www.medscape.com

Authors and Disclosures

Eamonn M.M. Quigley, **John Keohane**, Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland

From Current Opinion in Gastroenterology

Dyspepsia

Eamonn M.M. Quigley; John Keohane

Posted: 12/12/2008; Curr Opin Gastroenterol. 2008;24(6):692-697.

Abstract and Introduction

Abstract

Purpose of Review: This review critically evaluates the current status of dyspepsia and, in particular, recent advances in epidemiology, pathophysiology and management. The very definition of dyspepsia and of functional dyspepsia, in particular, continues to generate controversy; the Rome III redefinition of functional dyspepsia remains to be proven to be of clinical value. Overlap with gastroesophageal reflux and irritable bowel syndrome further complicate clinical definitions.
Recent Findings: Most studies of pathophysiology continue to focus on gastric sensory and motor functions, though some intriguing early data raise the possibility of an infective or immunological contribution. There have been few, if any, major breakthroughs in treatment; most recent studies address instead the niceties of *Helicobacter pylori* eradication and acid suppressive strategies.
Summary: This continued lack of progress in the area can only lead one to question some very basic concepts in this disorder, such as does functional dyspepsia, as we have come to know it, really exist as a distinct entity?

Introduction

Although the term 'dyspepsia' is widely used in the medical literature, it has been variably interpreted by clinicians and investigators alike. In the English language, it can be most readily translated as 'indigestion', a commonly used lay term, which encompasses a multitude of upper abdominal and lower retrosternal ills. Therein lies the dilemma of dyspepsia; its very definition. This imprecision becomes even greater when one focuses on that subgroup currently defined as functional dyspepsia in which an absence of objective endoscopic, radiological or pathological findings leaves the clinician dangling by the slim thread that is a symptom-based criterion. It should come as no surprise that functional dyspepsia has become a territory ravaged by pathophysiological confusion and therapeutic famine.

What is Dyspepsia?

In an era when the incidence of gastric cancer and peptic ulcer disease are decreasing, functional gastrointestinal disorders such as functional dyspepsia and irritable bowel syndrome (IBS) have achieved increasing prominence in the medical literature. Indeed, a recent study[1••] supports the high prevalence of functional dyspepsia and IBS in the community and the stability of their prevalence over time.

Before we rush to accept that functional dyspepsia is a major pestilence that must be recognized and eradicated, we must ask ourselves a fundamental question: what is dyspepsia? If we saw it, would we recognize it? A critical assessment of the literature suggests, surprisingly, that robust clinical definitions for dyspepsia remain elusive and that this term and its various qualifiers have been interpreted differently by both physician and patient alike for years. Dyspepsia is a symptom or constellation of symptoms, not a disease, and is,

therefore, prey to all of the influences that the expression and interpretation of symptoms are subject to. Language, culture, age, race,[2] psychological factors,[3] past experiences, to mention but a few, will all influence what a patient says and how you, as their clinician, interprets them and translates their words into 'medicalese'. Other factors influence the prevalence of dyspepsia: alcohol intake,[4] cigarette smoking, intake of nonsteroidal anti-inflammatory drugs and socioeconomic status.[5] Although body weight is associated with both gastroesophageal reflux disease (GERD) and dyspepsia, modest changes in body weight (up or down) do not appear to lead to additional symptoms.[6] Many of these same factors, as well as the severity and frequency of symptoms, will determine the patient's response to these symptoms and whether or not he or she decides to consult a physician.[7••]

Despite attempts by numerous committees and consensus groups to agree on a uniform definition, clinical trials continue to use different diagnostic terminology, rendering the interpretation of data challenging. The Rome II committee defined functional dyspepsia as the presence of abdominal pain or discomfort centered in the epigastrium and present for at least 12 weeks over the last 12 months, which cannot be explained by upper gastrointestinal investigation.[8] The more recent Rome III definition[9] requires symptoms to be present for the last 3 months, with symptom onset at least 6 months before diagnosis. In a major shift in emphasis, it also proposed that functional dyspepsia comprises at least two distinct subgroups: the postprandial distress syndrome, which features postprandial fullness and early satiety; and the epigastric pain syndrome, which features a more constant and less meal-related pain syndrome.[9] Patients with prominent heartburn are excluded from both Rome definitions. The Rome committee contends that as heartburn and dyspepsia arise from separate organs, the esophagus and the stomach, respectively, these entities should be separated in clinical definitions.[9] Such a clear separation is often impossible on clinical grounds given the overlap that exists between these disorders; however, it is clearly evident that dyspeptic patients with predominant heartburn are those most likely to respond to acid suppression, thereby supporting the value of identifying the predominant symptom in a given patient.[10]

