PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

*World J Gastroenterol* 2006 May 7; 12(17): 2701-2707
***World Journal of Gastroenterology*** ISSN 1007-9327


*TOPIC HIGHLIGHT*

**Andrew Seng Boon Chua, MD,** *Series Editor*

# Functional dyspepsia: Are psychosocial factors of relevance?

Sandra Barry, Timothy G Dinan

Sandra Barry, Timothy G Dinan, Department of Psychiatry and Alimentary Pharmacobiotic Centre, University College Cork, Cork, Ireland
Correspondence to: Professor Timothy G Dinan, Department of Psychiatry, Cork University Hospital, Wilton, Cork, Ireland. t.dinan@ucc.ie
Telephone: +353-21-4922593 Fax: +353-21-4922584
Received: 2006-03-03 Accepted: 2006-03-27

## Abstract

The pathogenesis of Functional Dyspepsia (FD) remains unclear, appears diverse and is thus inadequately understood. Akin to other functional gastrointestinal disorders, research has demonstrated an association between this common diagnosis and psychosocial factors and psychiatric morbidity. Conceptualising the relevance of these factors within the syndrome of FD requires application of the biopsychosocial model of disease. Using this paradigm, dysregulation of the reciprocal communication between the brain and the gut is central to symptom generation, interpretation and exacerbation. Appreciation and understanding of the neurobiological correlates of various psychological states is also relevant. The view that psychosocial factors exert their influence in FD predominantly through motivation of health care seeking also persists. This appears too one-dimensional an assertion in light of the evidence available supporting a more intrinsic aetiological link. Evolving understanding of pathogenic mechanisms and the heterogeneous nature of the syndrome will facilitate effective management. Co-morbid psychiatric illness warrants treatment with conventional therapies. Acknowledging the relevance of psychosocial variables in FD, the degree of which is subject to variation, has implications for assessment and management. Available evidence suggests psychological therapies may benefit FD patients particularly those with chronic symptoms. The rationale for use of psychotropic medications in FD is apparent but the evidence base to support the use of antidepressant pharmacotherapy is to date limited.



**Key words**: Functional dyspepsia; Psychosocial factors; Psychiatry; Pathophysiology

Barry S, Dinan TG. Functional dyspepsia: Are psychosocial factors of relevance? *World J Gastroenterol* 2006; 12(17): 2701-2707

http://www.wjgnet.com/1007-9327/12/2701.asp

## INTRODUCTION

Dyspepsia, an umbrella term for a number of gastrointestinal symptoms, is common with prevalence rates estimated at 26%-41%[1]. The spectrum of dyspeptic symptoms may be defined as those arising from the upper digestive tract unrelated to colonic function[1]. Potentially caused by a variety of underlying conditions, most often, no overt cause is elucidated. In such cases, in the absence of demonstrable organic abnormality using available diagnostic measures, the term functional dyspepsia (FD) is employed. Non-ulcer dyspepsia (NUD) and essential dyspepsia are used synonymously. This syndromal diagnosis, according to the 'Rome II' Consensus Report, is defined by 12 wk in the past 12 mo, of persistent or recurrent pain or discomfort in the upper abdomen, in the absence of organic disease and no association with bowel habit. Using these guidelines, patients may also be categorised as ulcer-like dyspepsia, motility-like dyspepsia or unspecified dyspepsia[2]. Though highly prevalent, the underlying pathogenesis is incompletely elucidated, seems diverse and is thus, inadequately understood.

Some investigators object to the separation of functional gastrointestinal disorders (FGID's) into different clinical entities, and indeed, there is considerable overlap between FD and the oft more studied irritable bowel syndrome (IBS)[3]. In at least 40% of patients presenting to gastroenterologists this overlap in symptomatology is sizeable[4,5]. In fact, it has been suggested that the current evidence is insufficient to determine whether the two syndromes are indeed two distinct processes or simply different manifestations of a single, broad-spectrum condition[3]. Data in relation to the role of psychosocial factors in IBS is bountiful but as yet, there is less available pertaining to FD. Even so, as with IBS, psychosocial factors have long been implicated in the predisposition, precipitation and perpetuation of this syndrome.

Review of the literature clearly reveals an association between psychosocial factors and FGID's including FD[6-9]. However, the precise role of psychosocial variables in FD remains elusive. To explain this observation, one could espouse a number of hypotheses, none of which are likely to be mutually exclusive: Psychosocial variables are intrinsic to the aetiopathogenesis of FD; Psychosocial difficulties arise secondarily to chronic digestive symptoms; FD is a physical manifestation of unconscious psychological conflict or distress; Psychosocial factors motivate increased help-seeking and medical consultation; Psychosocial factors influence symptom experience.

