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Vol. XXI, Issue 2 June 2013

# Functional Abdominal Pain

Visceral pain is prevalent and is a leading cause of health care utilization worldwide.[1] Unexplained abdominal pain is the sixth most common cause of hospital admission for any cause in women and the tenth most common cause in men.[2] In the United Kingdom, it has been estimated that nonspecific abdominal pain costs the economy in excess of £100 million per annum.[3] Functional abdominal pain (FAP) syndrome, defined according to the Rome III diagnostic criteria (see Table I), is characterized by frequent or continuous abdominal pain associated with some loss of daily activity.[4] Chronic visceral pain, in the absence of an identifiable structural, biochemical, or immunological abnormality, is a central defining feature of many of the functional gastrointestinal (GI) disorders (FGIDs), including the most prevalent example, irritable bowel syndrome (IBS). Thus, it is not surprising that FAP is often erroneously diagnosed as IBS. Nevertheless, the distinction between these two disorders is not purely nomenclatural because there are critical differences in their evaluation and management.

It is likely that FAP represents a relatively uncommon entity, with reported prevalence ranging from 1.7% to 0.5%, with a female preponderance.[5] This issue of *Pain*: *Clinical Updates* examines the pathophysiology, clinical evaluation, and management of FAP.

## Mechanisms of Chronic Pain in Functional Abdominal Pain

The Rome III criteria satisfy the research need for defining homogenous research populations, but they are not based on a fundamental understanding of the pathophysiology of FAP. To date, most of the basic mechanisms proposed to account for symptom genesis in FAP remain largely hypothetical because they are extrapolated from research in other chronic pain syndromes. Given that pain is such a complex and

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variable experience, it is not surprising that a neurophysiological dysfunction, whose sequelae include chronic deleterious pain, may arise at any level of the visceral neuraxis. This dysfunction may be conceptualized as peripheral augmentation of the visceral pain afferent signal, central sensitization around the spinal dorsal horn, alterations in descending modulation, or central amplification. However, before discussing these putative processes, we need to consider our contemporary understanding of

Table I
Rome III Diagnostic Criteria for Functional Abdominal Pain

All the following criteria must be fulfilled, with symptom onset at least 6 months prior to diagnosis:

- Continuous or almost continuous abdominal pain
- No relation to physiological events
- Some loss of daily functioning
- The pain is real and not feigned
- Insufficient symptoms to meet the criteria for another functional gastrointestinal disorder

the transduction of visceral pain in healthy individuals. Given our brief for this article, we have intentionally chosen to limit the complexity of the following section, but it is sufficient to provide the reader with a working understanding of how abnormalities can arise and contribute to the development of FAP. We refer the reader to a recently published relevant review by Knowles and Aziz.[6]

## Normal Visceral Pain Transduction

The application of a noxious stimuli to the GI tract results in the activation of peripheral nerve receptors that are sensitive to chemical, mechanical, or inflammatory stimuli.[6] This signal is then transduced via spinal visceral afferents, synapsing on the dorsal horn of the spinal cord, and is then conducted via the spinothalamic tract (STT), spinoreticular tract, and spinomesencephalic tracts to the brain. The STT terminates in the medial and posterior thalamus and thalamocortical fibers and then projects to the primary (S1) and secondary somatosensory cortices to form the basis of the sensory-discriminative aspect of the pain experience. Unlike somatic sensation, with extensive homuncular representation in S1, visceral sensation representation in S1 is less well localized and somewhat amorphous. The spinoreticular and spinomesencephalic pathways terminate in the medial thalamus, where they synapse with subsequent third-order thalamocortical fibers primarily ascending to the anterior cingulate cortex (ACC) and insula. These areas are salient in encoding the affective-motivational aspects of the noxious stimulus. As well as these ascending pathways, a variety of descending inhibitory pathways play a part in the perception of normal visceral sensation. Of particular note are pathways arising from the opioid-rich ACC, where inhibitory signals are transmitted to the periaqueductal gray either directly or via second-order neurons from the amygdala. Third-order opioidergic, serotoninergic, and second-order noradrenergic neurons have a dynamic interface with dorsal horn neurons where modulation, or gating, of ascending visceral afferent signals may occur.