What has led to such a dramatic shift in definition between the Rome II and Rome III criteria? Such variations, within the same essential framework, are reflective of basic difficulties in the clinical categorization of 'dyspeptic' symptoms. Symptoms are poor predictors of cause; Moayyedi *et al*.,[11] for example, demonstrated that neither the clinical impression of a primary care physician or specialist nor patient input into a computer model were of real value in distinguishing between organic and functional dyspepsia. Clinical trials conducted in patient populations with uninvestigated dyspepsia are likely, therefore, to be heterogeneous and may comprise some with GERD and peptic ulcers and others with functional dyspepsia. Thus, clarity of definition is mandatory; uninvestigated dyspepsia needs to be clearly differentiated from functional dyspepsia and dyspepsia of organic causation. Although Rome III offers another opportunity for investigators to link symptom pattern with pathophysiology and treatment response, initial reports suggest that the new classification can lead to the identification of distinct subgroups in the community;[12] whether this will translate into prediction of pathophysiology or treatment response, remains to be seen. Functional dyspepsia can be a significant problem; in one tertiary care-based study,[13] the impact on quality of life was more severe than that related to chronic liver disease, with comorbid anxiety and depression contributing considerably.

Overlap With Gastroesophageal Reflux Disease and Irritable Bowel Syndrome

We contend that attempts to separate GERD, IBS and dyspepsia are not only clinically challenging but also unrealistic. Clinical experience, as well as numerous prospective studies, attests to the frequency with which functional dyspepsia and GERD coexist. This topic has been reviewed by us elsewhere recently; suffice it to say that the overlap between functional dyspepsia and GERD is greatest for those with nonerosive disease and especially so for those with what is now termed functional heartburn (i.e. those in whom there is no evident association between symptoms and acid exposure).[14] It is thought that the clinical spectrum that extends from functional dyspepsia to nonerosive reflux disease (NERD) may be present in up to 70% of GERD patients in the community. These clinical entities have a considerable socioeconomic impact, with £250 million spent annually by UK general practitioners in the treatment of upper gastrointestinal disease, including GERD.[15] It is very difficult to estimate the true prevalence of the functional dyspepsia-NERD overlap syndrome due to the lack of

uniformity in the definitions used. El-Serag and Talley[16] found that the prevalence of uninvestigated dyspepsia ranged from 10 to 40% when they used a more inclusive definition of dyspepsia, which incorporated heartburn and regurgitation; when the definition was restricted to upper abdominal pain alone, the prevalence fell to 5-12%. This study also demonstrated that dyspepsia is, indeed, a worldwide problem and that the majority of patients with uninvestigated dyspepsia actually fall into the functional dyspepsia group.

It is apparent that, irrespective of the definitions used, both functional dyspepsia and NERD are interrelated and commonly encountered conditions in the community that have an impact on quality of life equivalent to complicated GERD, and, therefore, warrant appropriate treatment and investigation. A further reflection of overlap with GERD is the observation that functional dyspepsia patients swallow more air and, not surprisingly, are more likely to reflux air.[17]

Overlap with IBS is equally prevalent and may prove even more challenging to differentiate. Constipation delays gastric emptying and is commonly accompanied by upper gut symptoms; similarly, bowel symptoms are common in functional dyspepsia. Pain location is commonly used to differentiate between these disorders though the topography of pain location in IBS would suggest that overlap is very likely. Longitudinal studies of the behavior of functional gastrointestinal disorders also attest to overlap between functional dyspepsia and IBS; over 12 years of follow-up, 40% of patients with functional dyspepsia or IBS had switched symptomatology.[1••] Perhaps the time has come to jettison attempts to separate these disorders and instead, given the overlap that exists in symptoms and purported pathophysiologies, recognize IBS and functional dyspepsia as part of a spectrum.

