

Functional Abdominal Cramping Pain

Expert Practical Guidance

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Abstract: Functional abdominal cramping pain (FACP) is a common complaint, which may present either on its own or in association with a functional gastrointestinal disorder. It is likely caused by a variety of, probably partly unknown, etiologies. Effective management of FACP can be challenging owing to the lack of usable diagnostic tools and the availability of a diverse range of treatment approaches. Practical guidance for their selection and use is limited. The objective of this article is to present a working definition of FACP based on expert consensus, and to propose practical strategies for the diagnosis and management of this condition for physicians, pharmacists, and patients. A panel of experts on functional gastrointestinal disorders was convened to participate in workshop activities aimed at defining FACP and agreeing upon a recommended sequence of diagnostic criteria and management recommendations. The key principles forming the foundation of the definition of FACP and suggested management algorithms include the primacy of cramping pain as the distinguishing symptom; the importance of recognizing and acting upon alarm signals of

potential structural disease; the recognition of known causes that might be addressed through lifestyle adjustment; and the central role of antispasmodics in the treatment of FACP. The proposed algorithm is intended to assist physicians in reaching a meaningful diagnostic endpoint based on patient-reported symptoms of FACP. We also discuss how this algorithm may be adapted for use by pharmacists and patients.

Key Words: functional abdominal cramping pain, functional gastrointestinal disorder, antispasmodic, spasmolytic, primary care

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EXECUTIVE SUMMARY OF STATEMENTS AND RECOMMENDATIONS

Background

Functional abdominal cramping pain (FACP) is a common complaint that may present on its own or as a predominant symptom of a functional gastrointestinal disorder (FGID). Despite the studies suggesting a high prevalence of FACP in the general population, the Rome classification for FGIDs does not consider it to be a discrete symptomatic entity.

Definition

The expert panel proposes the following definition for FACP, as reported by patients with or without a diagnosed FGID:

“FACP refers to the sudden occurrence of mild-to-moderate, undulating, and recurring cramping pain in any part of the abdomen, lasting for seconds to minutes or up to a few hours, in the absence of any “red flag” signs/symptoms of structural organic disease or any strong association with defecation (which might indicate irritable bowel syndrome [IBS]), and typically not significantly interfering with daily activities.”

FACP could be perceived as reflecting part of the IBS spectrum but without a strong association with bowel irregularities. In situations where FACP is tightly linked with abnormalities of bowel evacuation, a diagnosis of IBS should be suspected, provided that patients fulfill the Rome IV diagnostic criteria.

Statements and Recommendations

Burden of FACP

- Health care professionals, including specialists, primary care physicians/general practitioners, and pharmacists, should be aware of FACP, the impact it can have on sufferers, and how to manage symptoms.

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Causes of FACP

- The causes of FACP in FGIDs are unclear but are probably multifactorial.

Diagnosis and Investigation of FACP in Primary Care

- When evaluating FACP in primary care, the first step is to rule out “red flags” (alarm signals) of structural organic disease, which necessitate referral to a specialist.
- A detailed evaluation of family history, medication, characteristics of pain, and eating/bowel habits should be undertaken in all patients presenting to primary care with FACP symptoms.
- In selected cases and at the discretion of the doctor, a physical examination (including bowel sounds and digital rectal examination), laboratory tests, and psychosocial assessment may also be appropriate. Abdominal ultrasound investigations may be helpful.

Clinical Management of FACP in Primary Care

- Mild, infrequent episodes of FACP may only require reassurance and advice (including avoidance of trigger foods), whereas more intensive and/or frequent episodes usually require therapeutic intervention.
- Many patients with FACP who present to primary care may require empirical treatment with an antispasmodic, the choice of which will depend on local availability and individual preference. If the first drug does not provide adequate symptom relief, it might be worthwhile to try an alternative antispasmodic.
- Patients who obtain little or no relief from their FACP with an antispasmodic may benefit from additional analgesia, for example, with acetaminophen (paracetamol).
- Patients with centrally mediated abdominal pain syndrome may respond to low doses of tricyclic antidepressants or selective serotonin reuptake inhibitors, or to the neuromodulator pregabalin.
- Relaxation training and targeted psychological interventions may be the helpful adjunctive therapies for selected patients who suffer from stress and/or have preexisting psychiatric comorbidities.

Self-management of FACP

- Self-management of FACP using over-the-counter products is appropriate for many patients with mild, non-persistent symptoms.
- To enable better self-care, patients and pharmacists require education and information on signs and symptoms to be aware of, and which treatments to use.

INTRODUCTION

Functional abdominal cramping pain (FACP) is frequently encountered in the general population. It may present either on its own or in association with a functional gastrointestinal disorder (FGID; also known as a disorder of gut-brain interaction), such as irritable bowel syndrome (IBS), functional dyspepsia, and biliary pain.^{1,2} Although national and international guidelines exist for managing the symptoms of IBS, including the abdominal pain,^{3–12}

recommendations for the general diagnosis and symptomatic management of FACP are lacking.

The lack of guidance on how to diagnose and manage FACP reflects the absence of a standard, accepted definition, and limited focused literature on this complaint. The Rome Foundation has developed and updated its own criteria, currently up to Rome IV, to diagnose FGIDs, including those associated with FACP, such as IBS, functional dyspepsia, biliary pain, postprandial distress syndrome, epigastric pain syndrome, and narcotic bowel syndrome (also referred to as opioid-induced gastrointestinal hyperalgesia).^{1,2,7,13,14} However, although the Rome criteria are a useful tool for gastroenterologists and researchers, they do not fully capture the presentation of FACP seen in everyday practice, nor are they practical enough to be used routinely by primary care physicians (PCPs)/general practitioners (GPs), pharmacists, or patients, whose primary objective—once structural, organic causation has been ruled out—is symptom alleviation. The present expert guidance attempts to address these issues by providing a consensus definition for FACP and by presenting recommendations for its diagnosis and clinical management, with a focus on primary care and self-management. To complement these recommendations, practical, easy-to-use algorithms have been constructed to aid physicians, pharmacists, and patients themselves in identifying and managing FACP.