Perhaps the most clinically useful way of conceptu-

alising a role for psychosocial factors in FD is within the biopsychosocial framework of disease as suggested by Drossman[10]. In this model, functional gastrointestinal disorders are seen as having mulitfactorial, bi-directional, rather than unicausal, unidirectional aetiology. This integrative view of illness, adopts the understanding that biological, psychological and social factors interact and said interaction accounts for the symptoms experienced, the patient's behavioural response and the outcome of the disorder. Many investigators now consider the 'Brain-Gut Axis' (BGA) to be the anatomical substrate, mediating this interaction[11]. At the very least, it provides a rough neurobiological framework for reciprocal connections between the brain and the gastrointestinal tract[12]. As a concept, it has emerged consequent to a convergence of research into brain-gut interactions and the effect of stress on such exchanges. The BGA is central to the biopsychosocial model in FD. To elaborate briefly, this axis is bi-directional and integrative with input from sensory sources (sight, smell, etc.) and somatosensory/viscerosensory sources, modified by cognitions and affects, and a neural circuit in the central nervous sysytem (CNS), the spinal cord, the autonomic nervous system (ANS) and enteric nervous system (ENS)[11]. Using this paradigm, chronic functional gastrointestinal symptoms can be seen as a result of dysregulation of intestinal motor, sensory and CNS activity, resulting from disturbance at some level of the BGA.

## EVIDENCE TO SUPPORT AN ASSOCIATION BETWEEN PSYCHOSOCIAL FACTORS AND FUNCTIONAL DYSPEPSIA

A myriad of psychosocial factors have been examined in the literature in relation to FD. These include psychological distress, personality traits, social support, life-events and life-stresses including abuse and bereavement. The issue of Psychiatric Disorder co-morbidity is often addressed within the same context. The associations between a number of these variables and FD are outlined below.

### *Psychological morbidity*

Studies have demonstrated a high prevalence of Psychiatric Disorder in patients with dyspepsia of unknown origin. In the midst of the debate concerning the significance of this relationship, speculation as to the potential for a shared pathophysiology has arisen[12]. The most common psychiatric co-morbidities in patients with functional dyspepsia are Anxiety Disorders, Depressive Disorders and Somatoform Disorders[6,13]. In a clinic based study, findings showed that 87% of patients with FD, compared to 25% of patients with organic dyspepsia, had a psychiatric diagnosis[13]. A larger study, utilising semi-structured psychiatric interview and psychometric tools, revealed that 34% percent of the FD patients versus 15% of the duodenal ulcer patients had a psychiatric diagnosis. Anxiety Disorders were again most common. A mere 1% of the healthy controls met criteria for a psychiatric diagnosis[6]. These findings are not consistent across studies but conflicting results may be explained by use of different sample populations. Interestingly, in contrast to the latter findings, an earlier study demonstrated no statistically significant difference between essential dyspepsia and duodenal ulcer patients on various psychometric test scores. However, elevated levels of neuroticism, anxiety and depression were demonstrated in FD patients compared to controls. No explanation was offered for lack of difference between the DU and FD patients[14]. Similarly, the results of a study examining psychosocial variables in organic dyspepsia and IBS, illustrated that the prevalence of formal psychiatric disorder did not differ significantly in both patient groups. The inclusion of chronic treatment resistant patients, who may account for the higher levels of psychopathology seen in other studies, was minimised by use of consecutive general practitioner referrals[15].

In a recent study, investigators sought to characterise relevant psychosocial variables and quality of life in a population of patients with functional dyspepsia, primarily referred from a primary care clinic, and in addition sought to correlate these variables with specific dyspeptic symptoms. It was hypothesised that if dyspeptic symptoms represented the physical manifestations of various aspects of psychological distress, a correlation should be evident between specific symptoms, measures of somatisation (the tendency to express emotional dysphoria as physical symptoms) and specific psychosocial variables. Self-report measures were used to evaluate symptomatology and psychological parameters. Results showed that, compared with healthy patients, patients with FD had significantly greater scores for dyspeptic symptoms, significantly greater psychiatric distress and significantly poorer quality of life. However, symptom severity and psychological distress did not correlate strongly. Thus, because of the lack of correlation, the authors concluded that digestive symptoms at that level of care are unlikely to represent physically manifested emotional distress. Instead, it would appear that dyspeptic symptoms are occurring against a background of psychiatric morbidity[16]. Studies, in addition to demonstrating greater psychiatric co-morbidity, have also revealed a greater tendency towards multiple extra-intestinal somatic complaints in FD patient groups[6]. This, together with overlapping symptoms in the various functional syndromes, contributes to the argument of proponents of a unitary somatisation syndrome[17].

Further studies have lent support to the notion that psychological distress, not necessarily warranting a psychiatric diagnosis, is involved in the causative pathway. Patients with NUD, at a clinic level, report more psychological distress than healthy controls[6,18]. However, a number of studies have demonstrated no psychological differences between people with functional bowel disorders who have not consulted a physician compared to community-based healthy controls[19]. This has engendered the assertion that psychosocial factors are not implicated in the aetiopathogenesis of FD and IBS, but rather serve to motivate health-care seeking i.e. act as confounding factors. More recently, in contrast to this dogma, elevated levels of psychological distress across all domains (except phobic anxiety) of the SCL-90-R, a measure of psychological state, have been demonstrated in a population-based study of subjects with functional GI disorders inclusive of both

consulters and non-consulters[9].

### Life events

Life-events are changes in a person's life that require adjustment and where the demands associated with such events exceed resources available, stress is the result. The association between FD and stress in life has often been suggested, though yet again in a minority of studies, inconsistent results have been reported[20,21]. Severe life stress has been found immediately before the onset of functional bowel disorders[22] and may precede consultation with a general practitioner in dyspepsia sufferers[23]. It has been suggested however, that there is a lack of community studies that have carefully evaluated whether stress is linked to disease or merely to health-care seeking[9].