Functional Dyspepsia: Pathophysiology

For some time, dysmotility has been the prime focus of interest in functional dyspepsia and a variety of motor abnormalities have been described, including delayed gastric emptying, impaired fundic accommodation, antral distension, unsuppressed postprandial fundic contractility and duodenal dysmotility.[18] Although some correlations between individual motor abnormalities and symptom patterns have been borne out,[19] individual symptoms remain a poor predictor of motor events (and vice versa) and the delineation of a motor deficit has not opened the therapeutic avenues once envisaged. This is most clearly illustrated by the disappointment of prokinetic agents.[20••] Several explanations may be advanced to explain this frustrating lack of progress: the heterogeneity of the patient population, the interrelationships that exist between all manifestations of gastric motor activity rendering it difficult to isolate one phenomenon and the lack of selectivity of available agents, not to mind the potential influence of stress and other central and neurohumoral factors. In regard to the latter, it has been shown that corticotropin-releasing hormone reduces basal fundic tone[19] and that ghrelin levels are lower in functional dyspepsia, independent of gastric emptying rate.[21] As an extension of the latter finding, Akamizu *et al*.,[22] by administering ghrelin, were able to increase hunger and show a trend towards an increase in weight gain among six patients with functional anorexia who fulfilled criteria for functional dyspepsia. Finally, it must also be remembered that accelerated, as well as delayed, gastric emptying can cause dyspeptic symptoms.[23]

Visceral hypersensitivity plays a major role in all functional disorders and is thought to be present in 30-40% of patients with functional dyspepsia based largely on the rather invasive barostat technique. The majority of functional dyspepsia patients describe their symptoms as being most prominent after food ingestion; the less invasive water load test has, therefore, been widely employed as a surrogate to assess the response of the stomach to distension. Using this approach, van den Elzen *et al*.[24] were able to show that, whereas antral distension limited water intake in functional dyspepsia, other symptoms such as bloating, pain and fullness were more closely related to the volume of the proximal stomach. One therapeutic approach that has been utilized in functional dyspepsia, as in other functional disorders, is the use of low-dose antidepressant therapy. The precise mode of action of these compounds in this setting is unclear. Choung *et al*.[25] could find no effect of low-dose nortriptyline or mirtazapine on satiation or gastrointestinal symptoms in response to a nutrient load in healthy volunteers.

Aberrant cerebral processing of visceral stimuli and visceral events has been well documented in functional

disorders of the esophagus and intestine but, until recently, was scarcely explored in functional dyspepsia. Now, Vandenberghe *et al*.[26••] have shown that, although functional dyspepsia patients and control participants both activate the lateral pain system in response to gastric distension, the medial pain system is not activated in functional dyspepsia. Furthermore, activation of components of the lateral pain system occurs at lower distending pressures among those functional dyspepsia patients who demonstrate evidence of visceral hypersensitivity.

In recent years, other avenues of pathophysiology have been explored in IBS, including genetics and the potential roles of infection and inflammation; some interest is now being shown in these areas in functional dyspepsia. Although evidence to date does not suggest a significant genetic contribution to functional dyspepsia,[27] some evidences have emerged to suggest an interaction between polymorphisms of genes responsible for components of the immune response and *Helicobacter pylori* infection among some patients with functional dyspepsia.[28] Others have shown differences in the phenotype of intraepithelial lymphocytes in *H. pylori*-negative functional dyspepsia patients[29] and others still prominent eosinophils in the first and second parts of the duodenum.[30••] The precise significance of these findings remain unclear; they do not appear to represent, at least in the case of eosinophilia, part of a generalized eosinophilic disorder;[30••] whether they reflect the mucosal response to some luminal factor remains to be defined. These findings not only raise new possibilities in the pathogenesis of functional dyspepsia but also reinforce the importance of the duodenum in this disorder.