METHODS

A panel of well-recognized experts in the field of FGIDs, based in Europe and Latin America, was convened for the purpose of addressing the agreed-upon unmet need for better guidance for diagnosing and treating FACP, as recalled by individuals who do not meet the criteria for a diagnosis of IBS under the Rome (IV) criteria. The focus of the meetings was on primary care management of FACP, as this reflects the main approach used in Europe and Southern/Latin America, of which the authors have expert knowledge. However, over-the-counter (pharmacist- and patient-led) self-management was also reviewed.

The panel met twice to discuss and agree on the definition of FACP. During the first meeting, the panel participated in workshop activities to agree upon a definition of FACP and to discuss its diagnosis and management. The format allowed time for all participants to input their views and was followed by group discussion and final agreement. To facilitate diagnosis and management, 3 draft algorithms (targeted at PCPs/GPs, pharmacists, and patients, respectively) were also developed, taking into consideration the professional guidelines, the quality of the clinical evidence for specific management strategies, and the panel’s own experience. The panel then participated in a second meeting to discuss further refinement and finalization of the algorithms. Consensus statements and recommendations from these expert meetings are presented. The panel note that, because of a lack of targeted literature on FACP, there was a need to refer closely to the data on FGIDs, especially IBS, and many of the statements and recommendations provided here are, therefore, similar to those in published guidelines for the diagnosis and management of abdominal pain in patients with FGIDs.

BURDEN OF FACP

Statement:

- Health care professionals, including specialists, PCPs/GPs, and pharmacists, should be aware of FACP, the impact it can have on sufferers, and how to manage symptoms.

Comments

FGIDs, many of which may be associated with FACP, are extremely common and can have a negative impact on the quality of life of sufferers and incur a substantial health care burden in terms of an increase in the consumption of medical therapies, a greater requirement for abdominal surgery, and additional medical consultations/referrals.^{15–18} The recently published global Rome Foundation epidemiological study of 73,076 people, based on the new Rome IV classification, found that 40.3% of respondents who completed the internet survey and 20.7% of those who completed the household survey met the criteria for at least 1 FGID.¹⁵ The prevalence of FGIDs was 1.3 to 1.7 times higher in women than in men.

FACP is frequently reported by patients either on its own or in conjunction with FGIDs. The true prevalence of FACP, in isolation from bowel movement irregularities, is difficult to ascertain because, up until now, there has been no uniform definition of FACP. Although definitions do vary, survey data suggest that the prevalence of FACP in the general population may range from 10% to 46%.^{19,20} In an internet-based, observational study of 720 women with abdominal pain, cramping, and discomfort, symptoms of FACP were reported to interfere with some respondents' daily activities (44% reported disruption very often/often), work and sleep quality, and social activities.²¹ Furthermore, in a large survey of IBS sufferers conducted by the American Gastroenterology Association, abdominal pain was identified as one of the most bothersome disease symptoms and a symptom that should be addressed.²² As well as impacting on patient quality of life,^{21,22} abdominal pain is also a most common reason for primary care consultation, with a mean consultation prevalence of 2.8% reported in a systematic review of 14 symptom-evaluating studies on abdominal pain in the general practice setting.²³

DEFINITION OF FACP

The latest Rome IV criteria focus on the diagnosis and overall management of FGIDs rather than on the specific presentation and symptomatic treatment of FACP (Supplemental Digital Content Table 1, <http://links.lww.com/JCG/A890>).^{1,2,7,13,24} Furthermore, although FACP has been reported in the literature without association with a particular disorder,^{19–21} there is no standardized definition. We, therefore, propose the following definition for FACP:

Definition of FACP:

FACP refers to the sudden occurrence of mild-to-moderate, undulating, and recurring cramping pain in any part of the abdomen, lasting for seconds to minutes or up to a few hours, in the absence of any "red flag" signs/symptoms of structural organic disease or any strong association with defecation (which might indicate IBS), and typically not significantly interfering with daily activities.

FACP could be perceived as reflecting part of the IBS spectrum but without a strong association with bowel irregularities. In situations where FACP is tightly linked with abnormalities of bowel evacuation, a diagnosis of IBS should be suspected, provided that patients fulfill the Rome IV diagnostic criteria.

CAUSES OF FACP

Statement:

- The causes of FACP in FGIDs are unclear but are probably multifactorial.

Comments

Although there is little information on the causes of FACP, it is the consensus view of the panel that mechanisms that underlie these symptoms are probably similar to those reported for the IBS spectrum. As in IBS, FACP, which may be peripherally and/or centrally mediated, may result from an interplay between psychological stress (leading to a dysregulated gut-brain interaction), mucosal immunity (immune activation resulting in chronic low-grade inflammation), visceral hypersensitivity, dysbiosis, and gut dysmotility (Fig. 1).^{25–27} The susceptibility of individuals to FACP and their experience of symptoms may depend on both genetic predisposition and external aggravators.

Data in FGIDs indicate that one of the most important external factors affecting gastrointestinal function and symptoms, including FACP, is stress.^{28–31} Although it is beyond the scope of this article to review this topic, there is evidence that stress promotes delayed gastric emptying and accelerated colonic transit,^{29,32} and that the stress response in the gut is mediated, largely, by corticotropin-releasing factor and its downstream signaling pathways.^{33,34}

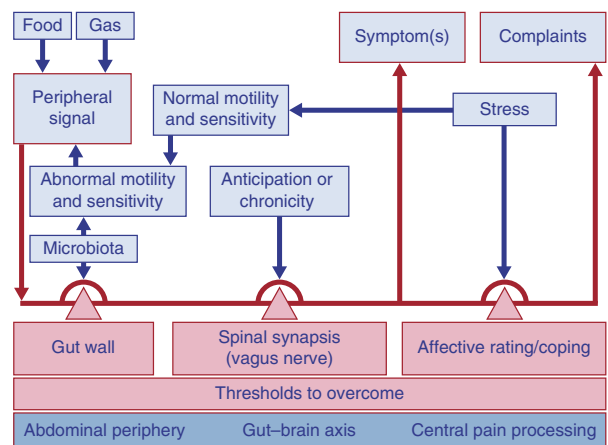


FIGURE 1. Current understanding of the pathophysiology of abdominal pain in functional gastrointestinal disorders. A peripheral signal is a prerequisite, that is, the pain is not merely a psychological event. This signal may originate from the intestinal contents (food or gas) or from changes in gastrointestinal motility and sensitivity; the latter may be altered by stress. To be recognized by the individual, the signal must overcome some thresholds: sensation within the gut wall, spinal synapsis, and—to be experienced as “uncomfortable”—the affective rating (the latter again being impacted by stress). Gut wall sensation and spinal synapsis may be lowered by the microbiota and anticipation or chronicity, respectively.

