial changes altered protein and carbohydrate metabolism in the gut.[37] A study from Japan also showed higher counts of *Veillonella* ($P = 0.046$) and *Lactobacillus* ($P = 0.031$) in IBS patients than in controls. Besides, they expressed significantly higher levels of acetic acid ($P = 0.049$), propionic acid ($P = 0.025$) and total organic acids ($P = 0.014$) than controls, which is related to symptoms such as abdominal pain, bloating and changes in bowel habits.[38] Another study demonstrated that the patients with IBS produced more H_2 but the total gas excretion was similar in both IBS patients and controls.[39] This may be associated with alteration in colonic fermentation by hydrogen-consuming bacteria, which may be an important factor in the pathogenesis of IBS.

Collins et al[40] have proposed that disruption of the balance between the host and intestinal microbiota produces changes in the mucosal immune system from microscopic to overt inflammation and this also results in changes in gut sensory-motor function and immune activity. Besides, these altered microflora may produce differences in fermented gas type and volume, which may be the causes of symptom in patients with bloating.[36,40,41]

There have been some reports to verify the relationship between the types of gas produced by colonic microflora and bloating. The low producers of methane reported significantly increased bloating and cramping after ingestion of sorbitol and fiber, and the high producers of methane revealed lower prevalence of severe lactulose intolerance than low producers. Hence, the role of methanogenic flora may be important in the pathogenesis of bloating.[42,43]

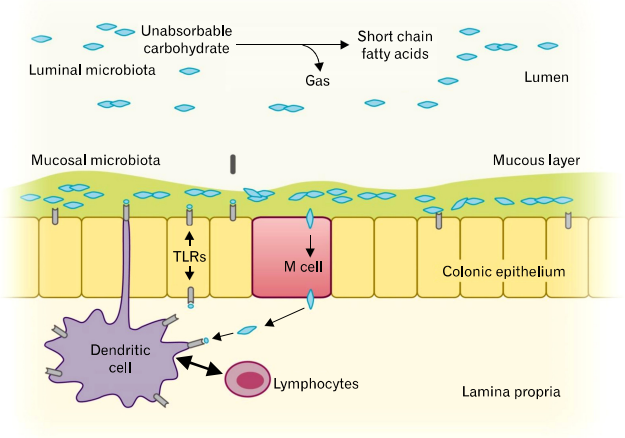

Figure 1. Luminal and mucosal colonic microbiota and their roles in gut homeostasis. Modified from Parkes et al.[35]

Small Intestinal Bacterial Overgrowth

The patients with IBS who specifically complain of bloating have been reported to have increased gas production from bacterial fermentation caused by small intestinal bacterial overgrowth (SIBO). Pimentel and colleagues had established the concept that SIBO might be a major pathogenesis of IBS.[44] Moreover, several studies found significant improvement of symptoms such as abdominal pain or bloating, when they were treated with antibiotics.[44-46] These findings, however, have not been supported by other studies;[47-49] they found mildly increased counts of small intestinal bacteria by culture to be more common in IBS, but the breath H_2 concentration was not significantly different between IBS patients and controls.[48] Also, there was no correlation between bacterial alteration and symptom pattern, and even lactulose breath test was considered as an unreliable method to detect an association between bacterial overgrowth and IBS.[47,48]

In another study, breath hydrogen concentration was similar in IBS group and control group, and did not correlate with pain ratings in IBS patients, owing to the lack of objective diagnostic measures and inconsistent data.[51]

It is unclear whether changes in small bowel bacterial flora could contribute to bloating in IBS patients, thus further studies are required to confirm these observations.

Intestinal Gas Accumulation

In the fasting state, the healthy GI tract contains only about 100 mL of gas distributed almost equally among 6 compartments - stomach, small intestine, ascending colon, transverse colon, descending colon and distal (pelvic) colon. Postprandial volume of gas increases by about 65%, primarily in the pelvic colon.[12] The excessive volume of intestinal gas has been proposed as the likely cause of bloating and distension, and many researchers have attempted to determine this view. A few studies using plain abdominal radiography demonstrated that intestinal gas volume was greater in patients with IBS than in controls (54% vs. 118%), however, the correlation between intra-abdominal gas contents and bloating was poor.[52,53] The vast majority of studies do not support that excessive gas induces bloating or abdominal pain. Lasser et al[54] conducted a study using argon washout technique, which demonstrated no differences in the accumulation of intestinal gas between patients with bloating and healthy subjects. More recent studies using CT scans combined with modern imaging analysis software have also shown that excess gas was not associated with abdominal bloating in most patients.[3] Thus, these observations suggest that increased volume of gas may not be the main mechanism of bloating, but rather impaired gas transit or distribution are more often the sources of problem.

Altered Gut Motility and Impaired Gas Handling

Various abnormal motility patterns have been described in IBS patients, but none of those parameters can be used as diagnostic markers.[55] Some authors have suggested that slow transit of food representing alteration in gut motility is related to bloating in IBS-C patients.[56] Also in a traditional experiment, normal volunteers being made constipated with loperamide, an agent known to slow transit, experienced bloating.[57] Recently, IBS-C patients with delayed orocecal and colonic transits have shown abdominal distension rather than bloating.[15] Although delayed gastric emptying and slow intestinal transit in IBS-C patients were reported in many Asian studies, there are still controversies to define these motor disturbances as unique features in Asian IBS patients. Besides, the association between altered gut motility and IBS symptoms is pretty obscure.[58] A recent study has also suggested that altered colon transit is of no or minor importance for IBS symptoms such as bloating or pain.[59]

