Pharmacological Treatment for Functional Dyspepsia and Irritable Bowel Syndrome: Current Standards and Promising Therapies

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Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are functional diseases without identified organic cause and introduced as part of the Rome III criteria published in 2006. Because of non-organic diseases, pharmacological treatment (not invasive surgical treatment) is the preferred therapy for such diseases. Meanwhile, evidence-based clinical practice guidelines for FD and IBS have been published in Japan. However, no definite therapeutic strategy for FD and IBS has yet been established. To understand more appropriate treatments according to the respective pathophysiology, this review introduces the several pharmacological treatments including current standards and proposes future promising therapies based on these guidelines. First, this review covered clinical evidence for standard and recommended drugs such as acid suppressants, prokinetics, probiotics, and bulking polymers for the management of FD and IBS. Next, this review progressed to propose future promising treatments for their managements. A comprehensive understanding of relevant therapeutic regimens and pharmacological treatment using drug candidates including future promising drugs is required for the optimal and more effective treatment of FD and IBS.

Keywords: acid suppression, gastrointestinal motility, neurotransmission, hypersensitivity, psychosomatization

Introduction

The disease classification of functional gastrointestinal disorders (FGIDs), which was introduced as part of the Rome III criteria published in 2006 includes functional esophageal disorders, functional dyspepsia (FD), irritable bowel syndrome (IBS), functional constipation, and functional abdominal pain syndrome. Among these disorders, FD and IBS may be representative...
diseases of FGIDs in clinics and hospitals. The pathophysiologies of FD and IBS involve multiple factors including psychosomatic factors associated with the central nervous system (CNS) and physiological disorders of the gastrointestinal tracts. Therefore, it may be difficult to comprehensively recognize the pathophysiology of FD and IBS. Accumulating evidence based on basic and clinical research has demonstrated detailed mechanisms of the pathophysiology of these diseases. As a result, some effective pharmacological treatment regimens have been proved and can improve symptoms in patients with FD and IBS. Meanwhile, evidence-based clinical practice guidelines for FD and IBS have been published in Japan. In these guidelines, the use of standard drugs according to the respective pathophysiology is recommended to treat these diseases. Although the drugs recommended in the above guidelines primarily target the gastrointestinal tract, such therapies do not always relieve such characteristic abdominal symptoms. Therefore, it is thought that a comprehensive understanding of relevant therapeutic regimens and drug candidates is required for the optimal treatment of FD and IBS.

This review summarizes the efficacies of the present pharmacological treatments for FD and IBS, and proposes promising therapeutic options incorporating other drugs.

1. Pharmacological Treatment for FD at Present

In general, a treatment strategy for FD must be established in accordance with the pathophysiology of this disease as well as other related diseases. The pathophysiologia of FD involves personality disorders, anxiety and depression, acid secretion, the autonomic nervous system, gastrointestinal motility, and Heli-cobacter pylori infection, and so on (Figure 1). Although various related factors are gradually going to be elucidated, no definite and conclusive treatment regimen has yet been established, presumably reflecting the complicated interaction of multiple factors of FD. In our institute, diagnostic and treatment flow (Figure 2) is recommended mainly according to the presence/absence of motility disorders (each prevalence rate of motility disorders in Figure 2 was derived from our previous report4), because motility disorders of gastric accommodation and emptying are important for the pathophysiology of FD among multiple factors. Initially, differential diagnosis must be performed by questionnaires, diagnostic criteria, and examinations for several organic diseases for patients with dyspeptic symptoms. After the diagnosis of FD, we evaluated the

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Figure 1. Possible pathogenesis of functional dyspepsia
severity of abdominal and psychological symptoms by the questionnaires such as the Gastrointestinal Symptom Rating Scale, the Zung Self-rating Depression Scale, and the State-Trait Anxiety Inventory, and the gastric motility as a functional test of the stomach. If gastric motility of patients with FD can be assessed in every institute, we believe this flow must be useful for its treatment and management. Because most institutes cannot easily assess gastric motility, many physicians must generally rely on dyspeptic symptoms when they treat patients with FD. Unfortunately, however, dyspeptic symptoms (e.g. abdominal pain and abdominal discomfort) alone do not necessarily indicate the presence of closely associated pathophysiology such as gastroduodenal motility disorders and excessive acid secretion.\textsuperscript{11} At present, treatment efficacy of FD using various drugs is generally reported as 50–60% in Japan. This section summarizes previous clinical reports that addressed efficacy of various treatments for FD.