Gastrointestinal function and symptoms can also be affected by eating habits and food intake. Although it is currently unknown whether FACP itself relates directly to eating patterns and/or the ingestion of specific trigger foods or food components, it is worth noting that, in many patients with IBS-related abdominal pain, diet and nutrition seem to have some role in evoking and sustaining the low-grade inflammation in the abdominal tissues and in altering the gut microbiota.^{26,27}

DIAGNOSIS AND INVESTIGATION OF FACP IN PRIMARY CARE

Ruling Out Organic Pathology

Recommendations:

- When evaluating FACP in primary care, the first step is to rule out “red flags” (alarm signals) of structural organic disease, which necessitate referral to a specialist.

Comments

When a patient first presents to primary care with symptoms of FACP, the first step is to rule out potentially serious organic disease. Key red flag signs and symptoms that could indicate structural disease are summarized in Table 1. Patients presenting with any indicators of organic disease require referral to a specialist for further investigation.

Investigations and Diagnosis

Recommendations:

- A detailed evaluation of family history, medication, characteristics of pain, and eating/bowel habits should be undertaken in all patients presenting to primary care with FACP symptoms.
- In selected cases and at the discretion of the doctor, a physical examination (including bowel sounds and digital rectal examination), laboratory tests, and psychosocial assessment may also be appropriate. Abdominal ultrasound investigations may be helpful.

Comments

As with FGIDs in general, a comprehensive patient assessment is needed to rule out red flags and to characterize

TABLE 1. Red Flag (Alarm) Signs That May Be Present in Patients With Functional Abdominal Cramping Pain (List Not Exhaustive)^{10,11,35–38}

“Red flag” signs
Family history of a gastrointestinal disease with a heritable component, eg, Colorectal cancer Inflammatory bowel disease (eg, Crohn’s disease, ulcerative colitis) Celiac disease
Recent weight loss that cannot be readily explained, or loss of appetite
Recent onset of anemia, or of unusual pale appearance (pallor)
Recent onset of fever
Presence of unexplained blood in stools
Presence of abnormal abdominal mass, or of fluid buildup in the abdomen (ascites)
Significant worsening of symptoms at night
Recent marked change in symptoms
Persistent vomiting or diarrhea
Onset of symptoms in patients aged 50 y or older

the FACP. We recommend that the assessment includes an evaluation of family history (especially for malignancy, gastrointestinal diseases, and other conditions that could affect their management), current and recent medication, characteristics of pain (nature, location, duration, quality, frequency, and severity), and eating/bowel habits (including known food allergies, intolerances, and triggers). In selected patients and at the discretion of the doctor, a physical examination (including bowel sounds and digital rectal examination) and limited laboratory tests may be appropriate, and psychosocial assessment may also be helpful, particularly if the patient has preexisting psychiatric comorbidities or there are indicators of significant psychological stress.^{11,35,37} The physical examination should assess the pain location and whether there is a palpable mass, abnormal or absent bowel sounds, rebound tenderness, rigidity/resistance, distension, and/or guarding. Experience in IBS shows that relevant laboratory tests might include complete blood cell counts and other targeted blood tests (eg, erythrocyte sedimentation rate, C-reactive protein, and/or celiac serology), thyroid and liver function tests, and stool studies (eg, fecal calprotectin and/or occult blood test), as indicated.^{5,11,35,38} Abdominal ultrasound investigations can sometimes be helpful and are cheap and simple to undertake in most settings.³⁹ There are also certain other signs and symptoms that may require additional evaluation. For example, for pain in women that seems to be related to the menses, a gynecologic evaluation should be considered.³⁸ Similarly, for pain brought on by physical exertion, a cardiology assessment should be sought. If the initial investigations raise concerns or are equivocal, referral for a computerized axial tomography scan might be considered.

Assuming none of the red flag signs/symptoms are present and no abnormalities are identified at the physical examination, laboratory tests, or other investigations, a diagnosis of FACP may be considered if the symptoms are described by the present definition. If the FACP is tightly related to changes in bowel evacuation, IBS is the most probable diagnosis and should be confirmed using the Rome IV criteria.

CLINICAL MANAGEMENT OF FACP IN PRIMARY CARE

Recommendations:

- Mild, infrequent episodes of FACP may only require reassurance and advice (including avoidance of trigger foods), whereas more intensive and/or frequent episodes usually require therapeutic intervention.
- Many patients with FACP who present to primary care may require empirical treatment with an antispasmodic, the choice of which will depend on local availability and individual preference. If the first drug does not provide adequate symptom relief, it might be worthwhile to try an alternative antispasmodic.
- Patients who obtain little or no relief from their FACP with an antispasmodic may benefit from additional analgesia, for example, with acetaminophen (paracetamol).
- Patients with centrally mediated abdominal pain syndrome may respond to low doses of tricyclic antidepressants or selective serotonin reuptake inhibitors, or to the neuromodulator pregabalin.
- Relaxation training and targeted psychological interventions may be the helpful adjunctive therapies for selected patients who suffer from stress and/or have preexisting psychiatric comorbidities.

Comments

The management of FACP depends on the intensity and frequency of presentation. The occurrence of mild, infrequent episodes often only requires reassurance and advice, whereas the presentation of more intensive and/or frequent symptoms will usually necessitate therapeutic intervention. It should be noted that FACP in patients with IBS (ie, FACP associated with changes in bowel habits or stool form, according to Rome IV criteria) should be managed in line with current IBS guidelines.^{3–11}

Among all patients presenting with FACP, there are many considerations for determining the optimal approach to symptom management. Patient-specific factors to be considered include age, sex, onset of pain, location of pain, duration of pain, pain variations, quality of pain, concomitant symptoms, lifestyle, aggravators, and relieving factors. Patients with mild FACP can usually be managed by reassuring them that the cause of their pain is not sinister and by advising them to avoid foods or drinks that may trigger and/or exacerbate symptoms and to avoid stress. Patients may be advised to return to their usual diet if a dietary elimination trial is unsuccessful. As recommended for IBS patients,¹¹ it also seems sensible to provide general guidance on maintaining a healthy diet and lifestyle.