However, there are some different points with respect to the intestinal gas handling or transit. In a study by Serra et al,[60] they have shown that infused gas into the jejunum resulted in distension and abdominal bloating in most of the IBS patients (18 of 20), while only 20% (4 of 20) of control subjects developed symptoms like that. Another study using gas challenge technique has demonstrated that small intestinal gas transit (especially, jejunum) was more prolonged in patients with bloating than in controls, whereas colonic transit was normal.[61] These data support that impaired small intestinal gas handling could be a mechanism of IBS or gas-bloating. Furthermore, a gas challenge test in healthy subjects during blocked rectal gas outflow showed that abdominal distension by girth measurement was similar in the jejunal and rectal infusion experiments, whereas abdominal symptoms including bloating were more significant in jejunal group.[62] These data indicate that gas related symptom perception is determined by intraluminal gas distribution, whereas abdominal distension depends on the volume of intestinal gas. Besides, the patients with IBS or FB are considered to evacuate intestinal gas less effectively, so that they are more likely to have symptoms of abdominal distension.[63,64] This aspect of bloating's mechanism has not been considered to be very relevant, but some researchers are interested in this view owing to the observations of anorectal function, especially in patients with constipation. Constipated patients with bloating plus distension exhibited a greater degree of anorectal dysfunction than those without distension. Moreover, self-restrained anal evacuation also increased symptom perception, while impaired gut propulsion caused by intravenous glucagon did not.[63,64]

Taken together, ineffective anorectal evacuation as well as impaired gas handling may be possible mechanisms of abdominal distension and bloating. However, the data on the link between altered food transit of gut and bloating are not consistent, although they probably account for bloating in some of the IBS patients.[56,57]

Abnormal Abdominal-diaphragmatic Reflexes

The abdominal cavity is determined by the placement of the walls of abdominal cavity including diaphragm, vertebral column and abdominal wall musculature. Even if there is no increase in

intra-abdominal volume, a change of the position of abdominal cavity components may produce abdominal distension.[7] Thus, there have been some efforts to evaluate the relationship between bloating and lumbar lordosis or weakened abdominal muscles. In one classic report, Sullivan suggested that the patients with bloating have weak abdominal muscles and frequently had recently gained weight than controls.[65] But another study measuring upper and lower abdominal wall activities using surface electromyography has suggested that there were no differences in abdominal muscle activities between the patients and the controls.[66] Moreover, in an early CT study, some IBS patients showed a tendency of lumbar lordosis but not consistent, and a change in lumbar lordosis did not correlate in any way with the changes in abdominal girth. Also, there were no noticeable changes in position of the diaphragm.[67]

Tremolaterra et al[68] reported that intestinal gas load was associated with a significant increment in abdominal wall muscle activity in healthy subjects. In contrast, the response to gas infusion was impaired in patients with bloating, and rather a paradoxical relaxation of the internal oblique muscles was noted.[68] Further study using modern CT analysis with electromyography from Barcelona group has provided a novel concept of abnormal abdomino-phrenic reflexes for abdominal bloating and distension. Since then, several studies have demonstrated that abdomino-phrenic dyssynergia is one of main factors for abdominal distension and bloating. In healthy adults, colonic gas infusion increases anterior wall tone and relaxes the diaphragm at the same time. On the contrary, patients with bloating have shown diaphragmatic contraction (descent) and relaxation of the internal oblique muscle with the same gas load.[4,69,70]

Visceral Hypersensitivity

The sensation of bloating may originate from abdominal viscera in patients with FGIDs, in whom normal stimuli or small variations of gas content within the gut may be perceived as bloating. Indeed, it has been well recognized that the patients with IBS have lower visceral perception threshold than healthy controls,[1,71] and it has been speculated that this process might be associated with the sensation of bloating. Kellow et al[72] revealed that threshold for perception of small bowel contraction was lower than normal in some patients with IBS. Also, altered rectal perception assessed by phasic balloon distension has been reported in IBS patients.[73] In addition, a gas challenge test proved a role of sensory disturbances in IBS patients,[60] and recent clinical experiment has demonstrated that bloating without visible distension is associated with visceral hypersensitivity.[74]

The autonomic nervous system may also contribute to modulation of the visceral sensitivity. Sympathetic activation is known to increase the perception of intestinal distention in FD patients; likewise, autonomic dysfunction could affect the visceral sensitivity in IBS patients.[75-77] This mechanism may play a role in bloating. Moreover, it has been proposed that visceral perception may be influenced by cognitive mechanism. That is, IBS patients with bloating pay more attention to their abdominal symptoms, which is a kind of hyper-vigilance.[78] Also, a report indicated that female patients with IBS had worsening of abdominal pain and bloating during their peri-menstrual phase, at which time heightened rectal sensitivity might have contributed to bloating, but not to distension.[24,79] Taken together, altered sensory threshold combined with altered conscious perception may explain the mechanism of bloating.

Food Intolerance and Carbohydrate Malabsorption

It is well recognized that dietary habits may be responsible for abdominal symptoms, and there have been efforts to prove the relationship between diet and IBS symptoms. Fiber overload has long been regarded as worsening factor of IBS symptoms through decreased small bowel motility or intraluminal bulking.[80,81] In addition, lactose intolerance may contribute to symptom development in IBS patients. In the small intestine, disaccharides are split by intestinal enzymes into monosaccharides which are then absorbed. If this process is not carried out, the disaccharide reaches the colon, in turn is split by bacterial enzymes into short chain carbonic acids and gases. Hence, malabsorption of lactose may produce the symptom of bloating in patients with IBS or FB.[11,82-84] Additionally, a new hypothesis is proposed, by which excessive delivery of highly fermentable but poorly absorbed short chain carbohydrates and polyols (collectively termed FODMAPs; fermentable oligo-, di- and mono-saccharides and polyols) to the small intestine and colon may contribute to the development of GI symptoms. FODMAPs are small molecules that are osmotically active and very rapidly fermentable compared with long-chain carbohydrates. These molecules induce relatively selective bacterial proliferation, especially of *bifidobacterium,* and it has been demonstrated indirectly that these can lead to expansion of bacterial populations in distal small intestine.[85-87] Thus, high FODMAP diet has demonstrated prolonged hydrogen production in the intestine, colonic distension by fermentation, increased colonic fluid delivery by osmotic load within the bowel lu-

men, and GI symptom generation.[88,89]