1) \textit{H. pylori} eradication therapy

There are many arguments regarding the association of \textit{H. pylori} infection with the pathophysiology of FD, as diagnosed according to the Rome III criteria.\textsuperscript{12,13} Meanwhile, a systematic review of \textit{H. pylori} eradication therapy for FD revealed a 10% relative risk reduction of symptoms in the treated group compared to the placebo group.\textsuperscript{14} The number needed to treat (NNT) was indicated to be 13 in this systematic review. Therefore, \textit{H. pylori} infection may be associated with the pathogenesis, at least in a subset of patients with FD. Notably, the Japanese national health insurance program covers the cost of eradication therapy in patients with \textit{H. pylori}-associated gastritis. However, in the course of daily management, many physicians find that dyspeptic symptoms such as abdominal pain and discomfort are not improved by \textit{H. pylori} eradication therapy alone. Nevertheless, the Japanese clinical guideline for FD notes the potential relation-
ship between *H. pylori* infection and FD, and therefore recommends *H. pylori* eradication therapy for a subgroup of *H. pylori*-positive patients with FD. Furthermore, a recent global consensus demonstrates the concept of *H. pylori*-associated dyspepsia. Specifically, that document proposes that patients whose dyspeptic symptoms are improved by *H. pylori* eradication should be diagnosed with *H. pylori*-associated dyspepsia but not FD. Therefore, it appears that *H. pylori*-associated gastritis should be excluded from the diagnostic criteria of FD. The algorithm of the Japanese clinical guideline for FD indicates that an examination of *H. pylori* infection and its eradication therapy should occur prior to the initiation of recommended treatments for FD. In other word, physicians must consider that *H. pylori* eradication therapy may be distinct from the standard treatment options in patients with FD.

2) Acid suppression therapy

Acid suppressants such as proton pump inhibitors (PPIs) and histamine type 2 receptor antagonists (H2RA) often are used to treat various gastrointestinal diseases, including gastroduodenal ulcers and gastro-esophageal reflux diseases. There also have been many clinical trials evaluating the efficacy of these acid suppressants for FD because it is reported that visceral hypersensitivity caused by gastric acid is closely associated with the pathogenesis of FD. In patients with FD, these trials indicated response rates for esomeprazole and lansoprazole that were 10–15% over placebo. Furthermore, a double dose of rabeprazole was effective (63.5%) for treatment of FD especially in patients with abnormal acid reflux into the esophagus. In Japan, an open label trial showed that the response rate of omeprazole was 67%, which was higher than that of other treatment groups (famotidine, mosapride, and teprenone). In addition, randomized controlled trials (RCTs) using rabeprazole (the SAMURAI study) showed that the complete and satisfactory relief rates of 20 mg rabeprazole were 11.4% and 17.1% over placebo in patients with non-ulcer dyspepsia in the Cochrane database systematic review. On the basis of these findings, the Japanese clinical guideline for FD proposed a statement that acid suppressants are effective for the treatment of patients with FD. However, the NNT of PPI in the treatment of FD was approximately 9 in this systematic review. Furthermore, PPIs and H2RAs provided the same level of efficacy and were effective for the treatment of FD, although there was a clear difference in acid suppression levels between the two drugs. Accordingly, it must be concluded that some problems remain to be elucidated for definitive establishment of acid suppressor therapy for FD, although acid suppressor therapy is recommended as a first-line therapy for FD.