Although an improvement in diet and lifestyle is likely to benefit the overall health of all patients, many patients with FACP may also require empirical medical treatment, usually with antispasmodics. These therapies are the most suitable for alleviating FACP, as they act directly on the smooth muscle of the gut to suppress the muscle cramps and spasticity that underlie the abdominal pain. They have also been shown to be efficacious in patients primarily defined by the presence of FACP symptoms.^{40,41} This approach, thus, contrasts with the global treatment of IBS, where the goal is to reduce overall symptoms including abdominal pain, distention, bloating, indigestion, and altered bowel patterns (constipation and/or diarrhea).¹² Most patients with FACP can be managed with on-demand medication but those with frequent or more severe symptoms may require a limited course of treatment. The ideal drug should be suitable for on-demand use and have a fast onset of action with a long-lasting effect, minimal systemic absorption, and few side effects.⁴² The choice of antispasmodic therapy will usually depend on local availability and individual preference. Types of antispasmodic medications, which are available as over-the-counter or prescription only products, depending on the market, include (1) antimuscarinics, for example, hyoscine butylbromide, dicycloverine hydrochloride (dicyclomine), and cimetropium; (2) the phosphodiesterase inhibitors drotaverine and papaverine; (3) the sodium channel blocker mebeverine; (4) the peripheral opiate receptor agonist trimebutine; (5) the calcium channel blockers otilonium and pinaverium; (6) the direct smooth muscle relaxant alverine (often given in combination with the antifoaming agent simethicone, which is used to reduce bloating, discomfort, and/or pain caused by excessive gas); and (7) the herbal medicinal product, peppermint oil.

Multiple meta-analyses and randomized controlled trials have shown that antispasmodic drugs are more efficacious than placebo at improving abdominal pain in patients with IBS.^{43–48} However, because of the lack of

head-to-head trials and sparsity of recent data, limited evidence exists to support differentiation of antispasmodic therapies. There are also very few studies, which have specifically investigated antispasmodics as a treatment for FACP.

Clinical evidence for the benefit of antispasmodic therapy in treating FACP as the primary symptom comes mainly from studies of hyoscine butylbromide.^{40,41,49,50} Two randomized, double-blind, placebo-controlled trials have demonstrated the efficacy, albeit limited, of hyoscine butylbromide (given in limited-duration courses or as on-demand treatment) in reducing the intensity and frequency of abdominal pain, with few side effects, in patients defined by the presence of FACP symptoms.^{40,41} In the first of these studies, involving 1637 patients with recurrent, crampy abdominal pain, hyoscine butylbromide was significantly more efficacious than placebo in improving pain intensity (measured on a 10 cm visual analog scale; adjusted mean change from baseline, -2.3 vs. -1.9 cm, respectively, $P < 0.0001$) and frequency [measured on a verbal rating scale (range: 0–3); adjusted mean change from baseline, -0.7 vs. -0.5 , respectively, $P < 0.0001$] when given for a limited period of 3 weeks.⁴⁰ In the second study of 175 patients with self-reported, recurrent, functional, cramping abdominal pain, on-demand hyoscine butylbromide significantly reduced the intensity of pain (measured on an 11-point numerical pain rating scale) experienced by patients during 2 distinct episodes compared with placebo (adjusted mean difference vs. placebo in change from baseline for episode 1, -0.7 , $P = 0.016$).⁴¹ Positive effects on quality of life have also been reported for hyoscine butylbromide treatment among patients with FACP, with greater improvements observed compared with standard analgesia regarding patients' ability to carry out daily activities, work quality, and symptoms experienced during stressful situations.²¹

In instances where an antispasmodic agent seems to be ineffective, and in the absence of an identified organic cause of FACP, it might be worthwhile to trial another antispasmodic with a different mechanism of action before attempting to introduce other treatment modalities. Although switching from 1 antispasmodic to another has not been evaluated, such trial and error seems justified if the pharmacology of the 2 agents is different. Further treatment options at this point may include the herbal medicinal products, peppermint oil or STW 5. Peppermint oil has antispasmodic properties and multiple clinical studies have shown that it can reduce abdominal pain in patients with IBS.^{4,43,44,47,48,51} Across Europe, peppermint oil is indicated as a “herbal medicinal product for the symptomatic relief of minor spasms of the gastrointestinal tract, flatulence and abdominal pain, especially in patients with IBS.”⁵² Evidence supporting the clinical efficacy/effectiveness of another herbal treatment, STW 5, to reduce abdominal pain is also available, but the data are less compelling than for antispasmodics (including peppermint oil), and mainly derived from a small number of studies in IBS or functional dyspepsia.^{21,53–55} Notably, rare cases of hepatotoxicity leading to liver failure have been reported during STW 5 treatment,^{56,57} resulting a label change to exclude its use in individuals with liver disease, as well as in pregnant or breastfeeding women.⁵⁸

Patients obtaining little or no relief from their FACP with antispasmodics may benefit from adjunctive analgesia

treatment. Acetaminophen (paracetamol) has been shown to be more efficacious than placebo and similar to hyoscine butylbromide in reducing the intensity and frequency of recurrent crampy abdominal pain in a large-scale clinical trial,⁴⁰ and is an important, well-tolerated, and widely available option for treating FACP. As FACP is unlikely to have the same pathophysiology in all afflicted patients, it is possible that patients responding to acetaminophen might not be the same as those responding to antispasmodic therapy. Nonsteroidal anti-inflammatory drugs, which are also commonly accessible, have been shown to be effective against intense ambulatory cramping pain of gastrointestinal or genitourinary origin.⁵⁹ However, these drugs are not appropriate for most patients with mild-to-moderate FACP because of their poor gastrointestinal side-effect profiles.⁶⁰ Opioid analgesics are best avoided, if possible, as their use can cause constipation, nausea, and vomiting, which may worsen symptoms of FACP. There is also a high risk of dependence and addiction with these drugs.⁶¹ Furthermore, high acute doses or chronic use of opioids may lead to the development of narcotic bowel syndrome, a FGID which, by definition, is associated with abdominal pain.¹