Intraluminal Contents

Levitt et al[90] suggested that abdominal bloating might develop without gas retention, but by other gut contents. They had undertaken randomized, double-blind, crossover study of gaseous symptoms by observing the responses of healthy subjects to dietary supplement with lactulose or 2 types of fibers (psyllium or methylcellulose). In lactulose group, gas passages, subjective perception of rectal gas and breath hydrogen excretion were significantly increased, but not in fiber groups. However, the sensation of bloating was increased in all 3 groups. Thus, it has been proposed that increased intra-abdominal bulk, not gaseous filling, might be a cause of abdominal bloating.[90] In another study, bran accelerated small bowel transit and ascending colon clearance without causing symptom in controls, but small bowel transit has not further been accelerated in IBS patients with bloating. Thus, they speculated that bran might cause increased bulking effect in the colon, which led to the exacerbation of bloating in IBS patients.[91] Francis and Whorwell[80] even proposed that use of the bran in IBS should be reconsidered, because excessive consumption of bran might give rise to symptoms such as bloating in IBS patients. Although more studies are needed for further understanding of their relationship, it could be possible that intraluminal bulking aggravates the bloating in some IBS patients.

Hard stool/Constipation

Many constipated patients complain of bloating.[14] Also there is a tendency of its being more common in IBS-C patients than IBS-D patients, though it is not statistically significant in some studies.[31,92-94] Distension of the rectum by retained feces slows small intestinal transit as well as colonic transit, probably explaining the aggravated bloating in constipated patients.[15,56] Thus it seems reasonable that constipation or hard/lumpy stool induces alteration of gut motility and thus maybe increases bacterial fermentation. In addition, constipation may accelerate bloating by intraluminal bulking effect in the same manner as bran.

Psychological Aspects

Bloating is a frequent complaint of women with IBS. Park et al[95] proposed that there was a tendency to increase the index of psychological distress when the bloating was more severe. Also, patients with bloating revealed increased anxiety and depression, which allows the hypothesis that psychological distress may contribute to the perceived severity of bloating.[96] Additionally, in large population surveys, bloating was significantly related with psychiatric dysfunction such as major depressive disorder, panic disorder and sleeping difficulties.[97,98] Nevertheless, other studies have failed to demonstrate the relationships between psychological distress and either bloating or distension.[14,99] However, it is unclear whether or not there is an actual relationship between bloating and psychosocial distress, and further studies are needed to demonstrate it.

Gender and Sex Hormones

In a population based study in USA, female gender was significantly associated with increased symptoms of bloating and distension in IBS, and similar findings have been reported so far.[21,100-102] Although the question of the gender role in IBS has been raised from many studies, the mechanisms of gender differences in bloating and distension are unclear. Some studies have suggested that bloating is one of the frequent symptoms of menstruation as aforementioned.[24,25] Hormonal effect has also been speculated, that is, the variation of reproductive hormones throughout the menstrual cycle and after the menopause may influence the gut motility and visceral perception.[24,79,103] Additionally, difference in symptom expression by gender is presented as a potential explanation.[31] Although more investigations regarding the underlying mechanisms for these disparities remain to be determined, it seems to be possible to speculate that the hormonal fluctuation may contribute to bloating in female IBS patients.

Treatment

Antibiotics

There has been an increasing acceptance of the use of the antibiotics to treat IBS symptoms, and it is plausible based on the presumption that altered gut flora or SIBO may contribute to gaseous distension or bloating symptom.[44,104,105]

Although some questions have been raised regarding the validity of the lactulose breath test in diagnosis of SIBO and the possibility of overdiagnosis,[106] much more data support the clinical use of antibiotics in this condition. Specifically, rifaximin, a rifamycin derivative, has largely been studied, and it showed superiority to placebo in relieving bloating in IBS or in patients who were diagnosed as SIBO (Table 2). As rifaximin is a non-absorbable antimicrobial agent, the risk of side effects or emergence of resistant organisms is expected to be low; therefore it is suitable for chronic administration.[44-46,107,108] Recently, a phase 3 multi-

Table 2. Studies for Rifaximin Treatment in Irritable Bowel Syndrome Patients

Author (yr)	Study design	Diagnostic criteria	IBS subtypes	Mean age / Female ratio (n) rifaximin vs. placebo	Drug dosage	Treatment duration (days)	RR for global symptoms (rifaximin, %)	RR for bloating
Sharara et al[45] (2006)	Double-blind, placebo-controlled, single center	70 met Rome II	All (IBS-D 20.0%, IBS-C 38.3%, IBS-M 41.7%)	42.2/52.4% (63) vs. 38.9/57.4% (61)	400 mg b.i.d.	10	41.3	NA (bloating score; 24.4 → 20.8) ($P = 0.001$)
Pimentel et al[109] (2011)	Double-blind, placebo-controlled, multi-center (TARGET 1)	Rome II	Excluded IBS-C	46.2/76.1% (309) vs. 45.5/70.7% (314)	550 mg t.i.d.	14	40.8	39.5%
Pimentel et al[109] (2011)	Double-blind, placebo-controlled, multi-center (TARGET 2)	Rome II	Excluded IBS-C	45.9/72.1% (315) vs. 46.3/70.3% (320)	550 mg t.i.d.	14	40.6	41.0%
Peralta et al[111] (2009)	Observational analysis, single arm, single center	Rome II	All (IBS-D 35.2%, IBS-C 20.4%, IBS-M 44.4%)	NA (54)	1,200 mg/day	7	NA	NA (symptom score; 2.3 → 0.8) ($P = 0.003$)
Yang et al[113] (2008)	Retrospective study, single center	Rome I	NA	NA (84)	1,200 mg/day	NA (follow-up duration; median 11 months)	69.0 (other antibiotics, 44.0)	NA
Pimentel et al[44] (2006)	Double-blind, randomized, placebo-controlled study, 2 centers	Rome I	All (%; NA)	39.1/67.4% (43) vs. 38.2/65.9% (44)	400 mg t.i.d.	10	36.40	NA
Jolley et al[112] (2011)	Retrospective study, single center	Rome III	All (IBS-D 28.0%, IBS-C 20.0%, IBS-M 15.0%, not reported in 37.0%; 1,200 mg/d group) (30.0%, 20.0%, 14.0% and 37.0% respectively; high dose group)	58.0/77.2% (162) vs. 60.0/72.8% (81) (high dose group)	1,200 mg/day vs. 2,400 mg/day (high dose group)	10	49.0 vs. 47.0 (high dose group)	NA