3) Prokinetic therapy

Various clinical studies suggest that gastrointestinal motility disorders are strongly associated with dyspeptic symptoms in the pathogenesis of FD. Therefore, prokinetics is suggested to be effective for FD treatment. Indeed, in patients with FD, the response rate for itopride reported to exceed that of placebo by 22%. However, subsequent report was not able to confirm the superiority of itopride. In a Japanese mega-clinical trial, mosapride was effective in relieving abdominal bloating and pain in patients with FD. Together with these findings, it may be easy to understand that some meta-analyses indicated the efficacy of prokinetics for FD. However, there also remain some problems such as the small number of subjects and the use in the previous clinical trials of agents that are now unavailable. Thus, the clinical utility of prokinetics in treatment of FD may be low in Western countries. Recently, acotiamide has been approved by Japanese health insurance for the treatment of meal-related symptoms of FD. As a pharmaceutical characteristic, the agent is a selective inhibitor of anticholinesterase and does not exhibit binding to serotonin receptors and dopamine receptors. Thus, the pharmacological action of acotiamide increases acetylcholine content in the enteric nerve endings via an inhibition of acetylcholinesterase; binding of acotiamide to the muscarinic receptor results in upregulation of gastrointestinal motility. As proven in several RCTs,
the effectiveness of acotiamide exceeded that of placebo by 17.4%, and the NNT of acotiamide was approximately 6 in this clinical trial.29 Accordingly, the Japanese clinical guideline for FD concludes that prokinetic therapy is recommended as a first-line therapy for FD, although further clinical trials will be required to evaluate other (non-acotiamide) prokinetics in the treatment of FD.

4) Antidepressants, anxiolytics, and kampo medicine therapy
The Japanese clinical guideline for FD sets a second-line concept of treatment for patients with refractory FD symptoms against the first-line therapy using acid suppressants and prokinetics. Considering the close association of psychosomatic factors with the pathogenesis of FD, it is easy to understand that antidepressants and anxiolytics are indicated to be effective for treatment of FD.5 However, there are only a few reports regarding the efficacy of psychosomatic agents for patients with FD, not only in Western countries but also in Eastern countries. Meanwhile, a Japanese multicenter RCT using tandospirone, an anxiolytic, showed significant efficacy in improving dyspeptic symptoms as well as psychosomatic symptoms of patients with FD.30 Furthermore, two meta-analyses showed the efficacy of antidepressants and anxiolytics for treatment of FD.31,32 However, the guideline concluded that more evidence for the use of antidepressants and anxiolytics for treatment of FD will be needed in Western and Eastern counties.

On the basis of alternative and complementary therapeutic options for general malaise, kampo medicines often are used for the treatment of various symptoms including epigastric pain, discomfort, bloating, and nausea. In addition, there have been two comprehensive reviews of the basic science and clinical evidence of kampo medicine therapy for upper gastrointestinal diseases.1,33 According to those review articles, rikkunshito has exhibited clinical efficacy based on a variety of parameters, including evidence of pharmaceutical improvement of gastrointestinal dysfunction in response to various kampo medicines.34–36 Therefore, rikkunshito is recommended as a treatment option in the Japanese guideline. However, more evidence using other (non-rikkunshito) kampo medicine also will be needed to increase treatment options of FD.

5) Lifestyle management, dietary treatment, and cognitive behavior therapy
Prior to pharmacological treatment, management of lifestyle and dietary habits may be generally required for patients with FD because a part of abdominal symptoms is meal-related dyspeptic symptom. However, there is no report such as an interventional study about the efficacy of lifestyle management for treatment of FD. Regarding with dietary treatment, there is a paper suggesting the possibility that FD symptoms in part might be reduced by avoiding a high fat diet.37 On the other hand, there is only one randomized clinical trial indicated that cognition-behavior therapy may be effective for controlling symptoms in patients with FD. However, further clinical study with larger samples will be needed because sample size of the previous paper was relatively small.38

2. Pharmacological Treatments of FD in the Future
Therapeutic response to the above conventional drugs is not always satisfactory for patients with FD. Therefore, more modalities of promising treatment and management for FD are needed to be established as soon as possible. It has been reported that sumatriptan and buspirone, a serotonin (5-HT) type 1 receptor agonist, ameliorate gastric accommodation disorders. Selective 5-HT reuptake inhibitors also are indicated to improve such disorders through 5-HT type 1 and type 4 receptors. Thus, these drugs could be candidates for treatment of FD because gastric accommodation disorder is thought to be an important factor in causing dyspeptic symptoms.8

In other works, drugs that treat visceral hypersensitivity have been proposed as potential therapies for FD, although no useful drugs have (to date) been reported. Notably, a review article has summarized many reports regarding this possibility.39 As an example, that review reported that fedotozine, a κ-opioid receptor agonist, can decrease the threshold of visceral pain against stimulation by gastric balloon distension. However,
asimadoline was considered to be a more likely candidate for FD treatment, given that fedotozine did not improve clinical symptoms in patients with FD. Other proposed treatment options have included alvimopan (a peripheral μ-opioid receptor antagonist), dextromethorphan (a N-methyl-D-aspartic acid receptor antagonist), aprepitant and talnetant (neurokinin receptor antagonists), a transient receptor potential vanilloid-1 receptor agonist, a mast cell stabilizer, and a gamma-aminobutyric acid receptor agonist, all of which are known to affect the neuronal pathway from the enteric neuron to the CNS. Thus, more candidates are expected to be available for patients with visceral hypersensitivity. However, further clinical trial using these drugs will be needed.