Patients with centrally mediated abdominal pain syndrome (formerly known as functional abdominal pain syndrome)—a severely limiting FGID with a strong central component and relative independence from motility disturbances, which presents as continuous, near continuous, or frequently recurrent abdominal pain lasting for at least 6 months²⁴—may respond to low doses of tricyclic antidepressants or selective serotonin reuptake inhibitors, or to the neuromodulator pregabalin. These therapeutic options, which are common, effective treatments for many nongastrointestinal medical and functional central pain syndromes,²⁴ have been shown to reduce abdominal pain in patients with IBS (where abdominal pain is mediated through both central and peripheral mechanisms),⁶² although any benefits must be weighed against the high likelihood of side effects.^{44,63–65}

Targeted psychological interventions, such as cognitive behavioral therapy, multicomponent psychological therapy, gut-directed hypnotherapy, and dynamic psychotherapy, have been shown to be helpful adjunctive therapies in managing abdominal pain in IBS^{11,63,65} and therefore may have a wider application in FACP management. Such interventions would be expected to be most helpful for patients with preexisting anxiety and/or depression. Relaxation training/activities may also benefit some patients whose symptoms are triggered or worsened by stressful situations that cannot be avoided.⁶³

Patients with FACP may also present with other co-occurring gastrointestinal symptoms, such as constipation or diarrhea. Though they should not be ignored, there is little evidence that treating these symptoms and improving bowel habits will, in isolation, improve FACP.^{66,67}

SELF-MANAGEMENT OF FACP

Recommendations:

- Self-management of FACP using over-the-counter products is appropriate for many patients with mild, nonpersistent symptoms.
- To enable better self-care, patients and pharmacists require education and information on signs and symptoms to be aware of, and which treatments to use.

Comments

Self-care of gastrointestinal symptoms that impact quality of life, but which are not associated with a significant impairment in a person’s ability to carry out daily activities and are not associated with obvious symptoms of structural disease, is commonplace.^{19,38,42} Rates of health care seeking, self-care (over-the-counter drug use), and overall medication use among patients with symptoms of FACP do, nevertheless, vary across countries and regions.^{19,38,42} For example, greater use of medications for managing FACP (comprising mainly over-the-counter products) has been reported in the United States and Latin America than in Europe (90% vs. 72%, respectively).¹⁹ Reasons for preferring self-management approaches among patients with FACP may include cultural differences in the perception of and response to symptoms, and limitations in access to drugs and physician care.^{38,42}

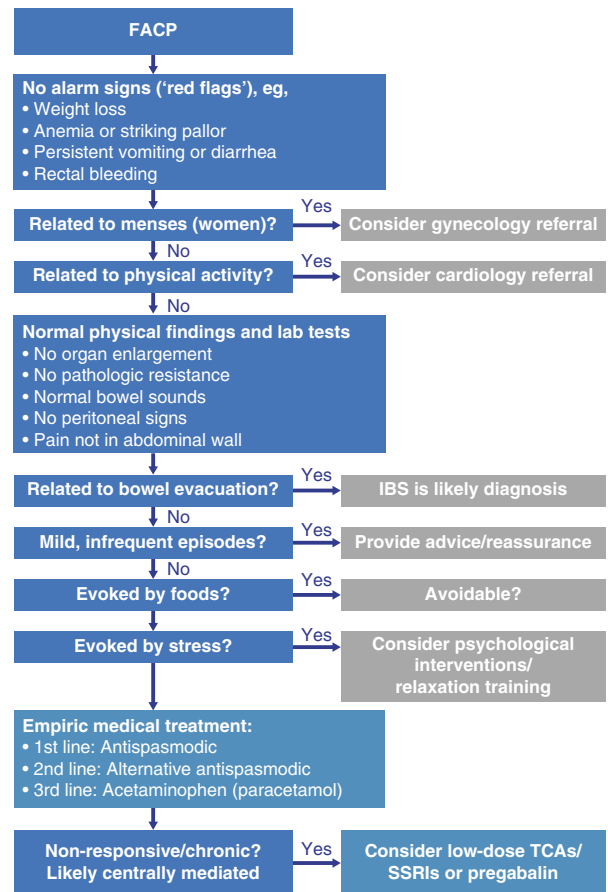


FIGURE 2. Algorithm for the symptomatic management of FACP, designed for use by physicians. FACP refers to the sudden occurrence of mild-to-moderate, undulating, and recurring cramping pain in any part of the abdomen, lasting for seconds to minutes or up to a few hours, in the absence of any “red flag” signs/symptoms of structural organic disease or any strong association with defecation (which might indicate IBS), and typically not significantly interfering with daily activities. FACP indicates functional abdominal cramping pain; IBS, irritable bowel syndrome; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Self-management of FACP typically involves the use of over-the-counter pharmaceuticals and/or nonpharmacologic products, with or without consultation with a pharmacist.^{19,42} As self-management of FACP is so common, particularly on first presentation of symptoms, both patients and pharmacists require education and information on signs and symptoms to be aware of (including red flags that may necessitate a health care consultation) and which treatments to use, which will vary depending on local practice and preferences, and product availability.

ALGORITHMS TO AID THE RECOGNITION AND MANAGEMENT OF FACP

A proposed algorithm for the optimal diagnosis and management of FACP by physicians, considered by the expert panel to be appropriate for use in primary care, is presented in Figure 2. This algorithm is based on the definition of FACP, and the management considerations outlined in the preceding sections. The starting point for the diagnosis is the core symptomatic manifestation of FACP, pain with cramping characteristics, which is generally considered to arise from primary gastrointestinal dysfunction. To establish the diagnosis of FACP, the critical first step is exclusion of a structural organic cause. This can be achieved through the recognition of alarm signals (“red flags”) related to other symptoms experienced and/or the patient’s family history of disease, and by considering the results of appropriate investigations, conducted as indicated by such signals. The algorithm considers the likelihood of an IBS diagnosis in cases where FACP symptoms are associated with bowel habit

alterations, thus emphasizing the distinction between IBS (as defined by the Rome IV criteria) and the definition of FACP proposed here. The algorithm also seeks to rule out abdominal pain of gynecologic or cardiac origin. For first-line treatment, antispasmodics are recommended for patients whose symptoms fulfill the consensus definition of FACP and who lack signals of a potential differential diagnosis or other avoidable explanatory factors. Additional treatment options are suggested for patients who fail to achieve satisfactory symptom alleviation with first-line antispasmodic therapy.