IBS, irritable bowel syndrome; RR, response rate; NA, not available; IBS-D, IBS with diarrhea; IBS-C, IBS with constipation; IBS-M, mixed IBS.

center trial proved that rifaximin provided significant improvement of IBS symptoms including abdominal pain and bloating in non-constipated IBS patients.[109] Pimentel et al[110] also suggested that neomycin normalized lactulose breath test and it contributed to the reduction of bloating in IBS patients. Besides, there have been several retrospective or observational studies, which support the efficacy of rifaximin treatment in IBS patients. Specifically, rifaximin turned the lactulose breath test to negative and significantly reduced the overall symptom scores.[111] Also, high dose rifaximin treatment (2,400 mg/day) was proved to be effective in patients who had incomplete response to usual dose of rifaximin.[112] Another retrospective study has revealed that rifaximin is superior to other antibiotics, such as neomycin, doxycycline, amoxicillin/clavulanate and ciprofloxacin in patients with IBS.[113] Therefore, antibiotics like rifaximin could be considered as a short course therapeutic regimen for bloating, mainly in IBS without constipation. Further studies are needed to determine how long these antibiotics should be given and whether drug resistance will be a problem.

Probiotics

Alteration in gut microbiota may produce or perpetuate the symptoms of bloating or distension, therefore many researchers postulated that modification of the gut microflora could improve gas related symptoms.[39] One placebo-controlled study conducted in IBS patients revealed a beneficial effect of *Bifidobacterium infantis* and they suggested immune-modulating role of that organism.[114] Another multicenter, clinical trial in women with IBS also showed that *B. infantis* relieved many of the symptoms of IBS, but just at a specific dosage (1×10^8 CFU/mL).[115] In addition, more recent experiments have shown that some probiotic strains significantly alleviate the bloating as well as overall symptoms.[116,117] One study from Korea has shown that multi-species probiotics given to IBS patients are effective in the relief of bloating, albeit not statistically significant over placebo.[118] In the most recent meta-analysis of probiotics for lower GI symptoms, specific probiotics are recommended in the management of bloating in IBS patients as moderate grade of evidence along with 70% level of agreement.[119]

On the contrary, many other studies have failed to prove favorable effects of the probiotics. Kim et al[120] evaluated the effectiveness of VSL#3, a composite probiotic containing *Bifidobacterium*, *Lactobacillus* and *Streptococcus* in IBS patients. VSL#3 reduced flatulence scores and retarded colonic transit without altering bowel function, but there was no significant reduction in bloating score with VSL#3.[120] Some experimental studies from Korea showed a trend towards amelioration of bloating, but failed to prove beneficial effect over placebo.[121,122] In addition, several other studies using *lactobacillus* strains reported unfavorable effect on bloating in IBS (Table 3).[41,123,124] Most of the studies were relatively small and there have been inconsistent results regarding the efficacy of probiotics on bloating. Hence, larger and well-designed trials are needed to prove whether the probiotics are reasonable to treat patients with bloating.

Prokinetics

Prokinetics have been used in the treatment of bloating in FD traditionally, in spite of the weak evidence for correlation between symptoms and underlying pathophysiological mechanisms. A number of studies have shown the beneficial effect of prokinetics such as dopamine antagonist, muscarinic antagonist, and serotonergic agents in FD, but studies conducted in IBS patients are relatively rare (Table 4). Several studies have suggested that cisapride, a 5-hydroxytryptamine 4 (5-HT_4) receptor agonist, significantly improves postprandial bloating in FD patients.[125,126] Levosulpiride turned out to be as effective as cisapride in the treatment of FD symptoms, such as bloating.[127] Acotiamide, a novel prokinetic agent, also provided relief of bloating in FD patients in a small study.[128]

Some researchers tried to investigate the efficacy of tegaserod, a selective 5-HT_4 partial agonist, in patients with IBS-C whose main symptom was not diarrhea, and they suggested significant relief in bloating with tegaserod.[129-132] However, tegaserod was withdrawn from the market in 2007 due to possible adverse cardiovascular effects. Additionally, neostigmine, a potent prokinetic drug, also exhibited significant effect in reducing objective abdominal distension as well as bloating in IBS or FB patients.[133] On the other hand, some other studies do not agree with the favorable action of prokinetics in IBS. One double-blind trial suggested that cisapride was not superior to placebo in the treatment of bloating and other abdominal symptoms of IBS, but it reduced difficulty of stool passage.[134] However, cisapride was also removed from the market due to the side effect. Another study conducted in IBS patients to evaluate the efficacy of domperidone showed no significant improvement of bloating.[135] In a small experimental study, pyridostigmine reduced the severity of bloating, but it did not reach the statistical difference across groups.[3] Although there are conflicting evidences regarding the effect of prokinetics on bloating, some of the prokinetics could be a treatment option for bloating.