## Peripheral Augmentation of Visceral Afferent Signaling

Peripheral augmentation of visceral afferent signaling may occur after repeated injury or inflammation. Up to a third of people who develop IBS report that their symptoms began following an episode of acute infection, an epiphenomenon known as

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postinfectious IBS (PI-IBS).[7] In this group, increased numbers of enterochromaffin cells, mast cells, and T-lymphocytes may be observed in the lamina propria in colonic biopsies, suggesting the presence of a low-grade inflammatory infiltrate. This inflammatory infiltrate is postulated to drive increased peripheral receptor sensitivity and enlarged receptive fields, the latter through recruitment and activation of hitherto silent nociceptors. Furthermore, stress, as represented by the presence of recent traumatic life events, and a neurotic personality trait were found to be the best predictors of who might develop PI-IBS. Interestingly, a recent important case control study demonstrated that 15.3% of patients undergoing gynecological surgery, for non-pain-related conditions, developed abdominal pain at 12 months compared with 3.6% of healthy controls who did not undergo surgery.[8] In a similar fashion to the PI-IBS data, psychological variables, such as anxiety, predicted the development of abdominal pain. From this evidence, it is likely that injury or inflammation in a psychologically predisposed individual may lead to the peripheral sensitization of visceral afferents, thus augmenting the ascending volley of nociceptive information to the spinal dorsal horn.

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## Central Sensitization

Increased afferent barrage to the spinal dorsal horn can result in central sensitization via increased presynaptic glutamate secretion, itself leading to the removal of the magnesium ion block of the *N*-methyl-D-aspartate (NMDA) receptor. In association with activation of other key enzymes, the overall consequence is increased responsiveness of the dorsal horn neurons, often outlasting the initiating insult. In addition, surrounding spinal dorsal horn neurons may be recruited, in a process termed heterosynaptic potentiation, thereby enlarging the field of sensitivity from which the original noxious stimulus arose. Sarkar et al.[9] have demonstrated the concept of central sensitization in a reproducible human esophageal model in which hydrochloric acid infused into the healthy distal esophagus was able to induce hyperalgesia in the exposed distal and unexposed proximal esophagus, suggesting that peripheral augmentation as well as central sensitization can occur in the GI tract after gut injury. Similarly, repetitive experimental stimulation of the human sigmoid colon can induce secondary hyperalgesia in the rectum in IBS patients owing to central sensitization.[10] Human pharmacological studies have demonstrated that antagonism of the NMDA receptor prevents

the development of, and can reverse, central sensitization within the esophagus.[11] In a recent study by Walker et al., a subgroup of FAP patients, termed "high pain dysfunctional patients," showed significantly greater thermal wind-up, thus suggesting that at least a subgroup demonstrated pathophysiology consistent with heightened central sensitization.[12]

## Disturbances in Descending Modulation

The central descending modulatory systems, largely residing in the ACC, that control visceral pain dynamically interface with the spinal dorsal horn, facilitating potential gating of afferent signals from the periphery and thereby allowing amplification or curtailment of this signal. It has been proposed that aberrancies in this system account, to a greater or lesser degree, for the pronociceptive state encountered in FAP. A recent study evaluated visceral sensory function in a small sample of FAP patients in comparison to patients with IBS and healthy controls.[13] This study demonstrated that rectal perceptual thresholds were significantly reduced in IBS, but interestingly, not in FAP, suggesting that pain reporting in FAP is less likely to be attributable to visceral hypersensitivity. Descending modulation of pain thus may differ in the two patient groups. There is increasing evidence in FGIDs that cognitive, emotional, autonomic, and spinal reflex pathways orchestrate supraspinal and spinal pain modulation. In particular, studies of endogenous pain modulation in visceral pain conditions have shown abnormal regulation in IBS and functional dyspepsia. A majority of patients with IBS have diminished pain inhibition or even pain facilitation compared with healthy controls. Brain imaging during specific activation of endogenous pain modulation consistently demonstrates a functional modulatory "hub" in healthy individuals in the frontal, limbic, and brainstem regions. Thus, Wilder-Smith has proposed that alterations in modulatory balance may well be a unifying pathophysiological mechanism across many FGIDs as it can be driven by both top-down mechanisms (i.e., central nervous system pathology) and bottom-up influences (i.e., peripheral immune activation or infection).[14] However, further validation is needed in other FGIDs, including FAP. Perhaps, therefore, in future, targeted therapeutic manipulation of these modulatory systems may be possible by both pharmacological and nonpharmacological means.