Dyspepsia: Management Strategies

What of the management of dyspepsia? In the patient with uninvestigated dyspepsia, the clinician may choose from a number of management approaches: test for *H. pylori* and treat accordingly (the so called 'test and treat' approach), proceed forthwith to endoscopy, or treat empirically with a proton pump inhibitor. In the latest updates of the Cochrane Collaboration Reviews on the pharmacological treatment for and the impact of *H. pylori* on dyspepsia, Moayyedi *et al*.[31,32] consider the relative merits of each of these approaches in considerable detail and conclude, first, that proton pump inhibitors (PPIs) are effective in the treatment of dyspepsia and, second, that although early endoscopy and *H. pylori* testing may benefit some patients, this approach is not cost effective. In a head-to-head comparison of the two approaches, Ford *et al*.[33] found that 'test-and-treat' was more cost effective than prompt endoscopy, though the latter was marginally more likely to result in a cure. Clearly, several factors will influence the choice of approach in a given patient, including, age and gender, as well as the background prevalences of *H. pylori* positivity, peptic ulceration and gastric cancer. The impact of the prevalence of *H. pylori* was nicely demonstrated by Barton *et al*.[34] who found that empiric PPI therapy was the most cost-effective approach among younger patients in whom infection was less likely, although a 'test-and-treat' strategy was more effective among 60 year olds. Endoscopy was the least cost-effective strategy across all age groups. In relation to endoscopy, it is also important to note that, when formally tested, the 'reassurance value' of a negative endoscopy could not be demonstrated in patients with functional dyspepsia.[35] In contrast, others found that a patient's knowledge of their *H. pylori* status led to less recourse to healthcare services in the following year.[36]

Traditionally, the clinician has also relied on the identification of 'alarm' symptoms to guide the initial management of the dyspeptic patient; the recent meta-analysis by Vakil *et al*.[37] makes for sobering reading in this regard. These authors found 'alarm' features poorly predictive of malignancy, with their sensitivity varying from zero to 83% and specificity from 40 to 98%. Although the clinical diagnosis of the clinician was very specific (97-98%), it was poorly sensitive (11-53%). These findings further reinforce the vague nature of the concept of dyspepsia.

What of the management of the patient who is deemed to have functional dyspepsia? Here, the options narrow further. Again we have the conclusions of an updated Cochrane Review to guide us. Of the various therapies evaluated, only prokinetics [relative risk reduction (RRR) 33%, 95% confidence interval (CI) 18-45%] and PPIs (RRR 13%, 95% CI 4-20%) were judged to have a significant benefit.[31] The benefits for all agents were, however, small. It is important to note that they expressed a concern that the prokinetic result could have been

favorably influenced by publication bias. Furthermore, some of these prokinetic agents have been withdrawn and others have never been approved for use in the United States. Hiyama *et al*.[20••] came to a similar conclusion and also pointed out that benefit for prokinetics had, for the most part, been shown in short-term studies only.

The overlap between GERD and functional dyspepsia undoubtedly influences the response to PPIs given that the 'overlap patient' most likely to respond to PPI therapy is the functional dyspepsia patient with heartburn. Similarly, a failure to exclude (or, perhaps the impossibility of excluding) all GERD patients from some functional dyspepsia studies may explain the response to PPIs in functional dyspepsia. Similarly, in a recent meta-analysis,[38] the benefits of PPI therapy in functional dyspepsia accrued only to those who were classified as 'reflux-like' or 'ulcer-like' and not to those who were 'motility-like'. Just as the presence of GERD symptoms may predict PPI responsiveness, the prominence of IBS-type symptoms augurs failure.[39] Overall, PPIs do work in dyspepsia, albeit in a minority of patients. For example, in a large population with heartburn, epigastric pain, or both symptoms, PPI therapy or a 'test-and-treat' strategy were equally effective at 1 year in terms of symptom resolution, impact on quality of life and cost effectiveness.[40] Unfortunately, an early response (i.e. 1 week) to PPI is not very predictive of long-term outcome.[41,42]