In a retrospective study using semi-structured interview and a number of psychometric tools, authors looked at the occurrence and perception of life events, personality factors and psychopathology of patients with FD, compared with DU patients and healthy controls. Results demonstrated that patients with FD experienced more life-events than both DU patients and controls. In addition, DU patients experienced more than controls. These findings were accounted for by differences in stressful life-events[7]. Moreover, the most prevalent types of severe events in all groups were changes in social activity, changes in job situation and illness in the family. Though, evaluation of stress is influenced by psychiatric co-morbidity, and indeed higher psychopathology scores were seen in the FD group, one could also argue conversely that the life-events precipitated the psychopathology. The authors suggest that the difference in perception of life-events may relate to an imbalance between stressors and coping abilities and that this may indirectly mediate gastric motor disturbances and abdominal discomfort. Similar findings were established in a clinic-based study which showed that highly threatening chronic difficulties were significantly more evident in the non-ulcerative dyspepsia group than controls, as were acute life-events which remained highly threatening one week after their onset[24].

A population based study, looked at a number of psychosocial variables, life-event stress inclusive, and their association with FGID's. Using the *life experiences survey*, it was demonstrated that subjects with higher negative change scores and greater total change scores were more likely to have a FGID. When the comparison was then limited to NUD patients only, subjects with higher positive change scores (indicating change with a positive impact) and higher total change scores were more likely to have NUD. Life-threatening events, in contrast to the latter study, were not associated with NUD[9].

### Personality and coping style

In one study examining personality, investigators hypothesised that patients with FD would have more nervous symptoms and a different personality pattern than healthy control subjects[25]. Interesting findings were illustrated. Using a personality inventory, the patient group reported a lower *detachment* score than the control group, the *detachment scale* relating to the individual's need for social distance and coldness in social relations. This finding would indicate a greater need for attachment, which could conceivably lead to frustration. Female patients scored lower *socialisation* and higher *suspicion* than female controls. The authors suggest their findings may reflect a relationship between personality and development of gastrointestinal symptoms. Higher levels of introversion and suspicion may hinder adequate coping with stress.

Previous personality studies, showed significantly more symptoms of anxiety and tension and higher scores for trait tension and hostility for FD patients compared with peptic ulcer disease patients[18]. Others would suggest that personality differences are minimised when IBS co-morbidity is excluded. It has been shown that individuals with FD, without IBS, have higher scores of anxiety, neuroticism and depression, than paired community controls, but the differences are relatively small[14]. Where IBS is an accepted co-morbidity the differences are more significant[26]. Neuroticism, characterised by an individual' s tendency to have an exaggerated responsiveness to physiological changes, may theoretically exert an influence on the recognition and reporting of symptoms[27].

Coping response is another psychological factor that has proposed relations to FD symptoms. With regard to the relationship between coping behaviours and well being, FD patients may adopt a distinct coping pattern that is related to their heightened level of anxiety[28]. It has been shown that a non-discriminative, action orientated coping pattern was found to be characteristic of FD regardless of stressor controllability. Consistent use of this coping strategy under all circumstances may not be useful in mitigating distress, may provoke anxiety, may not be useful in altering outcome and may prove costly in terms of psychological strain.

### Abuse

Studies suggest that abuse, both past and current, is an important risk factor for functional GI symptoms. It has been found that women outpatients with functional, as opposed to organic bowel disease, were nearly twice as likely to report sexual abuse[29]. Clinic-based studies may carry potential selection bias. However, a population based cross-sectional study, using a self-report questionnaire, has shown that subjects with an abuse history, in childhood or adulthood, were significantly more likely to report a history of dyspepsia or heartburn and that this association could not be explained by confounders for which the analysis accounted[30]. An interview-based study examining the prevalence of FGID's in women subject to ongoing abuse revealed that 71% had a FGID-67% having FD. This group also had higher levels of psychological distress[31].

These observations do not imply causality and the role of confounding co-morbidities to which the individual may be predisposed by virtue of the abuse, may be an issue[32]. It has also been observed that there is a high frequency of abuse history in other chronic pain conditions. Abuse may not be implicated in the aetiology of FGID but may be associated with a tendency to communicate psychological distress through physical symptoms[33].

### Psychosocial factors and health-care seeking

Aetiological issues aside, it is reasonable to hypothesise

that psychosocial factors may also exert their effect in FD through an influence on health-care seeking. Health-care seeking is determined by a plethora of factors including symptom severity, personality, coping skills, social support, sociodemographics, psychological morbidity and health-care availability[34]. Illness behaviour, which may be defined as how one perceives, evaluates and acts upon symptoms[35], is also critically involved in the decision to seek medical consultation. Intrinsic to this process are illness beliefs and attitudes. It has been suggested that the observed association between FD and psychosocial factors is in fact mediated through increased help-seeking prompted by elevated levels of psychosocial distress. This theory is derived from the findings by some investigators, in volunteer studies, identifying no differences across psychological parameters between healthy controls and FD patients who have not sought medical advice[36,37].