Table 3. Summary of Studies for Probiotics in Irritable Bowel Syndrome

Author (yr)	Study design	Criteria	IBS subtypes	Sample size	Probiotic strains (daily dose)	Duration (weeks)	Results
Nobaek et al[41] (2000)	RCT	Rome I	All (IBS-C, IBS-D, IBS-M)	60	*L. plantarum* DSM 9843 (299V) (5×10^7 CFU/mL)	4	Flatulence; improved in test group ($P < 0.05$) Pain, bloating; no benefit over placebo
O'Mahony et al[114] (2005)	RCT	Rome II	All	75	*L. salivarius* UCC 4331 or *B. infantis* 35624	8	Abdominal pain, bowel movement difficulty; significantly improved in *B. infantis* group (all $P < 0.05$) Bloating; improved in *B. infantis* group ($P < 0.05$) No benefit in *L. salivarius* group
Whorwell et al[115] (2006)	RCT	Rome II	All	362	*B. infantis* 35624 (3 groups; 1×10^6, 1×10^8 or 1×10^{10} CFU/mL)	4	Abdominal pain, bloating, incomplete evacuation, straining, passage of gas; improved only in 1×10^8 group (all $P < 0.05$)
Kim et al[120] (2005)	RCT	Rome II	All	48	VSL#3	4-8	Flatulence; improved in test group ($P < 0.01$) Failed to show improvement in bloating
Niv et al[124] (2005)	RCT	Rome II	All	54	*L. reuteri* ATCC 55730 (1×10^8 CFU/tablet, twice a day)	26	Abdominal pain, bloating, gases, visible abdominal swelling, GSS; improved, but no benefit over placebo
Guglielmetti et al[116] (2011)	RCT	Rome III	All	122	*B. bifidum* MIMBb75 (1×10^8 CFU/capsule, once a day)	4	Pain, distension/bloating, GSS; significantly reduced in test group (all $P < 0.0001$)
Choi et al[121] (2011)	RCT	Rome II	IBS-D, IBS-M	67	*S. boulardii* (2×10^{11} cells/day)	4	Quality of life; significant improvement in test group ($P < 0.05$) Bloating; no benefit over placebo
Kicha et al[122] (2012)	RCT	Rome III	IBS-D	50	A mixture of *L. acidophilus, L. plantarum, L. rhamnosus, B. breve, B. lactis, B. longum and S. thermophilus* (1×10^{10} CFU/day)	8	Adequate relief of overall IBS symptoms in test group ($P < 0.05$) Bloating; no benefit over placebo
Ducrotté et al[117] (2012)	RCT	Rome III	All	214	*L. plantarum* DSM 9843 (299V) (1×10^8 CFU/day)	4	Abdominal pain, bloating; improved in test group (all $P < 0.05$)
Yoon et al[118] (2013)	RCT	Rome III	All	49	A mixture of *B. longum, B. bifidum, B. lactis, L. acidophilus, L.rhamnosus* and *S. thermophilus* (5×10^9 cells/capsule, twice daily)	4	GSS; significantly relieved in test group ($P = 0.03$) Abdominal pain, bloating; improved, but no statistical significance over placebo

IBS, irritable bowel syndrome; RCT, randomized controlled trial; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; IBS-M, mixed IBS; *L. plantarum*, *Lactobacillus plantarum*; *L. salivarius*; *Lactobacillus salivarius*; *B. infantis*; *Bifidobacterium infantis*; *L. reuteri*, *Lactobacillus reuteri*; *B. bifidum*; *Bifidobacterium bifidum*; *S. boulardii*, *Saccharomyces bouladii*; *L. acidophilus*, *Lactobacillus acidophilus*; *L. rhamnosus*, *Lactobacillus rhamnosus*; *B. lactis*, *Bifidobacterium lactis*; *B. longum*, *Bifidobacterium longum*, *S. thermophilus*, *Streptococcus thermophilus*; GSS, global symptom score.

Table 4. Summary of Studies for Prokinetics in Irritable Bowel Syndome

Author (yr)	Study design	Diagnosic Criteria	IBS subtypes	Sample size	Prokinetics used (daily dose)	Duration (wk)	Results
Schütze et al[134] (1997)	RCT	Rome I	IBS-C	96	Cisapride (5 mg t.i.d., titrated to 10 mg t.i.d. if no response after 4 wk)	12	Bloating, GSS; not superior to placebo Difficulty of stool passage; significant improvement in test group ($P < 0.05$)
Müller-Lissner et al[129] (2001)	RCT	Rome I	All (IBS-D, IBS-C, IBS-M)	881	Tegaserod (2 mg or 6 mg b.i.d.)	12	Abdominal pain/discomfort; improved in both test groups ($P < 0.05$), more consistent efficacyover time in higher dose group Bloating; favorable trend in reduction in both test groups
Novick et al[130] (2002)	RCT	Rome I	All	1,519 (all female)	Tegaserod (6 mg b.i.d.)	12	Abdominal pain, bloating, stool consistency, GSS; improved in test group (all $P < 0.05$)
Kellow et al[131] (2003)	RCT	Rome II	Excluded IBS-D	520	Tegaserod (6 mg b.i.d.)	12	GSS; improved in test group ($P < 0.0001$) Abdominal pain, bloating, hard stools; improved in test group (all $P < 0.05$)
Tack et al[132] (2005)	RCT	Rome II	IBS-C	2,660 (all female)	Tegaserod (6 mg b.i.d.)	4	Abdominal pain, bloating, constipation; improved in test group (all $P < 0.0001$)
Chey et al[169] (2008)	RCT	Rome II	IBS-C, IBS-M	661 (all female)	Tegaserod (6 mg b.i.d.)	4	Overall symptom; relieved in test group ($P < 0.001$) Bloating; no benefit over placebo
George et al[170] (2008)	RCT	Rome II	IBS-C	510	Renzapride (1 mg, 2 mg or 4 mg o.d.)	12	Stool frequency, stool consistency; improved in 2 mg and 4 mg o.d. groups (all $P < 0.05$) Bloating; reduction in 1mg o.d. group ($P = 0.01$)

RCT, randomized controlled trial; GSS, global symptom score; IBS, irritable bowel syndrome; IBS-D, IBS with diarrhea; IBS-C, IBS with constipation; IBS-M, mixed IBS.