Given the relative ineffectiveness of PPI therapy in functional dyspepsia, as well as the reported prevalence of motor dysfunction in many of these patients, efforts have continued to find a prokinetic or motility-modulating agent that offers therapeutic benefit. Hopes were raised by a positive phase II study in functional dyspepsia with a new generation prokinetic agent, itopride,[43] only to be dashed by two subsequent and, as yet, unpublished negative phase III studies. Efforts continue to find a fundic relaxing agent that not only relieves symptoms but also has a favorable adverse event profile.[44]

The benefits of identifying those functional dyspepsia patients who are *H. pylori* positive and proceeding to eradication have also been assessed in several studies and meta-analyses with conflicting results. The confusing literature on this topic may be best summarized as demonstrating, at best, a small long-term (i.e. at 12 months) increase in cure rate among the eradicated but at the cost of testing and prescribing triple therapy for a very large number of functional dyspepsia patients who do not derive benefit.[45] Other factors such as a desire to prevent gastric cancer may dictate strategies.

What options are left to the frustrated and disappointed patient and physician? Talley[46] suggests turning to a central approach at this stage. In this regard, one is basing one's decisions more on clinical experience and extrapolation from IBS rather than on substantive evidence. Many, based on their experience in IBS and on the frequent overlap between IBS and functional dyspepsia (especially among those who are not responders to PPIs), as well as some data, will try either an antidepressant or an anxiolytic. Again reflecting experience in IBS, melatonin has also been shown to relieve symptoms in functional dyspepsia.[47] A recent meta-analysis[48] as well as yet another Cochrane review[49] evaluated the impact of psychological interventions in functional dyspepsia and concluded that there was insufficient evidence to confirm their efficacy, despite reports of benefits for both psychotherapy and hypnotherapy in individual studies.

It should come as no surprise in this climate of therapeutic nihilism that functional dyspepsia patients commonly resort to alternative remedies.[50,51] These are not to be dismissed as some, such the herbal extract, STW 5 or iberogast, have been shown to have modest efficacy in well conducted trials.[52]

Conclusion

In summary, precise definitions are needed for dyspepsia and functional dyspepsia, and future trials should include strict criteria to avoid unnecessary confusion. As we come to understand the pathophysiology of these complex disorders, novel agents (e.g. visceral analgesics) may offer therapeutic hope.

