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Functional Abdominal Pain

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Abstract Functional abdominal pain syndrome (FAPS) is a relatively less common functional gastrointestinal (GI) disorder defined by the presence of constant or frequently recurring abdominal pain that is not associated with eating, change in bowel habits, or menstrual periods (Drossman Gastroenterology 130:1377–1390, 2006), which points to a more centrally targeted (spinal and supraspinal) basis for the symptoms. However, FAPS is frequently confused with irritable bowel syndrome and other functional GI disorders in which abdominal pain is associated with eating and bowel movements. FAPS also differs from chronic abdominal pain associated with entities such as chronic pancreatitis or chronic inflammatory bowel disease, in which the pain is associated with peripherally acting factors (eg, gut inflammation or injury). Given the central contribution to the pain experience, concomitant psychosocial disturbances are common and strongly influence the clinical expression of FAPS, which also by definition is associated with loss of daily functioning. These factors make it critical to use a biopsychosocial construct to understand and manage FAPS, because gut-directed treatments are usually not successful in managing this condition.

Keywords Functional gastrointestinal disorders · Irritable bowel syndrome · Chronic abdominal pain · Functional abdominal pain syndrome · Biopsychosocial · Psychotropic agents · Psychological treatments · Complementary therapy

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Introduction

Although no clear definition exists, abdominal pain persisting for 6 months or longer is generally classified as chronic. Chronic abdominal pain may begin with disorders such as chronic pancreatitis, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and other functional gastrointestinal (GI) disorders in which there is a contribution from structural damage to end organs (including visceral neural sensitization); therefore, treatments targeting peripheral organs can be helpful. However, as these disorders persist or progress, the pain pattern becomes more constant, affects daily functioning, and becomes less responsive to peripherally acting treatments. At other times, chronic debilitating abdominal pain can occur in the absence of any known or identifiable end-organ damage. Both situations can fulfill diagnostic criteria for functional abdominal pain syndrome (FAPS), which is characterized by the presence of continuous or frequently recurrent abdominal pain associated with loss of daily functioning. As with other functional GI disorders, no structural or biochemical abnormalities can be found to explain the symptoms. The Rome III classification has symptom-based criteria to diagnose FAPS (Table 1) [2].

Table 1 Rome III criteria diagnostic criteria for functional abdominal pain

All criteria must be fulfilled for the past 3 months with symptom onset at least 6 months prior to diagnosis:

1. Continuous or nearly continuous abdominal pain.
2. No or only occasional relation of pain with physiological events (eg, eating, defecation, menses)
3. Some loss of daily functioning
4. The pain is not feigned (eg, malingering)
5. Insufficient symptoms to meet criteria for another functional gastrointestinal disorder that would explain the pain

Data from Drossman [1]

Epidemiology

FAPS was assigned a new category separate from functional bowel disorders in the Rome III classification system. The epidemiology of FAPS is incompletely known because of previous confusion with more common functional GI disorders (eg, IBS and functional dyspepsia) during diagnosis and because of a dearth of studies on this entity. However, FAPS is a less common functional disorder than either IBS or functional dyspepsia. Reported prevalence figures in North America range from 0.5% to 2% and do not differ from those reported in other countries [3]. It is more common in women (female to male ratio, 3:2), with prevalence peaking in the fourth decade of life. Patients with FAPS have high work absenteeism and health care use, and impose costs that are higher than other functional GI disorders [4]. In addition, patients with chronic abdominal pain syndromes (including IBS) tend to have increased risk of suicidal behavior, an association that is independent of their psychiatric comorbidities [5].

Clinical Features

History

A carefully taken history should include chronology of pain events, relationship of pain to a surgery or traumatic life events (abuse, undesired pregnancy, personal losses), and reasons behind current health-care seeking for a chronic problem. These factors help the physician to develop a multidimensional understanding of the patient's illness and current presentation. Several symptom-related behaviors are often seen in patients with FAPS. These patients usually complain of a generalized pain over a large anatomical area. The pain intensity can vary frequently and the patient's report of pain is often expressed in emotional terms (eg, "agonizing" or "sickening") [6, 7]. Patients may urgently report intense symptoms without a clear precipitating event. Patients with FAPS tend to minimize the role of psychosocial factors, request repeated diagnostic studies, and seek complete cure ("find and fix"). Health-care seeking is frequent, and they may see different providers for the same symptoms, seek referral to tertiary care centers, and have multiple emergency department visits. Such patients often tend to take minimal personal responsibility in their health care, and often place unrealistic expectations on the clinician [7]. A request for narcotic analgesics is also common. The abdominal pain may overlap with other functional pain conditions (eg, fibromyalgia). A history of physical or sexual abuse is common in patients with FAPS, as high as 40% in those attending gastroenterology clinics [8]. Other psychological factors may include major depression or anxiety disorder, somatoform disorder, and maladaptive coping [9]. The physician needs to pay attention to psychosocial elements, which can be crucial in revealing disease and illness patterns related to FAPS. Some key elements of psychosocial assessment are mentioned in Table 2.