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## Clinical Evaluation in Functional Abdominal Pain Patients

### Clinical History

A comprehensive history should be taken from the FAP patient that explores the chronology of pain events, particularly in relation to surgery, infection, or traumatic life events. In addition, the pattern or distribution of pain may be widespread, and abdominal pain may be just one of several types of pain complained about, thus raising the possibility of a concomitant somatization disorder. The intensity of abdominal pain seldom varies, with maximal pain being experienced for the majority of the time.[5] In addition, the patient's behavioral traits and belief systems may be useful in suggesting a functional disorder within an initial differential diagnosis. For instance, there may be a marked reluctance to consider the contribution of psychosocial factors to their symptoms and a reliance on escalating invasive investigations to discover an organic cause for the symptoms.

### Clinical/Physical Examination and Investigation

By definition, the clinical examination in a patient with FAP must fail to discover any significant abnormality. It is worth looking for abdominal scars relating to previous surgeries or investigations. Likewise, Carnett's test may be useful. In this test, a painful area is palpated before and after the patient tenses his or her abdominal wall, by essentially performing a sit-up against the resistance of the clinician's hand on his or her forehead. If the patient experiences pain with palpation against tense abdominal musculature, it suggests that the pain is emanating from the musculature of the anterior abdominal was rather than being intra-abdominal per se. A targeted investigational strategy to include standard hematological, biochemical, and immunological parameters is appropriate in the majority of patients. In patients with alarm features, or red flag signs, then an alternative diagnosis should be considered and investigated accordingly. To guide the diagnosis of FAP, the Rome Foundation has produced a useful algorithm (see Fig. 1).

## Management of Functional Abdominal Pain

There is an absence of international consensus with respect to the optimal management of FAP. Similarly, there are few randomized controlled trials (RCTs) of therapeutic interventions in adult FAP. Thus, interventions are largely based on evidence and anecdotal experience derived from other FGIDs and other chronic pain syndromes. Accordingly, the advice in the subsequent sections is based on evidence derived from other FGIDs in which chronic visceral pain is a prominent feature. Where an evidence base is lacking, advice is based on reports from other experts in the field. Treatment modalities can be usefully divided into general measures, pharmacological treatments, and psychological interventions. A summary overview of management steps for FAP in given in Fig. 2.

### General Measures

Central to a successful outcome in the management of all FGIDs, and of FAP in particular, is the doctor-patient relationship. In particular, validation of a patient's symptoms in a supportive multidisciplinary environment is an absolute cornerstone of treatment. For instance, many, if not most, of these patients may have been hitherto diagnosed with a FGID or may have experienced negative attitudes toward their symptoms on the part of nonspecialist clinicians, often for many years prior to