A number of studies have demonstrated elevated levels of psychosocial distress amongst consulters recruited at clinic, in comparison with non-consulters, with functional dyspeptic symptoms. One such study showed that the former have more worries about cancer and heart disease than the latter. Consulters interviewed also had experienced more stressful or threatening life-events over the previous 6 mo[38]. These are factors that may potentially motivate health-care seeking to ameliorate concern and gain reassurance. More recently, a critical review of the literature pertaining to predictors of health-care seeking for both IBS and FD, was undertaken. Authors concluded that psychosocial factors including life-event stress, psychological morbidity, personality, abuse, and abnormal illness attitudes and beliefs have been found to characterise those that seek help versus those that do not[34]. In a study that sought to examine the differences in behavioural and perceptual characteristics between non-consulters and consulters with FD in a Chinese population, it was found that non-consulters were distinguishable by their perceptual style, coping behaviours and psychological symptoms. Moreover, investigators found levels of anxiety and depression to be highest in consulters compared to non-consulters and healthy controls[39].

Others refute the generalisability of these findings. The results of a recent community based study, suggest that psychosocial factors are significantly associated with functional GI disorders in both consulters and non-consulters, at population level[9]. The debate thus clearly remains unresolved.

## ABNORMALITIES OF FUNCTION IN FUNCTIONAL DYSPEPSIA

Though the pathophysiology underlying FD is incompletely elucidated and seems heterogeneous, several mechanisms to explain symptom manifestation have been proposed. Motor abnormalities of the upper gut have been demonstrated including delayed gastric emptying, antroduodenal dysmotility and altered gastric compliance[40,41]. So too has gastric sensory dysfunction in the form of visceral hypersensitivity[42,43]. Infective and inflammatory processes have also been proposed which may involve *Helicobacter pylori* and acute gastric infection[44-46]. Different types of inflammation throughout the gut can leave a legacy resulting in abnormal function in apparently histologically normal organs, by means of proposed mechanisms including: defective resolution of inflammation, changes in mucosal function and persistent changes within the ENS[44]. In a review of the molecular basis of FGIDs, it has been suggested that mediators or regulators of mucosal inflammation, including cytokines, may trigger events that ultimately result in the manifestation of functional gastrointestinal disorders[47]. Abnormalities of receptor function, including central serotonin receptors have also been implicated[48,49].

### *Influence of psychosocial factors on abnormalities of function*

Using the brain-gut interaction construct, how then do psychosocial factors ultimately influence FD symptomatology? Stress is a characteristic shared by the various psychosocial factors that have a demonstrated association with FD. From a psychological perspective, stress is emergent when demand exceeds resources. More broadly, it is defined as 'any threat to the homeostasis of an organism, be it real or perceived, which may be posed by events in the outside world or within[50]. In recent times, the biological substrates of the stress response, in health and disease, have been recognised. In brief summary, centrally, interoceptive (systemic) stressors employ subcortical circuits, while exteroceptive (psychological) stressors engage pathways in the limbic forebrain, hippocampus and amygdala. Both circuits activate hypothalamic effector neurons. Corticotrophin releasing hormone (CRH), not only secreted in the hypothalamus, is an important mediator of the central stress response. The latter is generated by a network of integrative brain structures, in particular subregions of the hypothalamus, amygdala and periaqueductal grey. Mayer refers to this central circuitry as the 'emotional motor system' (EMS), which is under feedback control via ascending monoaminergic projections and circulating glucocorticoids. Outputs from the EMS play a role in mediating the peripheral response[50]. Neuro-endocrine systems are heavily implicated and include the hypothalamic-pituitary-adrenal (HPA) axis[51]. The autonomic nervous system and endogenous pain modulation system are also involved[50]. It is generally recognised that early life-trauma and chronic severe stress in adulthood can cause long-lasting, potentially irreversible, changes in the stress response system[52]. It is possible therefore that in vulnerable individuals the neurobiological substrates of stress, or maladaptive states thereof, operating on the BGA, form part of the link between psychosocial factors and FD.

Approximately one in three FD patients have a definable gastric motor abnormality[53]. In patients with FD, the effect of stress on antro-duodenal activity has been studied, revealing findings contrary to those seen in healthy controls[54]. In an experimental design, it was shown that antro-duodenal motility was diminished by stress in healthy controls. This was not the case in dyspeptic patients suggesting that FD may arise from the effect of stress on upper gut motility in susceptible individuals. The autonomic nervous system has been proposed as the

mediating mechanism for this effect. In an earlier study, antral motility and autonomic function in FD patients and healthy controls were investigated[55]. The effect of mental stress on antral motility was also examined. Findings confirmed autonomic dysfunction, specifically low vagal tone, in functional GI disorders. At baseline, post-prandial antral motility was on average reduced in FD patients compared to controls. Moreover, acute mental stress diminished post-prandial antral motility in healthy subjects but not in dyspeptics. In fact, some patients demonstrated increased motility. Subsequently, it was proposed that poor vagal tone may represent a mediating mechanism for the causal effects of personality on antral motility and related FD symptoms[56]. The relationship among a number of psychological factors, antral dysmotility and dyspeptic symptoms in FD patients were examined. Specifically, it was asked if any such relationship depends on vagal activity, by examining the relationship between these psychological factors and vagal tone. Findings showed that psychological predictors explained a substantial amount of the variance in task-related dyspeptic symptoms, vagal tone and gastric antral dysmotility. FD patients had lower scores on vagal tone and motility index in addition to the expected higher scores on epigastric discomfort. Symptoms appeared to be predicted by trait anxiety, depression and neuroticism and poor vagal tone was associated with neuroticism.