3. Pharmacological Treatments of IBS at Present

As for FD, a treatment strategy of IBS also must be established in accordance with respective pathophysiology. Since most pathophysiological factors of IBS are similar to those of FD, the pharmacological treatment regimen for IBS is similar to that of FD. However, as for FD, no definitive and conclusive treatment regimen has yet been established for IBS. Among various factors, systemic stress-associated brain-gut interaction has been suggested as a possible mechanism of lower abdominal pain and discomfort derived from the colon. In other words, the pathogenesis of IBS involves both the CNS and colon because some changes in CNS function alter perception and post-infectious mucosal inflammation is associated with abdominal symptoms of IBS.40,41 Therefore, ongoing research is investigating the brain-gut interaction to elucidate the pathophysiology of IBS and establish potential therapies. Corticotropin-releasing factor, a stress-associated mediator, is secreted under stress conditions, yielding upregulation of colonic motility and causing visceral hypersensitivity. In addition, 5-HT, a neurotransmitter, has been associated with the pathogenesis of IBS. Furthermore, because the 5-HT receptor is known to regulate emotion in the CNS, pain in the spinal cord, and motility in the gastrointestinal tract, the 5-HT pathway is indicated to play a significant role in the pathogenesis of IBS. Meanwhile, evidence-based clinical practice guidelines for IBS have been published in Japan.3 According to this guideline, step-1 therapy consists of diet therapy, behavioral modification, and gut-targeted pharmacotherapy for 4 weeks. Next, step-2 therapy employs psychopharmacological agents and simple psychotherapy for 4 weeks. Finally, step-3 includes a combination of gut-targeted pharmacotherapy, psychopharmacological treatments and/or specific psychotherapy. This section of the review summarizes previous clinical reports that addressed efficacy of various treatments for IBS.

1) Bulking polymers therapy

Polycarbophil calcium is a polyacrylic resin that is hydrophilic but insoluble in water. The compound maintains watery content in the gastrointestinal tract by acting like a soluble fiber, thereby regulating the transport of gastrointestinal content. The agent has been shown to ameliorate watery diarrhea and constipation in patients with IBS.42 Furthermore, the resin attenuates the decreased threshold for painful stimulation and the reduced compliance of the rectum. Thus, this agent is recommended to be one of first selective drugs for use in IBS treatment. The efficacy of polycarbophil calcium has been proven in placebo-controlled RCTs as well as in large-scale clinical trials conducted in Japan.43

2) Probiotic and prebiotic therapies

Accumulating lines of evidence based on basic and clinical research on probiotics and prebiotics have shown the efficacy of these modalities for treatment of IBS.44,45 As a result, probiotics and prebiotics are (respectively) strongly and weakly recommended for treatment of patients with IBS.3 However, there were somewhat inconsistent results among various reports depending on the respective bacterial species tested. Thus, further clinical trials will be needed before definite recommendations can be made, especially for a Japanese population.

3) Prokinetic therapy

Trimebutine maleate inhibits (via μ- and κ-opioid receptors) the release of acetylcholine from neurons in the myenteric plexus and has been proposed for use in the treatment of IBS. A systematic review indicated
that the agent improved gastrointestinal symptoms, including abdominal pain, along with defecation frequency and stool consistency. Therefore, the agent may be especially effective in patients with diarrhea-dominant IBS. In Western countries, the 5-HT3 receptor antagonist alosetron significantly improved abdominal pain and discomfort, defecation urgency, defecation frequency and loose stool/diarrhea in female (but not male) diarrhea-dominant IBS patients. In Japan, the 5-HT3 receptor antagonist ramosetron showed significant efficacy in male (but not female) diarrhea-dominant IBS patients. However, recently, the efficacy of ramosetron has been proved in female patients with diarrhea-dominant IBS. Although the differences in efficacy of the respective 5-HT3 receptor antagonist were due to a small number of patients recruited in the corresponding studies, 5-HT3 receptor antagonists are believed to relieve the symptoms of IBS via an increase in water absorption in the gut and regulation of the afferent nerve fiber from the gut. On the other hand, for patients with constipation-dominant IBS, 5-HT4 receptor agonists such as mosapride could be effective. However, there are few reliable data regarding the utility of 5-HT4 receptor agonists for IBS treatment.