Table 5. Summary of Studies for Spamolytics in Irritable Bowel Syndrome

Author (yr)	Study design	Diagnosic criteria	IBS subtypes	Sample size	Spasmolytics used (daily dose)	Duration (weeks)	Results
Battaglia et al[141] (1998)	RCT	Drossman's criteria for IBS	NA	325	Otilonium bromide (40 mg t.i.d.)	15	Abdominal pain, distension; significant reduction (all $P < 0.05$)
Dobrilla et al[171] (1990)	RCT	Clinical diagnosis and investigations	NA	70	Cimetropium (50 mg t.i.d.)	12	Severity and frequency of abdominal pain; significantly decreased ($P = 0.0005$ and 0.001, respectively) Abdominal distension; decreased, but not statistically significant ($P = 0.055$)
Glende et al[143] (2002)	RCT	Rome I	All (IBS-D, IBS-C, IBS-M)	378	Otilonium bromide (40 mg t.i.d)	15	Abdominal pain, distension; improved in test group (all $P < 0.05$)
Mitchel et al[172] (2002)	RCT	Rome II	All	107	Alverine (150 mg t.i.d.)	12	Abdominal pain, bloating, general well-being; failed to show benefit over placebo
Clave et al[140] (2011)	RCT	Rome II	All	356	Otilonium bromide (40 mg t.i.d.)	15	Abdominal pain ($P = 0.03$), bloating ($P = 0.02$), global efficacy ($P = 0.047$); significant benefit over placebo
Chang et al[173] (2011)	RCT	Rome II	All	117	Otilonium bromide (40 mg t.i.d.) Ormebeverine (100 mg t.i.d.)	8	Abdominal pain, flatulence, bloating, global assessment; relieved in both treatment group (all $P < 0.05$)

NA, not available; RCT, randomized controlled trial; IBS, irritable bowel syndrome; IBS-D, IBS with diarrhea; IBS-C, IBS with constipation; IBS-M, mixed IBS.

Antispasmodics

Various types of antispasmodics have been commonly used to relieve the symptoms of IBS, given the presumption that altered GI motility and smooth muscle spasm may give rise to the IBS symptoms.[136] Several studies have shown the efficacy of these drugs in IBS symptoms such as bloating, but some do not (Table 5).[137-142] Also data are limited since many of these agents (e.g., mebeverine, otilonium and trimebutine) are not licensed in the USA. There have been several reports that support the beneficial effect of otilonium.[141,143] Besides, in a few studies, peppermint oil, considered as a natural spasmolytic agent due to its calcium influx blocking effect, was also superior to placebo in reduction of abdominal distension and bloating.[144,145] One systematic review evaluated the efficacy and tolerability of mebeverine. In the meta-analysis, it was effective in the clinical improvement of abdominal pain or distension, but it did not reach a statistical significance.[146] Taken together, antispasmodics have shown some efficacy in the treatment of bloating, but the study results were inconsistent and it is difficult to draw definite conclusion about these conflicting views. Thus, larger studies are needed.

Dietary Interventions

Food intake may play a key role in perpetuating symptoms in IBS patients, so a careful history taking for diet should be taken. Many retrospective observational studies have shown that the reduced intake of large amounts of highly fermentable, poorly absorbed short chain carbohydrates (FODMAPs) may reduce bloating in IBS patients.[147-149] Finally, the low FODMAP diet was developed at Monash University in Melbourne,[150] and recently, the first prospective study confirming the efficacy of low FODMAP diet for IBS patients was reported. Besides, patients with IBS who had also fructose malabsorption were significantly more likely to respond to the low FODMAP diet than those without fructose malabsorption (Table 6).[151]

Gas Reducing Substances

One of the earliest pharmacological modalities used in treating distension and bloating was antifoaming agent, and a silicone derivative with surfactant, officially designated as "simethicone" is known as a traditional antifoaming agent, by which gases are evacuated and absorbed from the gut.[152] As most of the studies which investigated the therapeutic benefit of those agents were carried out in the subset of patients who have FD, their efficacy in IBS patients seems questionable. Bernstein et al[153] reported that

Table 6. Summary of Studies for Dietary Interventions in Irritable Bowel Syndrome

Author (yr)	Study design	Subjects included	Sample size	Dietary interventions	Results
Choi et al[147] (2008)	Prospective study, single arm, single center	IBS (Rome II)	26	Fructose-restricted diet (mean follow-up of 13 mo)	Abdominal pain, belching, fullness, bloating; significant relief (all $P < 0.02$)
Shepherd et al[149] (2008)	RCT	IBS (Rome II)	25	Low FODMAP diet before trial (median 24 mo) Fructan, fructose, fructan-fructose mix, or glucose drinks (for 2 wk)	Abdominal pain, bloating; significantly increased in fructan, fructose, and mix group compared with glucose group (all $P < 0.01$)
Ong et al[89] (2010)	Single-blind, crossover intervention trial	IBS (Rome III) vs. healthy subjects	15 vs. 15	Low (9 g/day) or high (50 g/day) in FODMAPs for 2 days	Abdominal pain, bloating, excessive flatus; increased with HFD in IBS patients (all $P < 0.01$)
de Roest et al[151] (2013)	Prospective study, single arm	IBS	90	low FODMAP diet (mean follow-up of 15.7 mo)	Abdominal pain, bloating, flatulence, diarrhea; significantly improved compared to baseline (all $P < 0.001$)

RCT, randomized controlled study; IBS, irritable bowel syndrome; FODMAPs, fermentable oligo-, di-, and mono-saccharides and polyols HFD, high FODMAP diet.

simethicone significantly relieved the frequency and severity of gas-related symptoms in patients with FGID. Holtmann[154] also conducted a randomized, placebo-controlled trial of simethicone, and suggested that simethicone was significantly better than placebo for overall symptom control in FD patients, in spite of unfavorable effect for bloating. More recently, prospective, multicenter trial to demonstrate a favorable action of activated charcoal-simethicone combination therapy revealed that the severity of fullness and bloating was significantly decreased in the therapy group compared with placebo (Table 7).[155]

Stimulants of Fluid Secretion

Lubiprostone and linaclotide are novel agents recently approved by the USA Food and Drug Administration, that enhance fluid secretion into the gut lumen and accelerate intestinal transit. These properties are considered to play a role in treatment of constipation, thus a number of clinical trials focusing in the chronic constipation or IBS-C have been conducted (Table 8). In 2 phase III trials, lubiprostone significantly improved the overall IBS symptoms including bloating in IBS-C.[156,157] Several multicenter, randomized trials of linaclotide in chronic constipation or IBS-C also demonstrated the beneficial effect in relieving abdominal bloating.[158,159] Thus so far, these 2 novel drugs offer a reasonable therapeutic approach for bloating mainly in IBS-C and functional constipation patients.