Several studies have established that patients with FD have enhanced sensitivity to gastric distension thus potentially allowing physiological stimuli to induce symptoms[43,57]. The mechanisms underlying visceral hypersensitivity are not fully clarified but there are several sources of evidence for a role of the central nervous system. Studies in experimental animals indicate that acute psychological stress seems to facilitate increased sensitivity to visceral stimuli[40]. Conceivably, psychosocial stressors may affect visceral sensation through an effect on central processing and/or modulation of afferent visceral information or on central cortisol receptors. With reference to the latter, a thorough characterisation of the HPA axis in FGID has not been reported. However, it has been demonstrated that chronic stress may result in HPA axis overactivity and thus hypercortisolaemia[52]. Brain regions involved in visceral sensation, and indeed mood regulation, express cortisol receptors and abnormal levels of cortisol can causes changes in these structures ultimately resulting in abnormal visceral sensation, affective disorders or both[12,50]. Imaging research has revealed considerable overlap between brain regions involved in processing visceral sensation and those important for emotional regulation[12,58,59]. From animal research, neonatal maternal separation in rats, a model of early-life stess, predisposes them to develop visceral hyperalgesia in response to psychosocial stress[60]. It is felt that this is probably CRH mediated.

Approximately 25% of FD cases develop acutely after an acute infectious illness often characterised by vomiting and fever[46]. It is well recognised that stress plays a role in immunological modulation[61]. Chronic stress renders individuals more vulnerable to intestinal infection and inflammation, which can be an important pathophysiological mechanism in post-infectious FGID[62].

## PSYCHOSOCIAL FACTORS AND MANAGEMENT OF FUNCTIONAL DYSPEPSIA

The association between psychosocial stressors and FD and the high rates of psychiatric co-morbidity in FD, clearly have implications for effective management. Taking a psychosocial history may help reduce return visits in IBS patients and this may also apply to other FGIDs[63]. Depression and anxiety have been shown to adversely affect outcome in IBS[64] as have pronounced health worries and poor psychosocial support. Overt psychiatric illness should respond to conventional treatment and if suspected, or if there is evidence of somatisation in other systems leading to multiple consultations across specialities, referral to a mental health profession may be considered[8]. As with IBS, treatment in FD is symptom driven. In reducing the likelihood of invalidating the patient's symptoms (secondary to lack of organic pathology) it may help to explain the mechanisms underlying brain-gut interactions. Acknowledging the relevance of psychosocial factors will no doubt meet with some resistance in certain patients.

If the role of psychosocial factors in FD remains to be fully clarified, then the role of psychological therapies is similarly undetermined. However, patients with FD may benefit from psychological treatments. This is particularly true of those with chronic symptoms unresponsive to conventional medical approaches. Psychotherapy has been defined as an interpersonal process designed to bring about modifications of feelings, cognitions, attitudes and behaviour, which have proved troublesome to the patient seeking help from a trained professional[65]. There are wide ranges of interventions that can be described as psychotherapeutic including cognitive-behavioural therapy (CBT), psychodynamic psychotherapy and group therapies. Psychodynamic therapies focus on how maladaptive ideas and behaviours have emerged whereas cognitive behavioural work concentrates on how maladaptive ideas and belief systems are maintained by the patient's environment and behaviour[66].

A systematic review to establish the effectiveness of psychotherapy and hypnosis in FD, revealed a paucity of randomised controlled trials investigating psychological intervention in FD[66]. The data available suggest that these techniques benefit FD but the authors conclude that the evidence is insufficient to confirm their efficacy. One particular study randomised patients to psychodynamic-interpersonal psychotherapy or supportive therapy, which consisted of sympathy and support for the same duration of time as the intervention arm. Patients recruited had chronic symptoms and a history of failed response to conventional pharmacological therapy. After 12 wk of treatment the intervention group were significantly better across parameters but after 12 mo, the symptom scores were similar between groups[67]. CBT has been found to be effective in the treatment of depression, anxiety disorders and of patients with medically unexplained symptoms[68]. A study comparing the outcome of cognitive therapy (attempts to change dysfunctional thoughts and behaviour

by cognitive restructuring, behavioural modelling and role-play) and a control group intervention (bimonthly therapist visits), in patients with FD, demonstrated significantly greater improvement in the former[69].

The rationale for using psychotropic medication rests in the level of psychiatric co-morbidity seen in patients with FD as mentioned earlier. Additionally, there is data to support the use of antidepressants in the relief of chronic pain[8]. A meta-analysis of the treatment of functional gastrointestinal disorders with antidepressant medications, identifying 3 randomised controlled trials evaluating FD, suggested that antidepressants (predominantly tricyclics) might reduce the symptoms of FGIDs. Of note, the majority of studies included, used antidepressant doses that are essentially sub-therapeutic for treatment of depression. The authors thus suggest that it is unlikely that the benefit observed is due entirely to the antidepressant effect of these drugs[70]. There is little data available on the use of selective serotonin reuptake inhibitors. It seems reasonable that choice of drug is tailored to the individuals dominant symptom pattern whilst remaining cognisant of side-effect profiles. Essentially, if used, psychotropics should be regarded as complimentary to an overall multi-component plan.