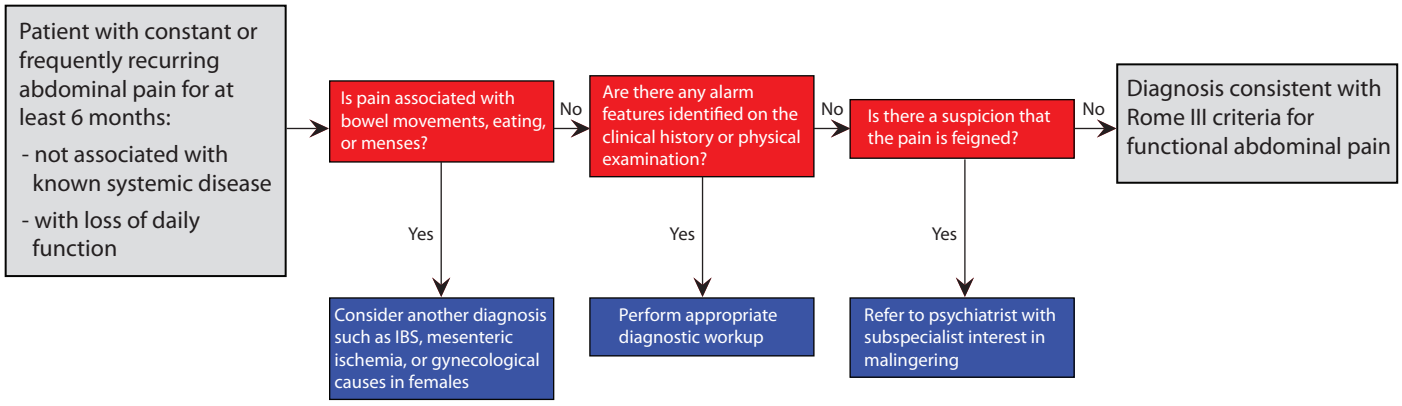


***Fig. 1.*** A suggested diagnostic algorithm for the diagnosis of FAP. Adapted from the Rome Foundation, with permission.

*Central to a successful outcome in the management of all FGIDs, and of FAP in particular, is the doctor-patient relationship*

receiving a definitive diagnosis of FAP. Patient education as to the pathophysiology of FAP is a prerequisite step before therapeutic interventions are commenced, thereby giving patients a rationale for a particular treatment choice, for instance using low-dose antidepressants as analgesics rather than as antidepressants per se. The clinician and the patient should also agree upon, and set, reasonable treatment goals in the context of regular outpatient reviews. Such reviews may be limited by local service provision, but they do allow definition of response or nonresponse to any particular intervention, thereby facilitating earlier escalation as appropriate. This approach, while it is relatively "resource intensive," does reduce the likelihood of patients seeking further consultations with other clinicians in the intervening period. A summary of the suggested management steps in given in Fig. 2.

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## Pharmacological Interventions

Pharmacological interventions in FAP are primarily targeted toward neuromodulation of the putative pathophysiological mechanisms.

### *Antidepressants*

Antidepressants are the mainstay of pain management in FAP and are widely used in the management of other FGIDs. A recent Cochrane meta-analysis provided evidence of a beneficial effect for antidepressants over placebo for improvement of abdominal pain, global assessment of wellbeing, and overall symptoms in IBS, with a number needed to treat (NNT) of 5, 4, and 4, respectively.[15] Furthermore, a subgroup analysis in this study demonstrated a statistically significant benefit for tricyclic antidepressants (TCAs) in improving abdominal pain and symptom scores.

*Tricyclic Antidepressants.* While their precise analgesic mechanism of action remains unclear, it is postulated that TCAs (e.g., amitriptyline, nortriptyline) may act upon at least three complementary sites. First, they indirectly modulate the central endogenous opioid system via their serotoninergic and noradrenergic properties. Second, they act by binding the NMDA receptor on the spinal dorsal horn. Finally, they directly inhibit sodium and potassium ion channels on spinal afferents. In our practice, we utilize low-dose TCAs at night (e.g., amitriptyline 10 mg) as first-line pharmacotherapy. Higher doses may cause somnolence and anticholinergic side effects, which might lead to noncompliance. Moreover, higher doses seldom display a linear relationship with serum concentrations, thus suggesting that lower doses are sufficient to induce central analgesia.