Antidepressants

Antidepressants such as selective serotonin reuptake inhibitor (SSRI) or tricyclic antidepressant (TCA) are believed to alleviate symptoms in FGIDs on the basis of their visceral analgesic properties as well as psychological aspects. However, one small study conducted in IBS patients with visceral hypersensitivity revealed that fluoxetine, one of the SSRI, was effective only in abdominal pain, not in other symptoms such as bloating.[160] Paroxetine was also evaluated in IBS patients who did not respond to high fiber diet. Overall well-being sensation was improved more with paroxetine than with placebo, but abdominal bloating was not.[161] However, there were also some positive results. That is, the SSRI, citalopram significantly improved abdominal bloating compared with placebo, though the therapeutic effect was independent of the effect on anxiety, depression and colonic sensitivity (Table 9).[162] Taken together, the results for the treatment of bloating and distension with antidepressants are partly contradictory, and there were few studies which explained the effect of TCA on bloating. Hence, larger, well-designed trials

Table 7. Summary of Studies for Gas-reducing Substances in Functional Gastrointestinal Disorder

Author (yr)	Study design	Subjects included	Sample size	Drugs used (daily dose)	Duration	Results
Bernstein et al[153] (1974)	RCT	FGID	41	Simethicone (50 mg, number of tablets unclear)	10 days	Fullness, bloating, distension; significant improvement in test group (all $P < 0.005$)
Holtmann et al[154] (2002)	RCT	FD	185	Simethicone (105 mg t.i.d.) or cisapride (10 mg t.i.d.)	8 wk	Overall symptom, fullness, pain; improved in both test groups Bloating; no benefit
Lecuyer et al[155] (2009)	RCT	Patients with fullness, bloating, nausea or slow digestion	132	Simethicone and activated charcoal (Carbosylane®)	3 mo	Overall complaints; no improvement over placebo Fullness, bloating; significant improvement in test group (all $P < 0.05$)
Wittmann et al[174] (2010)	RCT	IBS (Rome III)	412	Alverine citrate/Simethicone (60 mg/300 mg t.i.d.)	4 wk	Abdominal pain, discomfort; superior efficacy in test group ($P = 0.047$) Bloating; no evidence

RCT, randomized controlled study; FGID, functional gastrointestinal disorder; FD, functional dyspepsia; IBS, irritable bowel syndrome.

Table 8. Summary of Studies for Stimulants of Fluid Secrection in Functional Gastrointestinal Disorder

Author (yr)	Study design	Subjects included	Sample size	Drug used (daily dose)	Duration (wk)	Results
Johanson et al[156] (2007)	RCT	Chronic constipation	129	Lubiprostone (24 μg/day, 48 μg/day, or 72 μg/day)	3	Bloating; significant relief in all test groups ($P = 0.035$) SBM frequency; improved in a dose-dependent manner
Drossman et al[157] (2009)	RCT	IBS-C (by Rome II)	1,171	Lubiprostone (8 μg twice daily)	12	Overall response rate; higher in test group ($P = 0.001$) Abdominal pain, bloating, constipation severity; significant relief only in responders
Lembo et al[159] (2011)	RCT	Chronic constipation	1,276	Linaclotide (145 μg or 290 μg once daily)	12	CSBM; improved in both trials (all $P < 0.001$) Abdominal discomfort, bloating, constipation severity; improved in both trials (all $P < 0.05$)
Quigley et al[158] (2013)	RCT	IBS-C	1,608	Linaclotide (290 μg once daily)	12 or 26	Abdominal discomfort, bloating, stool consistency; significant improvements in both trials (all $P < 0.0001$)

RCT, randomized controlled trial; SBM, spontaneous bowel movement; IBS-C, IBS with constipation; CSBM, complete SBM.

Table 9. Summary of Studies for Antidepressants in Functional Gastointestinal Disorder

Author (yr)	Study design	Subjects included	Sample size	Antidepressant used (daily dose)	Duration	Results
Kuiken et al[160] (2003)	RCT	IBS	40	Fluoxetine (20 mg/day)	6 wk	Threshold for abdominal pain, bloating; no significant changes
Tabas et al[161] (2004)	RCT	IBS, not responding to high fiber diet	81	Paroxetine (10 mg/day)	12 wk	Overall well-being; significantly improved ($P = 0.01$) Abdominal pain, bloating; no benefit over placebo
Vahedi et al[175] (2005)	RCT	IBS-C (Rome II)	44	Fluoxetine (20 mg/day)	12 wk	Abdominal discomfort, stool consistency, bloating; significant relief in test group (all $P < 0.05$)
Tack et al[162] (2006)	RCT	IBS (Rome II)	23	Citalopram (20 mg/day for 3 wk, then 40 mg/d for 3 wk)	6 wk	Abdominal pain, bloating, overall well-being; significant relief in test group (all $P < 0.05$)
Vahedi et al[176] (2008)	RCT	IBS-D (Rome II)	54	Amitriptyline (10 mg/day)	2 mo	Abdominal pain, loose stools, diarrhea; significant improvement in test group (all $P < 0.05$) Flatulence; no benefit over placebo Bloating; not evaluated

RCT, randomized controlled study; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea.