In view of the prevalence of self-care among patients experiencing FACP, we propose how this algorithm might be adapted for pharmacists and patients to help support improved self-management of FACP, raise awareness of “red flag” signs/symptoms that should referral to or consultation with an appropriate physician, and highlight alternative approaches that patients might not consider intuitively (Figs. 3, 4). These algorithms could form the basis of the pharmacist and patient education needed to facilitate the recognition and effective self-treatment of FACP.

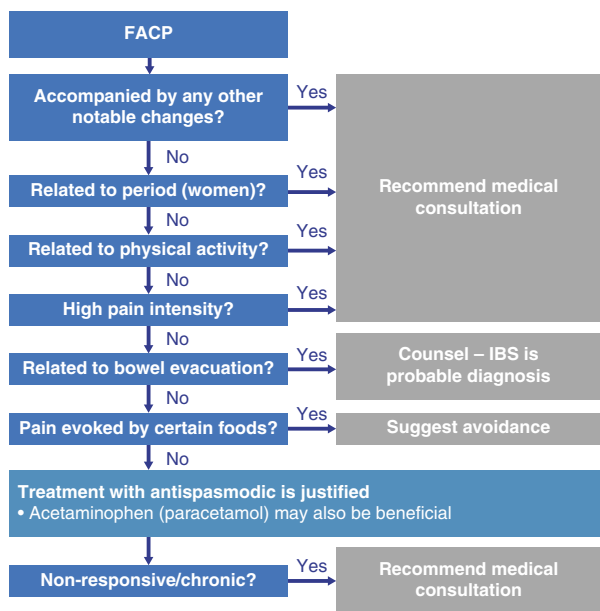


FIGURE 3. Algorithm for the symptomatic management of FACP, designed for use by pharmacists. FACP refers to the sudden occurrence of mild-to-moderate, undulating, and recurring cramping pain in any part of the abdomen, lasting for seconds to minutes or up to a few hours, in the absence of any “red flag” signs/symptoms of structural organic disease or any strong association with defecation (which might indicate IBS), and typically not significantly interfering with daily activities. FACP indicates functional abdominal cramping pain; IBS, irritable bowel syndrome.

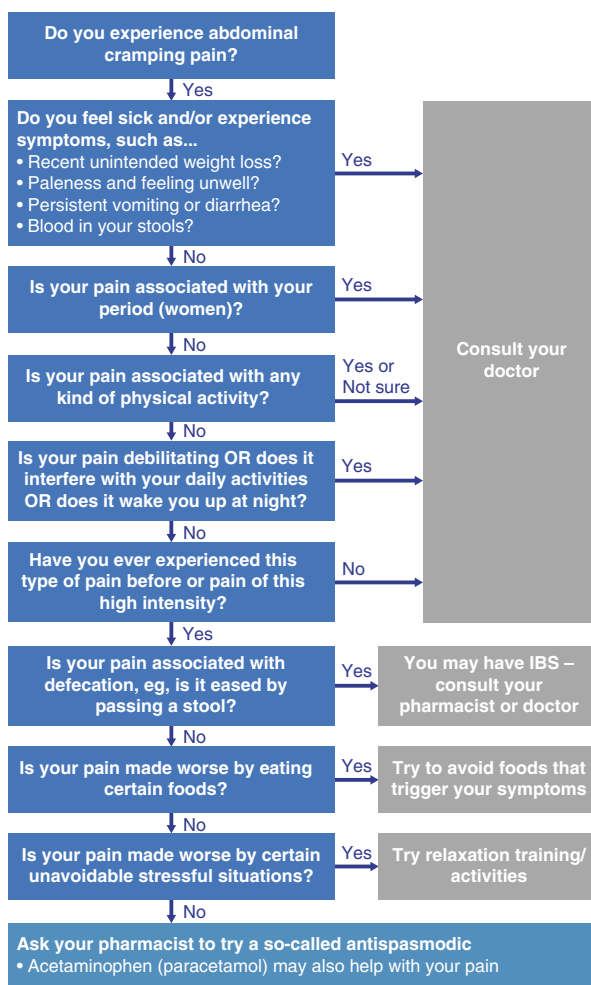


FIGURE 4. Algorithm for the symptomatic management of FACP, designed to aid patient self-care. FACP indicates functional abdominal cramping pain; IBS, irritable bowel syndrome.

CONCLUSIONS

FACP is a common presentation, occurring either alone or in association with FGIDs, which can impact on the quality of life of sufferers and place a burden on health care resources. Here, we have proposed a definition of FACP, which we believe has substantial potential utility to inform the diagnosis and management of this common and under-recognized condition. Although probably falling within the continuum of the IBS spectrum, but without a strong, direct association with bowel evacuation, studies to further investigate the presentation, course, and pathophysiology of FACP are needed. Recommendations for the diagnosis and management of FACP are provided (albeit based largely on the existing literature for FGIDs because of a lack of specific data on FACP), with a focus on primary care management. Algorithms for use by PCPs/GPs, pharmacists, and patients are also presented to aid the recognition and symptomatic management of FACP in the primary care and pharmacy settings.

In many countries across the world, the clinical diagnosis and management of patients with FACP is typically undertaken in primary care practice. Self-care, with the assistance of pharmacists as needed may, however, also serve as a successful handling approach for patients whose condition can be managed adequately with over-the-counter pharmaceuticals and/or non-pharmacologic approaches. This approach is especially relevant in settings where access to health care may be limited.