*Serotonin Norepinephrine Reuptake Inhibitors.* Serotonin and norepinephrine have been implicated as central mediators of endogenous analgesic mechanisms in descending pain pathways. Preclinical and clinical data indicate that serotonin-norepinephrine reuptake inhibitors (SNRIs), (e.g., duloxetine, venlafaxine) are among the most promising modern agents for the management of chronic pain. Pooled data from two RCTs containing 538 patients with fibromyalgia demonstrated the efficacy of duloxetine in reducing pain, lessening functional impairment, and increasing quality of life.[16] These results have been replicated in a further 6-month RCT, indicating a degree of durability of the analgesic effect.[17] On the basis of these data, it is our clinical practice to commence an SNRI (e.g., duloxetine 60 mg modified release, once daily) as a second-line treatment in patients who never responded to TCA therapy or whose response diminished over time, although to date there is a paucity of empirical data to directly support this practice.

## Psychological Therapies

While the literature is devoid of any RCTs examining the efficacy of psychological therapies in the treatment of FAP in adults,

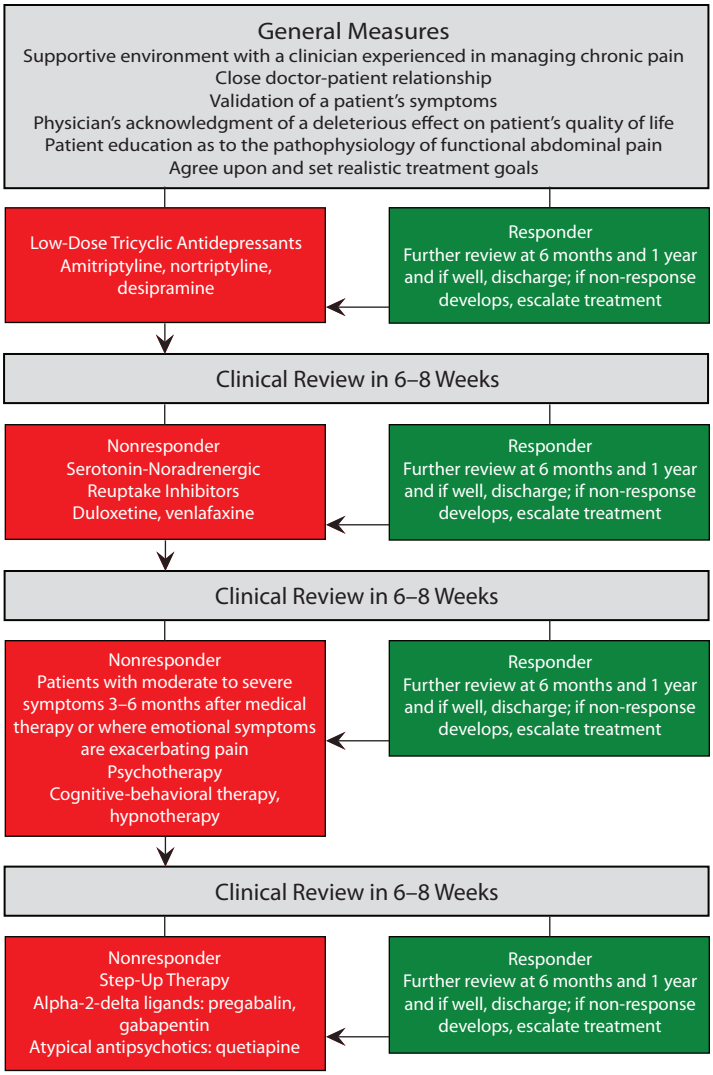


***Fig. 2.*** A suggested treatment algorithm for the management of FAP.

within pediatric populations with FAP and in adult populations with other FGIDs a diverse array of psychological treatments have been systematically evaluated. Examples include cognitive-behavioral therapy (CBT) and hypnotherapy. In our experience, the specific type of psychological therapy that is chosen is often largely dependent on local service availability. Given the limitations in availability, it is important to stratify and rationalize which patients to refer for such therapies. We would suggest that patients who have recalcitrant symptoms after 3 to 6 months of medical therapy or who have comorbid psychiatric disorders or stressful life events that trigger, or exacerbate, symptoms should be considered. However, we would concur with some experts who assert that specialized psychological therapies should be considered earlier in any treatment algorithm.