References

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

1. Halder SL, Locke GR 3rd, Schleck CD, *et al*. Natural history of functional gastrointestinal disorders: a 12-year longitudinal population-based study. Gastroenterology 2007; 133:799-807.
   •• This study describes in detail the natural history of functional gastrointestinal disorders (FGIDs) and of IBS and functional dyspepsia, in particular, and demonstrates that, although the point prevalence of both IBS and functional dyspepsia remained stable over the 12-year study period, there was substantial movement from one diagnosis to the other over time.
2. Minocha A, Wigington WC, Johnson WD. Detailed characterization of epidemiology of uninvestigated dyspepsia and its impact on quality of life among African-Americans as compared to Caucasians. Am J Gastroenterol 2006; 101:336-342.
3. Geeraerts B, Vandenberghe J, Van Oudenhove L, *et al*. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. Gastroenterology 2005; 129:1437-1444.
4. Halder SL, Locke GR, Schleck CD, *et al*. Influence of alcohol consumption on IBS and dyspepsia. Neurogastroenterol Motil 2006; 18:1001-1008.
5. Wildner-Christensen M, Hansen JM, De Muckadell OB. Risk factors for dyspepsia in a general population: nonsteroidal anti-inflammatory drugs, cigarette smoking and unemployment are more important than *Helicobacter pylori* infection. Scand J Gastroenterol 2006; 41:149-154.
6. Cremonini F, Locke GR, Schleck CD, *et al*. Relationship between upper gastrointestinal symptoms and changes in body weight in a population-based cohort. Neurogastroenterol Motil 2006; 18:987-994.
7. Ford AC, Forman D, Bailey AG, *et al*. Who consults with dyspepsia? Results from a longitudinal 10-yr follow-up study. Am J Gastroenterol 2007; 102:957-965.
   •• This study identifies factors which lead an individual with dyspepsia to seek medical care.
8. Talley NJ, Stanghellini V, Heading RC, *et al*. Functional gastroduodenal disorders. Gut 1999; 45(Suppl 2):II37-II42.
9. Tack J, Talley NJ, Camilleri M, *et al*. Functional gastroduodenal disorders. Gastroenterology 2006; 130:1466-1479.
10. Veldhuyzen van Zanten SJO, Flook N, Chiba N, *et al*, and for the Canadian Dyspepsia Working Group. An evidence-based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter pylori*. CMAJ 2000; 162:3-23.
11. Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia? JAMA 2006; 295:1566-1576.
12. Choung RS, Locke GR, Schleck CD, *et al*. Do distinct dyspepsia subgroups exist in the community? A population-based study. Am J Gastroenterol 2007; 102:1983-1989.
13. Haag S, Senf W, Häuser W, *et al*. Impairment of health-related quality of life in functional dyspepsia and chronic liver disease: the influence of depression and anxiety. Aliment Pharmacol Ther 2008; 27:561-571.
14. Keohane J, Quigley EMM. Functional dyspepsia and non-erosive reflux disease: clinical interactions and their implications. Med Gen Med 2007; 9:31-36.
15. Vakil N, van Zanten SV, Kahrilas P, *et al*. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006; 101:1900-1920.
16. El-Serag HB, Talley NJ. Systematic review: the prevalence and clinical course of functional dyspepsia. Aliment Pharmacol Ther 2004; 19:643-654.
17. Conchillo JM, Selimah M, Bredenoord AJ, *et al*. Air swallowing, belching, acid and nonacid reflux in patients with functional dyspepsia. Aliment Pharmacol Ther 2007; 25:965-971.
18. Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. Gastroenterology 2004; 127:1239-1255.
19. van den Elzen BD, van den Wijngaard RM, Tytgat GN, Boeckxstaens GE. Influence of corticotropin-releasing hormone on gastric sensitivity and motor function in healthy volunteers. Eur J Gastroenterol Hepatol 2007; 19:401-407.