Physical Examination

An observation of pain behavior is also important during physical exam because patients with FAPS are likely to have absence of autonomic arousal and exhibit the "closed eyes sign" (ie, eyes closed during examination, as opposed to eyes open in fearful anticipation—commonly seen in patients with an acute abdomen) [10]. The patient's reports of pain intensity may be distracted during examination (eg, "stethoscope sign"). The presence of many abdominal scars might prompt investigation of the nature of the symptoms preceding surgery, exposing nonspecific symptoms prompting the surgery or exploratory investigations. Abdominal wall pain should be excluded using the Carnett's test [11]. When present, abdominal wall pain increases with raising the head and contracting the rectus abdominis muscle, whereas visceral pain decreases. However, FAPS can also produce increased pain during abdominal wall contraction, probably from central sensitization with viscerosomatic referral.

Investigations

As with other functional GI disorders, diagnostic tests to exclude organic disease should not be performed routinely

Table 2 Psychosocial assessment in evaluation of functional abdominal pain syndrome

1. Life history of illness
- Evaluate if acute vs chronic and presence of other chronic pain conditions
2. Reasons for seeking care now
- Associated concerns, triggers, worsening functional and/or psychosocial status
3. Life history of traumatic events
- Access history of abuse, personal, or family losses
4. Patient's understanding of illness
- Recognizing mind-body interactions vs looking for an organic cause
5. Impact of pain on activities and quality of life
- Planning diagnostic and treatment decisions
6. Associated psychiatric diagnosis
- Diagnosing and treating Axis I and Axis II psychiatric disorders
7. Role of family and culture
- Recognizing dysfunctional family interactions and cultural belief systems
8. Associated psychosocial impairment and available resources
- Helping to seek social networks and avoiding maladaptive coping (catastrophizing)

in the absence of alarm symptoms (eg, unexplained weight loss, abdominal mass, bloody bowel movements, anorexia) [12]. If the physical examination is negative, no further diagnostic studies are indicated. Further testing only reinforces the concept that another diagnosis is being missed and can increase the patient's behavior to seek additional tests for their condition. It also may lead the patient to lose confidence in the physician's competency, which can impair the therapeutic alliance. Several prospective and retrospective studies have suggested that diagnostic failures occur very rarely [13•].

Differential Diagnosis

Various other functional GI disorders should first be considered when making a diagnosis of FAPS. If the pain is associated with alterations in bowel movements (frequent, loose stools and/or harder, infrequent stools), IBS should be considered. If the pain is in the epigastrium or right upper quadrant, is severe, and recurs at different intervals (not daily), a diagnosis of functional gall bladder disease or sphincter of Oddi dysfunction should be entertained. If the pain is in epigastrium and does not fulfill criteria for functional gall bladder disease, functional dyspepsia should be considered [14].

An important differential to consider is chronic mesenteric ischemia, which is characterized by pain exacerbated by eating and pain out of proportion to physical findings. This finding becomes more important when considering new onset of abdominal pain in an older patient with history of atherosclerotic vascular disease and with associated nausea, vomiting, or weight loss.

FAPS also needs to be differentiated from feigned pain or malingering, in which false or exaggerated symptoms are produced intentionally for a secondary gain (avoiding work, seeking disability or malpractice compensation, or obtaining narcotic pain medications). A similar differential would be a factitious disorder, in which illness is feigned but external incentives are not the motivation for symptom production [14].

Pathophysiology

Unlike acute pain, chronic pain has a multidimensional construct with sensory, emotional, and cognitive contributions to the pain experience, which are related to abnormalities in neurophysiological functioning at peripheral, spinal, and supraspinal levels [15]. In chronic pain, peripheral contribution in the form of increased afferent visceral stimuli does not play as great a role as central nervous system (CNS) upregulation of incoming visceral afferent signals, which can bring even regulatory (normally subliminal) signals to a point of conscious awareness and distress. In a recent study, rectal thresholds and compliance were significantly reduced in IBS but not in FAPS [16]. The pathophysiology of chronic pain can be best understood in terms of the following mechanisms: 1) ascending visceral pain transmission; 2) peripheral amplification of visceral afferent signals; 3) descending modulation of pain; and 4) central amplification and the role of psychological distress.