In conclusion, functional dyspepsia is a heterogeneous disorder in which the role of psychosocial factors continues to be the subject of debate. The suggestion that psychological morbidity and social stressors serve to motivate physician consultation, rather than possessing an aetiological role in symptom pathogenesis, has been challenged. Despite inconsistent findings, it is evident that there is a high level of psychiatric co-morbidity with FD and that anxiety disorders predominate. Individuals with FD appear to experience a greater number of life-events, which are not limited to those of negative impact, compared to healthy controls. A recent or remote history of abuse is a non-specific risk-factor for symptoms of FD. The speculation that functional gastrointestinal disorders and psychopathology share common pathophysiology is interesting and warrants further examination. The evolving appreciation and delineation of brain-gut interactions and CNS processing continues to enhance our understanding of the complex mechanisms underlying symptom generation, interpretation and presentation.

## ACKNOWLEDGMENTS

Ted Dinan is in receipt of funding from the Scientific Foundation of Ireland through the Alimentary Pharmacobiotic Centre and also from the Wellcome Trust and Health Research Board (Ireland).

## REFERENCES

1 **Jones MP**. Evaluation and treatment of dyspepsia. *Postgrad Med J* 2003; **79:** 25-29
2 **Talley NJ**, Stanghellini V, Heading RC, Koch KL, Malagelada JR, Tytgat GN. Functional gastroduodenal disorders. *Gut* 1999; **45 Suppl 2:** II37-II42
3 **Cremonini F**, Talley NJ. Review article: the overlap between functional dyspepsia and irritable bowel syndrome -- a tale of one or two disorders? *Aliment Pharmacol Ther* 2004; **20 Suppl 7:** 40-49
4 **Talley NJ**, Dennis EH, Schettler-Duncan VA, Lacy BE, Olden KW, Crowell MD. Overlapping upper and lower gastrointestinal symptoms in irritable bowel syndrome patients with constipation or diarrhea. *Am J Gastroenterol* 2003; **98:** 2454-2459
5 **Stanghellini V**, Tosetti C, Barbara G, De Giorgio R, Cogliandro L, Cogliandro R, Corinaldesi R. Dyspeptic symptoms and gastric emptying in the irritable bowel syndrome. *Am J Gastroenterol* 2002; **97:** 2738-2743
6 **Haug TT**, Svebak S, Wilhelmsen I, Berstad A, Ursin H. Psychological factors and somatic symptoms in functional dyspepsia. A comparison with duodenal ulcer and healthy controls. *J Psychosom Res* 1994; **38:** 281-291
7 **Haug TT**, Wilhelmsen I, Ursin H, Berstad A. What are the real problems for patients with functional dyspepsia? *Scand J Gastroenterol* 1995; **30:** 97-100
8 **Drossman DA**, Creed FH, Olden KW, Svedlund J, Toner BB, Whitehead WE. Psychosocial aspects of the functional gastrointestinal disorders. **Gut** 1999; **45 Suppl 2:** II25-II30
9 **Locke GR 3rd**, Weaver AL, Melton LJ 3rd, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. *Am J Gastroenterol* 2004; **99:** 350-357
10 **Drossman DA**. Gastrointestinal illness and the biopsychosocial model. *J Clin Gastroenterol* 1996; **22:** 252-254
11 **Wilhelmsen I**. Brain-gut axis as an example of the bio-psychosocial model. *Gut* 2000; **47 Suppl 4:** iv5-7; discussion iv10
12 **Van Oudenhove L**, Demyttenaere K, Tack J, Aziz Q. Central nervous system involvement in functional gastrointestinal disorders. *Best Pract Res Clin Gastroenterol* 2004; **18:** 663-680
13 **Magni G**, di Mario F, Bernasconi G, Mastropaolo G. DSM-III diagnoses associated with dyspepsia of unknown cause. *Am J Psychiatry* 1987; **144:** 1222-1223
14 **Talley NJ**, Fung LH, Gilligan IJ, McNeil D, Piper DW. Association of anxiety, neuroticism, and depression with dyspepsia of unknown cause. A case-control study. *Gastroenterology* 1986; **90:** 886-892
15 **Dinan TG**, O'Keane V, O'Boyle C, Chua A, Keeling PW. A comparison of the mental status, personality profiles and life events of patients with irritable bowel syndrome and peptic ulcer disease. *Acta Psychiatr Scand* 1991; **84:** 26-28
16 **Jones MP**, Sharp LK, Crowell MD. Psychosocial correlates of symptoms in functional dyspepsia. *Clin Gastroenterol Hepatol* 2005; **3:** 521-528
17 **Wessely S**, Nimnuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999; **354:** 936-939
18 **Langeluddecke P**, Goulston K, Tennant C. Psychological factors in dyspepsia of unknown cause: a comparison with peptic ulcer disease. *J Psychosom Res* 1990; **34:** 215-222
19 **Smith RC**, Greenbaum DS, Vancouver JB, Henry RC, Reinhart MA, Greenbaum RB, Dean HA, Mayle JE. Psychosocial factors are associated with health care seeking rather than diagnosis in irritable bowel syndrome. *Gastroenterology* 1990; **98:** 293-301
20 **Hui WM**, Shiu LP, Lam SK. The perception of life events and daily stress in nonulcer dyspepsia. *Am J Gastroenterol* 1991; **86:** 292-296
21 **Talley NJ**, Piper DW. A prospective study of social factors and major life event stress in patients with dyspepsia of unknown cause. *Scand J Gastroenterol* 1987; **22:** 268-272
22 **Creed F**, Craig T, Farmer R. Functional abdominal pain, psychiatric illness, and life events. Gut 1988; 29: 235-242
23 **Morris C**. Non-ulcer dyspepsia. *J Psychosom Res* 1991; **35:** 129-140
24 **Bennett E**, Beaurepaire J, Langeluddecke P, Kellow J, Tennant C. Life stress and non-ulcer dyspepsia: a case-control study. *J Psychosom Res* 1991; **35:** 579-590
25 **Jonsson BH**, Theorell T, Gotthard R. Symptoms and personality in patients with chronic functional dyspepsia. *J Psychosom Res* 1995; **39:** 93-102
26 **Bennett EJ**, Piesse C, Palmer K, Badcock CA, Tennant CC, Kellow JE. Functional gastrointestinal disorders: psychological, social, and somatic features. *Gut* 1998; **42:** 414-420
27 **Larsen RJ**. Neuroticism and selective encoding and recall of symptoms: evidence from a combined concurrent-retrospective study. *J Pers Soc Psychol* 1992; **62:** 480-488