20. Hiyama T, Yoshihara M, Matsuo K, *et al*. Meta-analysis of the effects of prokinetic agents in patients with functional dyspepsia. J Gastroenterol Hepatol 2007; 22:304-310.
•• This study nicely summarizes the frustrations of prokinetic studies in functional dyspepsia; overall there is no benefit for prokinetics; some individual drugs show some modest benefits.
21. Takamori K, Mizuta Y, Takeshima F, *et al*. Relation among plasma ghrelin level, gastric emptying, and psychologic condition in patients with functional dyspepsia. J Clin Gastroenterol 2007; 41:477-483.
22. Akamizu T, Iwakura H, Ariyasu H, *et al*, FD Clinical Study Team. Repeated administration of ghrelin to patients with functional dyspepsia: its effects on food intake and appetite. Eur J Endocrinol 2008; 158:491-498.
23. Lawal A, Barboi A, Krasnow A, *et al*. Rapid gastric emptying is more common than gastroparesis in patients with autonomic dysfunction. Am J Gastroenterol 2007; 102:618-623.
24. van den Elzen BD, Bennink RJ, Holman R, *et al*. Impaired drinking capacity in patients with functional dyspepsia: intragastric distribution and distal stomach volume. Neurogastroenterol Motil 2007; 19:968-976.
25. Choung RS, Cremonini F, Thapa P, *et al*. The effect of short-term, low-dose tricyclic and tetracyclic antidepressant treatment on satiation, postnutrient load gastrointestinal symptoms and gastric emptying: a double-blind, randomized, placebo-controlled trial. Neurogastroenterol Motil 2008; 20:220-227.
26. Vandenberghe J, Dupont P, Van Oudenhove L, *et al*. Regional cerebral blood flow during gastric balloon distension in functional dyspepsia. Gastroenterology 2007; 132:1684-1693.
•• This study extends observations made with advanced imaging techniques in IBS to functional dyspepsia.
27. Lembo A, Zaman M, Jones M, Talley NJ. Influence of genetics on irritable bowel syndrome, gastro-oesophageal reflux and dyspepsia: a twin study. Aliment Pharmacol Ther 2007; 25:1343-1350.
28. Arisawa T, Tahara T, Shibata T, *et al*. Genetic polymorphisms of molecules associated with inflammation and immune response in Japanese subjects with functional dyspepsia. Int J Mol Med 2007; 20:717-723.
29. Gargala G, Lecleire S, François A, *et al*. Duodenal intraepithelial T lymphocytes in patients with functional dyspepsia. World J Gastroenterol 2007; 13:2333-2338.
30. Talley NJ, Walker MM, Aro P, *et al*. Nonulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. Clin Gastroenterol Hepatol 2007; 5:1175-1183.
•• From data generated in a population study in Sweden, the authors report a significant association between duodenal mucosal eosinophilia and dyspepsia.
31. Moayyedi P, Soo S, Deeks J, *et al*. Pharmacological interventions for nonulcer dyspepsia. Cochrane Database Syst Rev 2006:CD001960.
32. Moayyedi P, Soo S, Deeks J, *et al*. Eradication of *Helicobacter pylori* for nonulcer dyspepsia. Cochrane Database Syst Rev 2006:CD002096.
33. Ford AC, Qume M, Moayyedi P, *et al*. *Helicobacter pylori* 'test and treat' or endoscopy for managing dyspepsia: an individual patient data meta-analysis. Gastroenterology 2005; 128:1838-1844.
34. Barton PM, Moayyedi P, Talley NJ, *et al*. A second-order simulation model of the cost-effectiveness of managing dyspepsia in the United States. Med Decis Making 2008; 28:44-55.
35. van Kerkhoven LA, van Rossum LG, van Oijen MG, *et al*. Upper gastrointestinal endoscopy does not reassure patients with functional dyspepsia. Endoscopy 2006; 38:879-885.
36. Ford AC, Forman D, Nathan J, *et al*. Clinical trial: knowledge of negative *Helicobacter pylori* status reduces subsequent dyspepsia-related resource use. Aliment Pharmacol Ther 2007; 26:1267-1275.
37. Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology 2006; 131:390-401.
38. Wang WH, Huang JQ, Zheng GF, *et al*. Effects of proton-pump inhibitors on functional dyspepsia: a meta-analysis of randomized placebo-controlled trials. Clin Gastroenterol Hepatol 2007; 5:178-185.
39. Gwee KA, Hwang JE, Ho KY, *et al*. In-practice predictors of response to proton pump inhibitor therapy in primary care patients with dyspepsia in an Asian population. J Clin Gastroenterol 2008; 42:134-138.
40. Delaney BC, Qume M, Moayyedi P, *et al*. *Helicobacter pylori* test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). BMJ 2008; 336:651-654.

41. Talley NJ, Vakil N, Lauritsen K, *et al*, STARS I Study Group. Randomized-controlled trial of esomeprazole in functional dyspepsia patients with epigastric pain or burning: does a 1-week trial of acid suppression predict symptom response? Aliment Pharmacol Ther 2007; 26:673-682.
42. van Zanten SV, Flook N, Talley NJ, *et al*, STARS II Study Group. One-week acid suppression trial in uninvestigated dyspepsia patients with epigastric pain or burning to predict response to 8 weeks' treatment with esomeprazole: a randomized, placebo-controlled study. Aliment Pharmacol Ther 2007; 26:665-672.
43. Holtmann G, Talley NJ, Liebregts T, *et al*. A placebo-controlled trial of itopride in functional dyspepsia. N Engl J Med 2006; 354:832-840.
44. Boeckxstaens GE, Tytgat GN, Wajs E, *et al*. The influence of the novel 5-HT1A agonist R137696 on the proximal stomach function in healthy volunteers. Neurogastroenterol Motil 2006; 18:919-926.
45. Jin X, Li YM. Systematic review and meta-analysis from Chinese literature: the association between *Helicobacter pylori* eradication and improvement of functional dyspepsia. Helicobacter 2007; 12:541-546.
46. Talley NJ. How to manage the difficult-to-treat dyspeptic patient. Nat Clin Pract Gastroenterol Hepatol 2007; 4:35-42.
47. Klupin'ska G, Poplawski T, Drzewoski J, *et al*. Therapeutic effect of melatonin in patients with functional dyspepsia. J Clin Gastroenterol 2007; 41:270-274.
48. Hojo M, Miwa H, Yokoyama T, *et al*. Treatment of functional dyspepsia with antianxiety or antidepressive agents: systematic review. J Gastroenterol 2005; 40:1036-1042.
49. Soo S, Moayyedi P, Deeks J, *et al*. Psychological interventions for nonulcer dyspepsia. Cochrane Database Syst Rev 2005:CD002301.
50. von Arnim U, Peitz U, Vinson B, *et al*. STW 5, a phytopharmacon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. Am J Gastroenterol 2007; 102:1268-1275.
51. Melzer J, Rösch W, Reichling J, *et al*. Meta-analysis: phytotherapy of functional dyspepsia with the herbal drug preparation STW 5 (Iberogast). Aliment Pharmacol Ther 2004; 20:1279-1287.
52. Pilichiewicz AN, Horowitz M, Russo A, *et al*. Effects of Iberogast on proximal gastric volume, antropyloroduodenal motility and gastric emptying in healthy men. Am J Gastroenterol 2007; 102:1276-1283.