Ascending Visceral Pain Transmission

Figure 1a depicts the principal visceral (colonic) afferent pathways projecting to the spinal cord, and then ascending to the thalamus and midbrain. These are the spinothalamic, spinoreticular, and spinomesencephalic tracts. The spinothalamic tract terminates in the medial and posterior thalamus from where thalamocortical fibers project to the

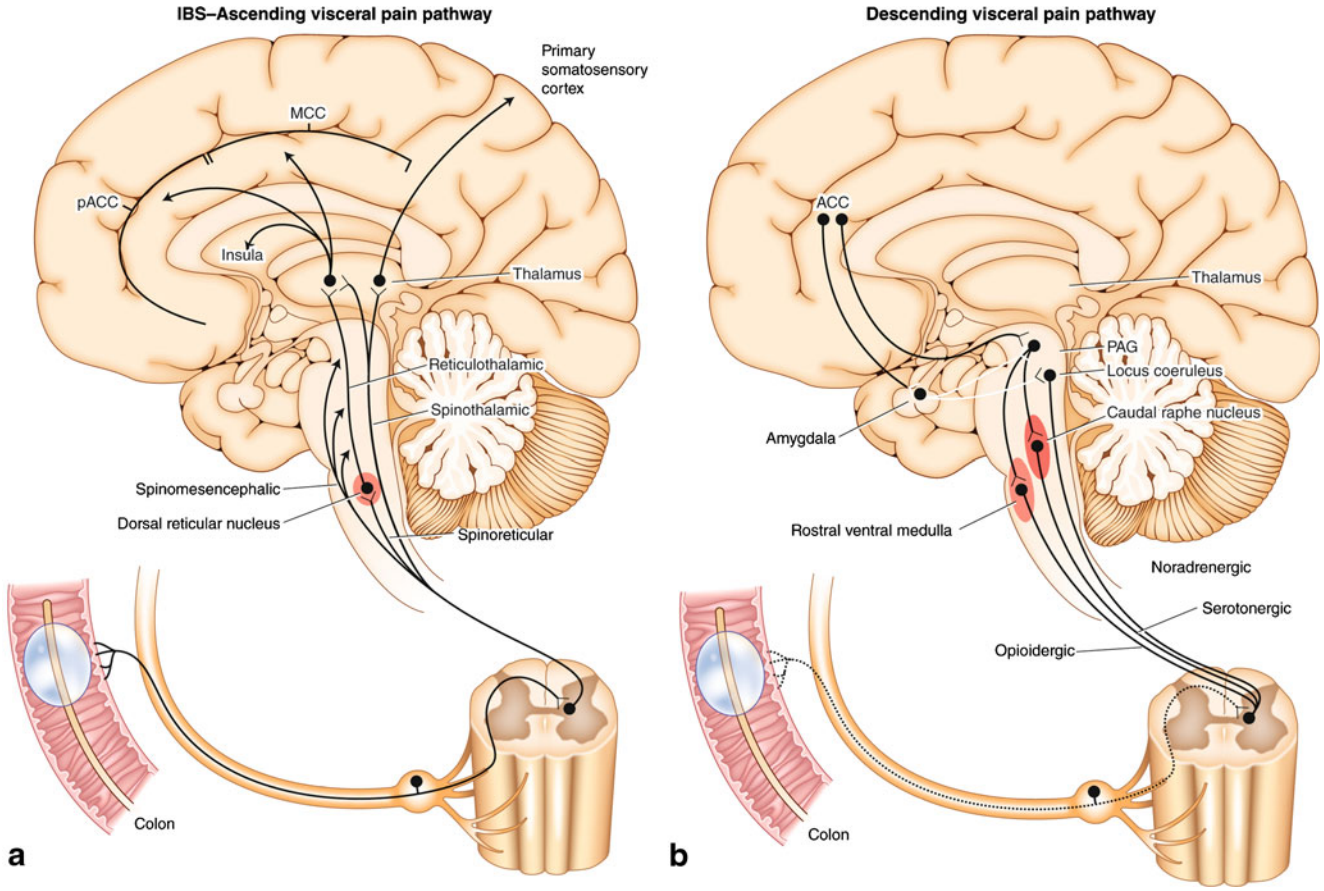

Fig. 1 **a** Neuroanatomic pathways mediating visceral pain sensation. **b** Descending inhibitory pathway for visceral pain. ACC—anterior cingulate cortex; IBS—irritable bowel syndrome; MCC—midcingulate cortex; pACC—perigenual anterior cingulate cortex; PAG—periaqueductal gray