REFERENCES

1. Schmulson MJ, Drossman DA. What is new in Rome IV. *J Neurogastroenterol Motil.* 2017;23:151–163.
2. Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features and Rome IV. *Gastroenterology.* 2016;150:1262–1279.e2.
3. Vasant DH, Paine PA, Black CJ, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. *Gut.* 2021;70:1214–1240.
4. Layer P, Andresen V, Allescher H, et al. Update S3-leitlinie reizdarmsyndrom: definition, pathophysiologie, diagnostik und therapie des reizdarmsyndroms der Deutschen Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS) und der Deutschen Gesellschaft für Neurogastroenterologie und Motilität (DGNM). June 2021. Available at: https://www.dgvs.de/wp-content/uploads/2021/07/Leitlinie-RDS_20210629_final.pdf. Accessed September 8, 2022.
5. NICE National Institute for Health and Care Excellence. Irritable bowel syndrome in adults: diagnosis and management. Clinical guideline [CG61]. Available at: <https://www.nice.org.uk/guidance/cg61>. Accessed September 8, 2022.
6. Asociación Española de Gastroenterología (AEG). Documento de actualización de la Guía de Práctica Clínica sobre el síndrome del intestino irritable. 2017. Available at: <https://s3-eu-west-1.amazonaws.com/ueg-elearning/ueg-guidelines/other-pdfs/79.pdf>. Accessed September 8, 2022.
7. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. *Gastroenterology.* 2016;150:1393–1407.e5.
8. Mearin F, Ciriza C, Minguez M, et al. Clinical practice guidelines: Irritable bowel syndrome with constipation and functional constipation in adults: concept, diagnosis, and healthcare continuity (part 1 of 2). *Aten Primaria.* 2017a;49:42–55.
9. Mearin F, Ciriza C, Minguez M, et al. Irritable bowel syndrome with constipation and functional constipation in adults: treatment (part 2 of 2). *Aten Primaria.* 2017b;49:177–194.

10. Carmona-Sánchez R, Icaza-Chávez ME, Bielsa-Fernández MV, et al. The Mexican consensus on irritable bowel syndrome. *Rev Gastroenterol Mex.* 2016;81:149–167.
11. Quigley EM, Fried M, Gwee KA, et al. World Gastroenterology Organisation Global Guidelines Irritable Bowel Syndrome: a global perspective update September 2015. *J Clin Gastroenterol.* 2016;50:704–713.
12. Lacy BE, Pimentel M, Brenner DM, et al. ACG Clinical Guideline: management of irritable bowel syndrome. *Am J Gastroenterol.* 2021;116:17–44.
13. Stanghellini V, Chan FK, Hasler WL, et al. Gastroduodenal disorders. *Gastroenterology.* 2016;150:1380–1392.
14. Cotton PB, Elta GH, Carter CR, et al. Rome IV. Gallbladder and sphincter of Oddi disorders. *Gastroenterology.* 2016;150:1420–1429.e2.
15. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. *Gastroenterology.* 2021;160:99–114.e3.
16. Aziz I, Palsson OS, Törnblom H, et al. The prevalence and impact of overlapping Rome IV-diagnosed functional gastrointestinal disorders on somatization, quality of life, and healthcare utilization: a cross-sectional general population study in three countries. *Am J Gastroenterol.* 2018;113:86–96.
17. Shivaji UN, Ford AC. Prevalence of functional gastrointestinal disorders among consecutive new patient referrals to a gastroenterology clinic. *Frontline Gastroenterol.* 2014;5:266–271.
18. Chuah KH, Beh KH, Mahamad Rappek NA, et al. The epidemiology and quality of life of functional gastrointestinal disorders according to Rome III vs Rome IV criteria: a cross-sectional study in primary care. *J Dig Dis.* 2021;22:159–166.
19. Quigley EM, Locke GR, Müller-Lissner S, et al. Prevalence and management of abdominal cramping and pain: a multinational survey. *Aliment Pharmacol Ther.* 2006;24:411–419.
20. Sandler RS, Stewart WF, Liberman JN, et al. Abdominal pain, bloating, and diarrhea in the United States: prevalence and impact. *Dig Dis Sci.* 2000;45:1166–1171.
21. Enck P, Koehler U, Weigmann H, et al. Abdominal pain, cramping or discomfort impairs quality of life in women: an internet-based observational pilot study focussing on impact of treatment. *Z Gastroenterol.* 2017;55:260–266.
22. American Gastroenterological Association (AGA). IBS in America survey summary findings. December 2015. Available at: <https://www.multivu.com/players/English/7634451-aga-ibs-in-america-survey/docs/survey-findings-pdf-635473172.pdf>. Accessed September 8, 2022.
23. Viniol A, Keunecke C, Biroga T, et al. Studies of the symptom abdominal pain—a systematic review and meta-analysis. *Fam Pract.* 2014;31:517–529.
24. Keefer L, Drossman DA, Guthrie E, et al. Centrally mediated disorders of gastrointestinal pain. *Gastroenterology.* 2016;150:1408–1419.
25. Black CJ, Drossman DA, Talley NJ, et al. Functional gastrointestinal disorders: advances in understanding and management. *Lancet.* 2020;396:1664–1674.
26. Barbara G, Feinle-Bisset C, Ghoshal UC, et al. The intestinal microenvironment and functional gastrointestinal disorders. *Gastroenterology.* 2016;150:1305–1318.
27. Ford AC, Sperber AD, Corsetti M, et al. Irritable bowel syndrome. *Lancet.* 2020;396:1675–1688.
28. Pellissier S, Bonaz B. The place of stress and emotions in the irritable bowel syndrome. *Vitam Horm.* 2017;103:327–354.
29. Bhatia V, Tandon RK. Stress and the gastrointestinal tract. *J Gastroenterol Hepatol.* 2005;20:332–339.
30. Chang L. The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. *Gastroenterology.* 2011;140:761–765.
31. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol.* 2016;1:133–146.
32. Mönnikes H, Tebbe JJ, Hildebrandt M, et al. Role of stress in functional gastrointestinal disorders. Evidence for stress-induced