28 **Cheng C**, Hui WM, Lam SK. Coping style of individuals with functional dyspepsia. *Psychosom Med* 1999; **61:** 789-795
29 **Drossman DA**, Leserman J, Nachman G, Li ZM, Gluck H, Toomey TC, Mitchell CM. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. *Ann Intern Med* 1990; **113:** 828-833
30 **Talley NJ**, Fett SL, Zinsmeister AR, Melton LJ 3rd. Gastrointestinal tract symptoms and self-reported abuse: a population-based study. *Gastroenterology* 1994; **107:** 1040-1049
31 **Perona M**, Benasayag R, Perello A, Santos J, Zarate N, Zarate P, Mearin F. Prevalence of functional gastrointestinal disorders in women who report domestic violence to the police. *Clin Gastroenterol Hepatol* 2005; **3:** 436-441
32 **Olden KW**. Are psychosocial factors of aetiological importance in functional dyspepsia? *Baillieres Clin Gastroenterol* 1998; **12:** 557-571
33 **Drossman DA**, Talley NJ, Leserman J, Olden KW, Barreiro MA. Sexual and physical abuse and gastrointestinal illness. Review and recommendations. *Ann Intern Med* 1995; **123:** 782-794
34 **Koloski NA**, Talley NJ, Boyce PM. Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. *Am J Gastroenterol* 2001; **96:** 1340-1349
35 **Mechanic D**. Sociological dimensions of illness behavior. *Soc Sci Med* 1995; **41:** 1207-1216
36 **Drossman DA**, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC, Burger AL. Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. *Gastroenterology* 1988; **95:** 701-708
37 **Whitehead WE**, Bosmajian L, Zonderman AB, Costa PT Jr, Schuster MM. Symptoms of psychologic distress associated with irritable bowel syndrome. Comparison of community and medical clinic samples. *Gastroenterology* 1988; **95:** 709-714
38 **Lydeard S**, Jones R. Factors affecting the decision to consult with dyspepsia: comparison of consulters and non-consulters. *J R Coll Gen Pract* 1989; **39:** 495-498
39 **Cheng C**. Seeking medical consultation: perceptual and behavioral characteristics distinguishing consulters and non-consulters with functional dyspepsia. *Psychosom Med* 2000; **62:** 844-852
40 **Lee KJ**, Kindt S, Tack J. Pathophysiology of functional dyspepsia. *Best Pract Res Clin Gastroenterol* 2004; **18:** 707-716
41 **Smith ML**. Functional dyspepsia pathogenesis and therapeutic options--implications for management. *Dig Liver Dis* 2005; **37:** 547-558
42 **Mertz H**, Fullerton S, Naliboff B, Mayer EA. Symptoms and visceral perception in severe functional and organic dyspepsia. *Gut* 1998; **42:** 814-822
43 **Mertz H**. Review article: visceral hypersensitivity. *Aliment Pharmacol Ther* 2003; **17:** 623-633
44 **Spiller RC**. Inflammation as a basis for functional GI disorders. *Best Pract Res Clin Gastroenterol* 2004; **18:** 641-661
45 **Perri F**, Clemente R, Festa V, Annese V, Quitadamo M, Rutgeerts P, Andriulli A. Patterns of symptoms in functional dyspepsia: role of *Helicobacter pylori* infection and delayed gastric emptying. *Am J Gastroenterol* 1998; **93:** 2082-2088
46 **Tack J**, Demedts I, Dehondt G, Caenepeel P, Fischler B, Zandecki M, Janssens J. Clinical and pathophysiological characteristics of acute-onset functional dyspepsia. *Gastroenterology* 2002; **122:** 1738-1747
47 **Holtmann G**, Liebregts T, Siffert W. Molecular basis of functional gastrointestinal disorders. *Best Pract Res Clin Gastroenterol* 2004; **18:** 633-640
48 **Chua A**, Keating J, Hamilton D, Keeling PW, Dinan TG. Central serotonin receptors and delayed gastric emptying in nonulcer dyspepsia. *BMJ* 1992; **305:** 280-282
49 **Dinan TG**, Mahmud N, Rathore O, Thakore J, Scott LV, Carr E, Naesdal J, O'Morain CA, Keeling PW. A double-blind placebo-controlled study of buspirone-stimulated prolactin release in non-ulcer dyspepsia--are central serotoninergic responses enhanced? Aliment Pharmacol Ther 2001; 15: 1613-1618