primary somatosensory cortex. This pathway regulates sensory discrimination and localization of visceral and somatic stimuli. The spinoreticular tract conducts sensory information from the spinal cord to the reticular formation in the brainstem, the latter associated with the reflexive, affective, and motivational properties of noxious stimulation. The reticulothalamic tract projects from the dorsal and caudal medullary reticular formation (dorsal reticular nucleus) to the medial thalamus. Thalamocortical projections from the medial thalamus transmit sensory input to different areas of the brain, such as the cingulate cortex and insula, which are involved with the processing of noxious visceral and somatic information. The brain regions innervated by these pathways that are activated in response to painful colorectal stimuli include the thalamus, anterior insula, amygdala, and anterior cingulate cortex (ACC). The ACC is comprised of two components, perigenual ACC and midcingulate cortex, with the former involved in affect and the latter in behavioral response modification. This multicomponent integration of nociceptive information explains the variability in the experience and reporting of pain [7]. A recent observation of interest was the absence of hypertension-related hypoalgesia in adults who had a history of chronic visceral pain in childhood. This was found to persist whether or not they had FAPS as adults, suggesting that chronic visceral pain as a child can cause long-lasting dysfunction in overlapping systems modifying pain and blood pressure that continues even after childhood FAPS resolves [17].

Peripheral Amplification of Visceral Afferent Signals

Although peripheral amplification from visceral inflammation and injury contributes less to the genesis of chronic pain, it can also occur. This circumstance relates to increased peripheral receptor sensitivity or increased excitability of spinal or supraspinal pain regulatory systems [18]. Frequent or recurrent pain episodes or painful procedures can later become generalized to a chronic and persistent symptom presentation, as shown with persistent abdominal (eg, IBS) pain developing after gynecological operations [19•, 20]. Again, psychological predisposition (eg, anxieties about the outcome of the procedure or a poor coping style) contributes to the development of the postoperative pain and neuroticism; indeed, one's vulnerability to stress has been associated with perpetuation of pain after cholecys-

tectomy [21]. However, preoperative treatment with local or regional anesthesia or nonsteroidal anti-inflammatory drugs may reduce the severity of postoperative pain [18]. This finding suggests that the CNS response to peripheral injury can be reduced by reduction of afferent input to the spinal cord and CNS prior to sensitization. Therefore, recurrent peripheral injury (eg, repeated abdominal operations in the psychologically predisposed host) might sensitize intestinal receptors, making perception of even baseline afferent activity more painful.

Descending Modulation of Pain

To understand how emotional distress can downregulate incoming visceral signals, it is necessary to readdress the fundamental concept of brain-gut regulation of pain via the gate-control theory and the descending modulation of painful stimuli [22]. Figure 1b shows this central descending inhibitory system, believed to originate in the opioid-rich ACC and possibly also from other cortical regions. It is postulated that activation of this region by peripheral/visceral afferent activity might, in part, serve to downregulate these signals. Descending connections from the ACC and the amygdala to pontomedullary networks, including the periaqueductal gray, rostral ventral medulla, and the raphe nuclei, activate inhibitory pathways via opioidergic, serotoninergic, and noradrenergic systems to the dorsal horn of the spinal cord, which acts like a "gate" to increase or decrease the projection of afferent impulses arising from peripheral nociceptive sites to the CNS [7].