4) Other pharmacological therapies
A variety of candidates for IBS treatment are described in the evidence-based clinical practice guidelines for IBS, including anticholinergics, anti-diarrheal agents, laxatives, enemas, antidepressants, anxiolytics, anti-psychotics or mood stabilizers, and kampo medicines. Although these drugs may be effective for some patients with IBS, a weak recommendation for the relevant applications are weak, because there are few clinical data regarding treatment efficacy for IBS.

5) Lifestyle management, dietary treatment, and cognitive behavior therapy
As well as treatment for FD, management of lifestyle and dietary habits is usually performed for patients with IBS. A recent RCT showed that a low fermentable oligo-di-mono-saccharide and polyol diet, eliminating high fat foods and avoiding spicy foods, is effective for patients with IBS. In addition, a meta-analysis, a fiber-rich diet was effective for constipation, but not for abdominal pain in IBS patients. Other behavioral modifications, such as eliminating alcohol and smoking, getting good sleep, and taking rest, also might reduce IBS symptoms. Accordingly, a Japanese guideline for IBS suggests weak recommendation of management of lifestyle and dietary habits and behavioral modification. This guideline suggested that cognitive behavioral therapy also improves overall IBS symptoms and QOL three months after treatment than regular therapy or waiting for treatment initiation. However, to conclude definitely, further clinical study with larger samples will be needed.

4. Pharmacological Treatments of IBS in the Future
As with the treatment of FD, IBS-relevant agents developed in the near future are expected to include those that affect gut microbiota and visceral hypersensitivity. Various bacterial changes such as species, content, and balance are caused by intestinal infection and are indicated to be important for the pathogenesis of IBS. In general, it is reported that Bifidobacterium and Lactobacillus have beneficial effects on the pathogenesis of IBS, but Clostridium and Escherichia coli have unpleasant effects on it. In the cluster analyses of fecal microbiota, some clusters may affect the pathogenesis of IBS. Briefly, an increase in bacteria in the Firmicute phylum, a decrease in bacteria in the Bacteroidetes phylum, and their imbalance are indicated to be pathogenesis-associated factors for IBS. On the basis of these findings, novel probiotics and antibiotics are expected to be available as pharmacological treatments for patients with IBS. It has been reported that Bifidobacterium infantis improves stool conditions of patients with IBS via regulation of inflammatory cytokines. In other works, clinical trials have tested the antibiotic rifaximin as a treatment for IBS; notably, this compound is not absorbed into the gastrointestinal tissues after oral administration, and so effectively serves as a topical treatment within gastrointestinal tract. In double-blind, placebo-controlled trials for patients with IBS without constipation, rifaximin significantly relieved global IBS symptoms (including bloating, abdominal pain, and loose or
watery stools) compared to placebo controls.53 On the other hand, there is a recent report indicating the efficacy of linaclotide for patients with constipation-dominant IBS. Linaclotide, a 14-amino acid peptide agonist for guanylate cyclase-C, increases intestinal secretion and transit in the duodenum and small intestine. These pharmacological functions can directly maintain watery content in the stool and upregulate gastrointestinal transit. Additionally, this peptide decreases the hypersensitivity of visceral pain threshold. In a placebo-controlled study, linaclotide for 12 weeks significantly improved symptoms in patients with constipation-dominant IBS, including abdominal pain and bowel symptoms.54 These findings indicate the possible efficacy of linaclotide for Japanese patients with IBS. As with FD, drugs to treat visceral hypersensitivity are expected in the field of IBS. However, further clinical trial will be needed.

In conclusion, the pathogenesis of FGIDs such as FD and IBS has not been completely elucidated, and definite pharmacological therapeutic strategies have not been established. Therefore, pharmacological treatment of FGIDs must be performed step by step according to the evidence-based clinical practice guidelines for FGIDs published in 2014. However, it is hoped that various candidates, including novel drugs and compounds repurposed from other fields, will be developed and tested for the treatment of abdominal symptoms in placebo-controlled RCTs in the near future.

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