### *Cognitive-Behavioral Therapy*

CBT encourages patients to acknowledge their maladaptive beliefs regarding their pain in order to facilitate a reconceptualization of their symptoms, thus giving them tools to improve active coping. Therapy is also directed at aiding patients to develop an awareness of the interdependent and interrelated features of their pain experience. Again, it is important to set realistic treatment goals, in that the aim of therapy, rather than a "complete cure," is to allow patients to perform their regular daily activities without significant hindrance. While the evidence suggests improvement in composite scores of GI symptoms, to date, there is an absence of data suggesting improvements in objective physiological parameters.

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### *Hypnotherapy*

Hypnotherapy is well established in the treatment of IBS, with a robust evidence base. Hypnosis is used to induce a state of general relaxation, and patients are encouraged to use imagery or visualization so that they may attempt to take charge of their pain. Interestingly, in addition to improving clinical outcomes, hypnotherapy also displays a trend toward normalizing of rectal sensitivity in patients with constipation-predominant IBS.[18]

## Step-Up Therapy

A small, but significant, group of FAP patients may remain refractory to these standard interventions, and "step-up" therapy should be considered in addition to standard interventions. We would strongly argue that "step-up" therapy should not include the use of opioid analgesics, which over time may result in opioid-induced hyperalgesia and potentially the narcotic bowel syndrome.[19]

### *Alpha-2-Delta Ligands*

Gabapentin and pregabalin are used in the treatment of a number of chronic pain states. These compounds bind with high affinity to $\alpha_2\delta$ subunits of voltage-gated calcium channels, where their main analgesic action is exerted. This effect is widely distributed throughout the CNS, particularly in areas involved in pain signaling, including the amygdala, ACC, and insula. Both gabapentin and pregabalin have been demonstrated to alter pain and sensory thresholds to rectal distension in IBS patients.[20,21] They should therefore be considered as adjunctive therapies for those with intransigent symptoms.

### *Atypical Antipsychotics*

There is literature supporting the use of low-dose atypical antipsychotic medication such as quetiapine in the treatment of FAP. In addition to their effect in reducing symptoms of depression, such drugs lead to an observable reduction in anxiety and improvements in sleep patterns. Very preliminary anecdotal data suggest that approximately 50% of patients who have not improved with other therapies derive some benefit.[22]

## Conclusions

FAP is a relatively uncommon disorder characterized by chronic unexplained visceral pain. According to the current definition, FAP is likely to represent a heterogeneous group of patients whose symptoms are likely to be attributable to multiple pathophysiologies, yet our understanding of these mechanisms remains incomplete. Clinical evaluation should encompass a detailed history, and only targeted investigations should be undertaken. Treatment options often necessitate a variable combination of pharmacological, psychological, and step-up interventions.

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*Adam D. Farmer, PhD, MRCP*
*Department of Gastroenterology*
*Shrewsbury & Telford Hospitals NHS Trust*
*Princess Royal Hospital, Apley Castle*
*Telford, Shropshire, TF1 6TF, United Kingdom*

*Centre for Digestive Diseases*
*Wingate Institute of Neurogastroenterology*
*Blizard Institute*
*Barts and the London School of Medicine & Dentistry*
*Queen Mary University of London, London, United Kingdom*
*a.farmer@qmul.ac.uk*

*Qasim Aziz, PhD, FRCP*
*Centre for Digestive Diseases*
*Wingate Institute of Neurogastroenterology*
*Blizard Institute*
*Barts and the London School of Medicine & Dentistry*
*Queen Mary University of London, London, United Kingdom*
*q.aziz@qmul.ac.uk*





Printed in the U.S.A.