Central Amplification and the Role of Psychological Distress

As noted earlier, although peripheral sensitization might influence the onset and short-term continuation of pain, the CNS is preeminently involved in the predisposition and perpetuation of chronic pain. Comorbid psychiatric diagnosis, major life stress, a history of sexual or physical abuse, poor social support, and maladaptive coping are associated with more severe and chronic abdominal pain and poorer health outcome [23]. Early-life stress in genetically predisposed individuals may lead to a permanently enhanced stress responsiveness, which in turn may result in alterations in stress-induced pain modulation systems. The links between emotional distress and chronic pain might be mediated through impairment in the limbic system's ability to modulate visceral signals. Recent studies suggest that the motivational-affective component of the limbic or medial pain system, specifically the ACC, is dysfunctional in IBS and other chronic painful conditions [24]. In response to a painful stimulus, there is differential activation of the perigenual ACC, an area rich in opioids associated with emotional encoding, and the posterior ACC, also called the rostral midcingulate cortex. The latter is an area associated with unpleasantness, fear (along with the amygdala), and motor pain behavior. When using PET and functional magnetic resonance imaging (fMRI) to evaluate the ACC response to rectal distention or the anticipation of distention, IBS patients preferentially activate the midcingulate cortex and have less activation of the perigenual ACC relative to control subjects [25, 26]. It is possible that, in IBS, activation of the descending inhibitory pain pathway originating in the opioid-rich perigenual ACC is supplanted by activation of the midcingulate cortex, the area associated with fear and unpleasantness. In addition, there is a strong correlation between life stress and maladaptive coping with ACC activation. Notably, antidepressant and psychological treatments are associated with a return of the dysfunctional ACC reactivity to a more normal state [27, 28]. This finding also occurs in patients with depression [29]. These data suggest that emotional disturbances might aggravate the dysfunctional central pain regulatory pathways seen in chronic pain.

Treatment

Because there are no well-designed clinical trials specifically for FAPS, treatment recommendations for patients with FAPS are empirical and often extrapolated from observations in IBS [30••, 31••]. A key issue in management of FAPS is establishing an effective patient-physician relationship. Factors that contribute to an effective patient-physician relationship include empathy toward the patient, patient education, validation of the illness, reassurance, treatment negotiation, and establishment of reasonable limits in time and effort (Table 3). Treatments are mostly targeted at neuromodulation of the CNS (spinal and supraspinal). These include psychotropic agents, behavioral approaches, and complementary treatment strategies. Before implementing specific forms of therapy, the following general aspects of care should be considered: setting of treatment goals, helping the patient take responsibility, basing treatment on symptom severity and the degree of disability, and referring to a mental health care professional, or, if available, to a multidisciplinary pain treatment center in selected patients, particularly those with refractory symptoms. Also, if malingering is suspected, referral to a mental health professional should be made. Unfortunately, important aspects of managing FAPS, such as establishing a confident diagnosis and creating an effective patient-physician relationship, are often overlooked. This situation leads to patient and physician dissatisfaction and perpetuates a vicious cycle of additional health-care seeking, investigations, and procedures.

Table 3 Treatment approach for functional abdominal pain syndrome

Establishing an effective patient-physician relationship
1. Empathize
2. Educate
3. Validate
4. Reassure
5. Negotiate the treatment
6. Set reasonable limits
The treatment plan
1. Set reasonable treatment goals
2. Help the patient take responsibility
3. Base treatment on symptom severity and degree of disability
4. Medications
5. Mental health referral
6. Specific psychological treatments
7. Multidisciplinary pain treatment center referral

Pharmacological Therapies

The rationale for using antidepressants in low doses relates to reducing afferent signals from the gut, or to modulating bowel symptoms. Higher dosages are used when psychiatric comorbidities are present that can aggravate the pain. Brain imaging studies indicate that antidepressants may play a role in downregulating afferent visceral signals [28].

The emerging concept of neuroplasticity with loss of cortical neurons in psychiatric trauma, and neurogenesis (ie, regrowth of neurons) with clinical treatment, provides the rationalization for the use of central treatments [32]. With post-traumatic stress disorders (PTSD) neuronal death occurs in key areas, such as dentate ganglion of the hippocampus [33], and recent fMRI studies show reduced neuron density in other areas of the brain, including cortical regions involved in emotional and pain regulation [34] in patients with chronic pain including IBS [35]. Notably, recent data suggest that antidepressant (and possibly psychological) treatments may restore lost neurons. Levels of brain-derived neurotrophic factor, a precursor of neurogenesis, increase with antidepressant treatment and correlate with longer periods of treatment and with the degree of recovery from depression [36]. Furthermore, the longer patients are treated with antidepressants, the lower is the frequency of relapse or recurrence of the depression [37]. These findings provide insight into how the CNS functions in response to emotional trauma and its associations with chronic visceral and somatic pain, and their treatments. Similar to hippocampal cell loss in PTSD, cortical density is reduced in the anterior cingulate and prefrontal cortex and thalamus—regions that interface between emotion and pain regulation—in patients with severe depression or chronic pain [34]. These new data on the effect on neuronal growth regulation in key areas of the central pain matrix provide new and important opportunities for research and patient care using antidepressants for treating FAPS.