- alterations in gastrointestinal motility and sensitivity. *Dig Dis*. 2001;19:201–211.
33. Tache Y, Larauche M, Yuan PQ, et al. Brain and gut CRF signaling: biological actions and role in the gastrointestinal tract. *Curr Mol Pharmacol*. 2018;11:51–71.
 34. Taché Y, Kiank C, Stengel A. A role for corticotropin-releasing factor in functional gastrointestinal disorders. *Curr Gastroenterol Rep*. 2009;11:270–277.
 35. Moayyedi P, Mearin F, Azpiroz F, et al. Irritable bowel syndrome diagnosis and management: a simplified algorithm for clinical practice. *United European Gastroenterol J*. 2017;5:773–788.
 36. Aziz I, Simrén M. The overlap between irritable bowel syndrome and organic gastrointestinal diseases. *Lancet Gastroenterol Hepatol*. 2021;6:139–148.
 37. Stemboroski L, Schey R. Treating chronic abdominal pain in patients with chronic abdominal pain and/or irritable bowel syndrome. *Gastroenterol Clin North Am*. 2020;49:607–621.
 38. Hunt R, Quigley E, Abbas Z, et al. Coping with common gastrointestinal symptoms in the community: a global perspective on heartburn, constipation, bloating, and abdominal pain/discomfort May 2013. *J Clin Gastroenterol*. 2014;48:567–578.
 39. Maconi G, Hausken T, Dietrich CF, et al. Gastrointestinal ultrasound in functional disorders of the gastrointestinal tract—EFSUMB consensus statement. *Ultrasound Int Open*. 2021;7:E14–E24.
 40. Mueller-Lissner S, Tytgat GN, Paulo LG, et al. Placebo- and paracetamol-controlled study on the efficacy and tolerability of hyoscine butylbromide in the treatment of patients with recurrent crampy abdominal pain. *Aliment Pharmacol Ther*. 2006;23:1741–1748.
 41. Lacy BE, Wang F, Bhowal S, et al. On-demand hyoscine butylbromide for the treatment of self-reported functional cramping abdominal pain. *Scand J Gastroenterol*. 2013;48:926–935.
 42. Mueller-Lissner S, Quigley EM, Helfrich I, et al. Drug treatment of chronic-intermittent abdominal cramping and pain: a multi-national survey on usage and attitudes. *Aliment Pharmacol Ther*. 2010;32:472–477.
 43. Ford AC, Talley NJ, Spiegel BMR, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ*. 2008;337:a2313.
 44. Ruepert L, Quartero AO, de Wit NJ, et al. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*. 2011;8:CD003460.
 45. Martínez-Vázquez MA, Vázquez-Elizondo G, González-González JA, et al. Effect of antispasmodic agents, alone or in combination, in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *Rev Gastroenterol Mex*. 2012;77:82–90.
 46. Brenner DM, Lacy BE. Antispasmodics for chronic abdominal pain: analysis of North American treatment options. *Am J Gastroenterol*. 2021;116:1587–1600.
 47. Khanna R, MacDonald JK, Levesque BG. Peppermint oil for the treatment of irritable bowel syndrome: a systematic review and meta-analysis. *J Clin Gastroenterol*. 2014;48:505–512.
 48. Alammam N, Wang L, Saberi B, et al. The impact of peppermint oil on the irritable bowel syndrome: a meta-analysis of the pooled clinical data. *BMC Complement Altern Med*. 2019;19:21.
 49. Ge Z, Yuan Y, Zhang S, et al. Efficacy and tolerability of two oral hyoscine butylbromide formulations in Chinese patients with recurrent episodes of self-reported gastric or intestinal spasm-like pain. *Int J Clin Pharmacol Ther*. 2011;49:198–205.
 50. Tytgat GN. Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain. *Drugs*. 2007;67:1343–1357.
 51. Hills JM, Aaronson PI. The mechanism of action of peppermint oil on gastrointestinal smooth muscle. An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig. *Gastroenterology*. 1991;101:55–65.
 52. European Medicines Agency. Committee on Herbal Medicinal Products. European Union herbal monograph on *Mentha x piperita* L., aetheroleum. Final – Revision 1. 15 January 2020. EMA/HMPC/522410/2013. Available at: https://www.ema.europa.eu/en/documents/herbal-monograph/european-union-herbal-monograph-mentha-x-piperita-l-aetheroleum-revision-1_en.pdf. Accessed September 8, 2022.
 53. Madisch A, Holtmann G, Plein K, et al. Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. *Aliment Pharmacol Ther*. 2004;19:271–279.
 54. Ottillinger B, Storr M, Malfertheiner P, et al. STW 5 (Iberogast®)—a safe and effective standard in the treatment of functional gastrointestinal disorders. *Wien Med Wochenschr*. 2013;163:65–72.
 55. Grundmann O, Yoon SL, Mason S, et al. Gastrointestinal symptom improvement from fiber, STW 5, peppermint oil, and probiotics use—results from an online survey. *Complement Ther Med*. 2018;41:225–230.
 56. Sáez-González E, Conde I, Díaz-Jaime FC, et al. Iberogast-induced severe hepatotoxicity leading to liver transplantation. *Am J Gastroenterol*. 2016;111:1364–1365.
 57. Gerhardt F, Benesic A, Tillmann HL, et al. Iberogast-induced acute liver failure-reexposure and in vitro assay support causality. *Am J Gastroenterol*. 2019;114:1358–1359.
 58. Reuters.com. Bayer adds label warning after death linked to stomach relief drops. September 12, 2018. Available at: <https://www.reuters.com/article/us-bayer-iberogast-idUSKCN1LS1LA>. Accessed September 8, 2022.
 59. del Valle-Laisequilla CF, Flores-Murrieta FJ, Granados-Soto V, et al. Ketorolac tromethamine improves the analgesic effect of hyoscine butylbromide in patients with intense cramping pain from gastrointestinal or genitourinary origin. *Arzneimittelforschung*. 2012;62:603–608.
 60. Sostres C, Gargallo CJ, Lanás A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Res Ther*. 2013;15:S3.
 61. Juurlink DN, Dhalla IA. Dependence and addition during chronic opioid therapy. *J Med Toxicol*. 2012;8:393–399.
 62. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nat Rev Dis Primers*. 2016;2:16014.
 63. Ford AC, Lacy BE, Harris LA, et al. Effect of antidepressants and psychological therapies in irritable bowel syndrome: an updated systematic review and meta-analysis. *Am J Gastroenterol*. 2019;114:21–39.
 64. Saito YA, Almazar AE, Tilkes KE, et al. Randomised clinical trial: pregabalin vs placebo for irritable bowel syndrome. *Aliment Pharmacol Ther*. 2019;49:389–397.
 65. Ford AC, Moayyedi P, Lacy BE, et al. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. *Am J Gastroenterol*. 2014;109:S2–S26.
 66. Chapman RW, Stanghellini V, Geraint M, et al. Randomized clinical trial: macrogol/PEG 3350 plus electrolytes for treatment of patients with constipation associated with irritable bowel syndrome. *Am J Gastroenterol*. 2013;108:1508–1515.
 67. Efskind PS, Bernklev T, Vatn MH. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. *Scand J Gastroenterol*. 1996;31:463–468.