50 **Mayer EA**. The neurobiology of stress and gastrointestinal disease. *Gut* 2000; **47:** 861-869
51 **Chrousos GP**, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. *JAMA* 1992; **267:** 1244-1252
52 **Claes SJ**. Corticotropin-releasing hormone (CRH) in psychiatry: from stress to psychopathology. *Ann Med* 2004; **36:** 50-61
53 **Stanghellini V**, Tosetti C, Paternic inverted question marko A, Barbara G, Morselli-Labate AM, Monetti N, Marengo M, Corinaldesi R. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996; **110:** 1036-1042
54 **Hveem K**, Hausken T, Svebak S, Berstad A. Gastric antral motility in functional dyspepsia. Effect of mental stress and cisapride. *Scand J Gastroenterol* 1996; **31:** 452-457
55 **Hausken T**, Svebak S, Wilhelmsen I, Haug TT, Olafsen K, Pettersson E, Hveem K, Berstad A. Low vagal tone and antral dysmotility in patients with functional dyspepsia. *Psychosom Med* 1993; **55:** 12-22
56 **Haug TT**, Svebak S, Hausken T, Wilhelmsen I, Berstad A, Ursin H. Low vagal activity as mediating mechanism for the relationship between personality factors and gastric symptoms in functional dyspepsia. *Psychosom Med* 1994; **56:** 181-186
57 **Holtmann G**, Gschossmann J, Neufang-Huber J, Gerken G, Talley NJ. Differences in gastric mechanosensory function after repeated ramp distensions in non-consulters with dyspepsia and healthy controls. *Gut* 2000; **47:** 332-336
58 **Derbyshire SW**. A systematic review of neuroimaging data during visceral stimulation. Am J Gastroenterol 2003; 98: 12-20
59 **Ballenger JC**, Davidson JR, Lecrubier Y, Nutt DJ, Lydiard RB, Mayer EA. Consensus statement on depression, anxiety, and functional gastrointestinal disorders. *J Clin Psychiatry* 2001; **62 Suppl 8:** 48-51
60 **Coutinho SV**, Plotsky PM, Sablad M, Miller JC, Zhou H, Bayati AI, McRoberts JA, Mayer EA. Neonatal maternal separation alters stress-induced responses to viscerosomatic nociceptive stimuli in rat. *Am J Physiol Gastrointest Liver Physiol* 2002; **282:** G307-G316
61 **O'Brien SM**, Scott LV, Dinan TG. Cytokines: abnormalities in major depression and implications for pharmacological treatment. *Hum Psychopharmacol* 2004; **19:** 397-403
62 **Collins SM**. Stress and the Gastrointestinal Tract IV. Modulation of intestinal inflammation by stress: basic mechanisms and clinical relevance. *Am J Physiol Gastrointest Liver Physiol* 2001; **280:** G315-G318
63 **Owens DM**, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician-patient interaction. *Ann Intern Med* 1995; **122:** 107-112
64 **Creed F**. The relationship between psychosocial parameters and outcome in irritable bowel syndrome. *Am J Med* 1999; **107:** 74S-80S
65 **Strupp HH**. Psychotherapy research and practice – an overview. In: Bergin AE, Garland SL, editor(s). Handbook of psychotherapy and behaviour change. 2nd edition. New York: Wiley 1978
66 **Soo S**, Moayyedi P, Deeks J, Delaney B, Lewis M, Forman D. Psychological interventions for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2005; CD002301
67 **Hamilton J**, Guthrie E, Creed F, Thompson D, Tomenson B, Bennett R, Moriarty K, Stephens W, Liston R. A randomized controlled trial of psychotherapy in patients with chronic functional dyspepsia. *Gastroenterology* 2000; **119:** 661-669
68 **Speckens AE**, van Hemert AM, Spinhoven P, Hawton KE, Bolk JH, Rooijmans HG. Cognitive behavioural therapy for medically unexplained physical symptoms: a randomised controlled trial. *BMJ* 1995; **311:** 1328-1332
69 **Haug TT**, Wilhelmsen I, Svebak S, Berstad A, Ursin H. Psychotherapy in functional dyspepsia. *J Psychosom Res* 1994; **38:** 735-744
70 **Jackson JL**, O'Malley PG, Tomkins G, Balden E, Santoro J, Kroenke K. Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis. *Am J Med* 2000; **108:** 65-72


**S- Editor** Pan BR **E- Editor** Bai SH