The tricyclic antidepressants (eg, desipramine, nortriptyline, and amitriptyline) or the new serotonin norepinephrine reuptake inhibitors (SNRIs—duloxetine, venlafaxine, and desvenlafaxine) are of particular value in treating chronic pain syndromes owing to their combined noradrenergic and serotonergic effects [38]. These agents have generally been more successful than selective serotonin reuptake inhibitors, which are more useful for treating associated psychiatric comorbidities (eg, anxiety, depression, and obsessional symptoms) and in targeting global symptoms and coping rather than pain. Low doses of SNRIs (desipramine, 25–75 mg, at night or duloxetine, 30 mg, in the daytime) can be initiated and increased to full dosages if needed, particularly when depression is also present, and continued for 6 to 12 months, or longer if needed. Narcotic analgesics should be weaned because of the possibility of developing narcotic bowel syndrome [39•].

Augmentation strategies can be useful for patients with refractory pain symptoms that are not responsive to single antidepressants or other treatments. Most gastroenterologists are not familiar with this method of treatment; however, because such strategies are commonly used in psychiatry, a psychiatric consultation to plan treatment is recommended. Thus, patients who are refractory to usual dosages of antidepressants or who are experiencing side effects should be offered additional psychotropic medication to augment the clinical effect, because these medications act on different neuroreceptor. Recently, we used a low-dose atypical antipsychotic agent (eg, quetiapine, 25–100 mg) that acts on dopamine receptors for augmenting the antidepressant treatment in our patients with chronic pain syndromes [40]. This class of agents has antianxiety and sleep benefits, and may also have independent analgesic effects. Preliminary data from our clinic shows that about 50% of patients with chronic and severe FAPS who previously failed on antidepressants and who are prescribed quetiapine with an antidepressant stay on the antidepressant, and most who do so achieve some benefit.

Gabapentin and pregabalin are increasingly being prescribed for chronic neuropathic pain conditions, including peripheral neuropathies, and more recently for fibromyalgia. Their benefit for visceral or central pain syndromes is not established, although a few case reports have suggested benefit for visceral pain. These remain potential options for the treatment of FAPS.

In summary, anecdotal reports and observed benefits of some compounds in other chronic pain conditions provide the basis for pharmacological treatment of FAPS, pending scientific evidence from controlled clinical trials.

Psychological Therapy

No psychological treatment study has specifically targeted adult FAPS. However, studies in other painful functional GI disorders and nongastrointestinal pain conditions suggest that psychological treatments would be beneficial [30••]. Interventions of potential benefit include cognitive behavioral therapy, dynamic or interpersonal psychotherapy, hypnotherapy, and stress management. Referral to pain treatment centers for multidisciplinary treatment programs may be the most efficient method of treating disability from refractory chronic pain. Based on the literature in IBS, these treatments may not improve the pain as much as the patient's adaptation to the pain and enhancement of coping strategies ("the pain is still there but it doesn't bother me as much"). Furthermore, these treatments can show up to 70% benefit and, importantly, their effects are additive to other medical treatments, the benefit continues after the treatment period ends, no medical side effects have been reported, and treatment may reduce health care costs [41]. Critical to implementing psychological treatment is that the referring physician must help the patient accept the value of these treatments as part of their ongoing plan of care.

Complementary Therapies

Complementary and alternative therapies (eg, spinal manipulation, massage, and acupuncture) are commonly are used by patients with chronic pain disorders, including FAPS; however, data supporting their use are limited. Few reports have described the use of transcutaneous electrical nerve stimulation in patients with FAPS, and results of uncontrolled studies are indeterminate.

Conclusions

Functional abdominal pain is a chronic debilitating condition characterized by the presence of constant or frequently recurring abdominal pain associated with loss of daily function. It can cause significant impairment in quality of life and is frequently seen in the context of psychosocial disturbances such as abuse, anxiety, depression, or personal losses. Management can be extremely challenging and defies the principles of the biomedical model of care. An in-depth understanding of the patient's symptoms, illness behavior, and appropriate treatment is best planned under the realm of the biopsychosocial model of care, which begins with establishment of a strong physician-patient relationship [42]. Peripherally acting treatments often fail because the pain of FAPS seems to be predominantly driven by the central nervous system. Treatment trials are virtually nonexistent, and strategies are extrapolated from the treatment of other painful functional GI disorders (eg, IBS). These involve psychotropic agents, behavioral approaches, and complementary treatment strategies. Alliance with a mental health professional may be beneficial for optimizing these treatments, especially in refractory symptoms and if a factitious disorder or malingering is suspected.

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