Table 10. Summary of Studies for Opioid Agents in Functional Gastrointestinal Disorder

Author (yr)	Study design	Subjects included	Sample size	Drug used (daily dose)	Duration (wk)	Results
Fraitag et al[164] (1994)	RCT	NUD	146	Fedotozine (10, 30 or 70 mg t.i.d.)	6	Postprandial fullness, bloating, abdominal pain and nausea; significant relief in 30 mg and 70 mg groups
Read et al[177] (1997)	RCT	FD	271	Fedotozine (30 mg t.i.d.)	6	Epigastric pain, postprandial fullness, nausea; significant improvement in test group Bloating; not evaluated
Hawkes et al[166] (2002)	RCT	IBS-C, IBS-M (Rome II)	28	Naloxone (10 mg b.i.d.)	8	Abdominal pain, bloating, straining, urgency to defecate; improved, but no significant differences over placebo
Mangel et al[165] (2008)	RCT	IBS (Rome II)	596	Asimadoline (0.15, 0.5 or 1.0 mg b.i.d.)	12	Abdominal pain, bloating; improved only in IBS-D with both 0.5 mg and 1.0 mg dose
Szarka et al[178] (2007)	RCT	IBS (Rome II)	100	Asimadoline (on demand/up to 1.0 mg q.i.d.)	4	Abdominal pain/discomfort, frequency of bowel movements; not improved Bloating; not evaluated

RCT, randomized controlled trial; NUD, nonulcer dyspepsia; FD, functional dyspepsia; IBS-C, IBS with constipation; IBS-M, mixed IBS; IBS-D, IBS with diarrhea.

with SSRIs and TCAs are warranted to identify the efficacy of these drugs on bloating and distension.

Opioid Agents

There have been a few reports that propose the usefulness of opioid agents in IBS patients (Table 10). The kappa receptor agonist, fedotozine has been shown to increase the threshold of perception to colonic distension and reduce visceral sensation.[163] It has also demonstrated its superiority to placebo in relieving postprandial fullness and bloating in FD patients.[164] In a phase II trial, asimadoline, a novel kappa-opioid agonist, has yielded excellent efficacy results on pain and bloating in IBS-D patients.[165] A small study has suggested that naloxone is beneficial in reducing the bloating score in IBS-C or IBS-M patients, but there were no significant differences in the results with naloxone and placebo.[166] Though a recent review also makes a suggestion of the use of opioid agonists in IBS-D patients,[167] their role in bloating is uncertain to date.

Summary

Abdominal bloating is a frequent and bothersome, but poorly understood clinical problem. The terms of bloating and distension are often confused, but these 2 symptoms should be considered to be separate, as they probably have different pathophysiological mechanisms. The possible mechanisms of bloating are complex and maybe various mechanisms are combined in symptom generation. Important mechanisms of bloating are impaired gas handling and hypersensitivity. Also, recent evidences are beginning to emphasize that patients with bloating may have an altered bacterial flora, SIBO, and abdomino-phrenic dyssynergia. Other less-established factors for bloating are food intolerance, intraluminal bulking and psychological factors (Fig. 2).

On approaching to the treatment of abdominal bloating, clinicians should consider a heterogeneous condition produced by a combination of various mechanisms. Currently, there is no treatment which has indisputably proven to be effective for bloating. Treatment strategy for bloating may include pharmacologic approach, dietary modification, and psychological therapy. Taken together, 5-HT_4 agonists, antibiotics such as rifaximin, some probiotics, and also novel agents, lubiprostone and linaclotide are substantiated to be effective in some degree in the treatment of bloating. Dietary intervention with low FODMAP is also newly qualified treatment option. Though the evidence is weak, antifoaming agents and antidepressants could be consid-

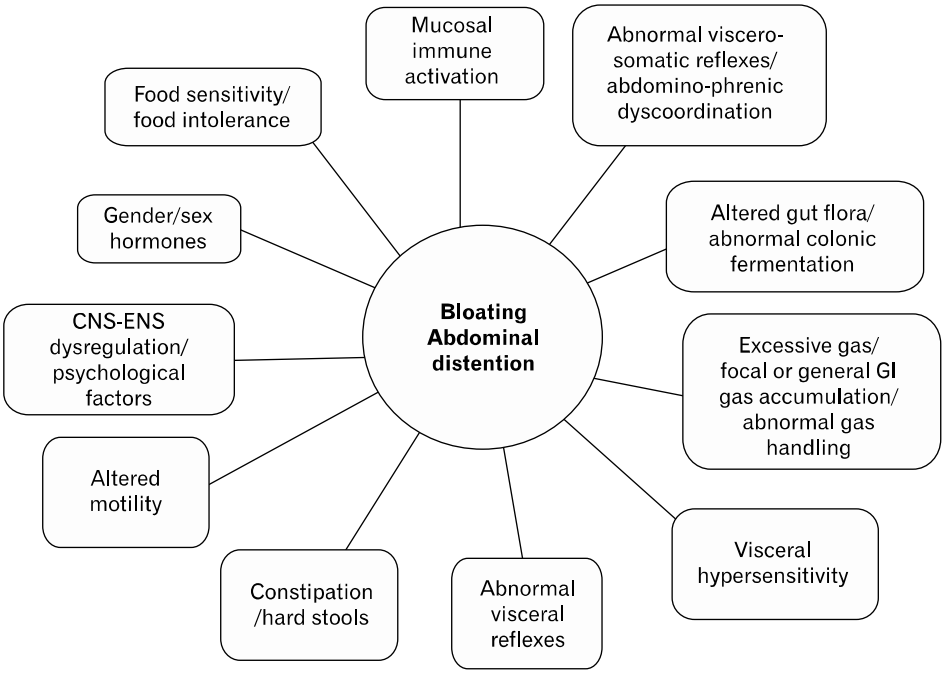

Figure 2. Potential mechanisms behind bloating and visible distension in functional gastrointestinal disorders. Modified from Simrén.[168] CNS, central nervous system; ENS, enteric nervous system; GI, gastrointestinal.

ered in some patients. Of course a careful history and physical examination should be the first step and reassurance and education are likewise important.

Though the whole mechanism and treatment strategies are yet to be fully elucidated, this article proposes a framework for assessing and managing the patients with bloating.

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