References

1. Halder SL, Locke GR 3rd, Schleck CD, *et al*. Natural history of functional gastrointestinal disorders: a 12-year longitudinal population-based study. Gastroenterology 2007; 133:799-807.
•• This study describes in detail the natural history of functional gastrointestinal disorders (FGIDs) and of IBS and functional dyspepsia, in particular, and demonstrates that, although the point prevalence of both IBS and functional dyspepsia remained stable over the 12-year study period, there was substantial movement from one diagnosis to the other over time.
2. Minocha A, Wigington WC, Johnson WD. Detailed characterization of epidemiology of uninvestigated dyspepsia and its impact on quality of life among African-Americans as compared to Caucasians. Am J Gastroenterol 2006; 101:336-342.
3. Geeraerts B, Vandenberghe J, Van Oudenhove L, *et al*. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. Gastroenterology 2005; 129:1437-1444.
4. Halder SL, Locke GR, Schleck CD, *et al*. Influence of alcohol consumption on IBS and dyspepsia. Neurogastroenterol Motil 2006; 18:1001-1008.
5. Wildner-Christensen M, Hansen JM, De Muckadell OB. Risk factors for dyspepsia in a general population: nonsteroidal anti-inflammatory drugs, cigarette smoking and unemployment are more important than *Helicobacter pylori* infection. Scand J Gastroenterol 2006; 41:149-154.
6. Cremonini F, Locke GR, Schleck CD, *et al*. Relationship between upper gastrointestinal symptoms and changes in body weight in a population-based cohort. Neurogastroenterol Motil 2006; 18:987-994.
7. Ford AC, Forman D, Bailey AG, *et al*. Who consults with dyspepsia? Results from a longitudinal 10-yr follow-up study. Am J Gastroenterol 2007; 102:957-965.
•• This study identifies factors which lead an individual with dyspepsia to seek medical care.
8. Talley NJ, Stanghellini V, Heading RC, *et al*. Functional gastroduodenal disorders. Gut 1999; 45(Suppl

2):II37-II42.
9. Tack J, Talley NJ, Camilleri M, *et al*. Functional gastroduodenal disorders. Gastroenterology 2006; 130:1466-1479.
10. Veldhuyzen van Zanten SJO, Flook N, Chiba N, *et al*, and for the Canadian Dyspepsia Working Group. An evidence-based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter pylori*. CMAJ 2000; 162:3-23.
11. Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia? JAMA 2006; 295:1566-1576.
12. Choung RS, Locke GR, Schleck CD, *et al*. Do distinct dyspepsia subgroups exist in the community? A population-based study. Am J Gastroenterol 2007; 102:1983-1989.
13. Haag S, Senf W, Häuser W, *et al*. Impairment of health-related quality of life in functional dyspepsia and chronic liver disease: the influence of depression and anxiety. Aliment Pharmacol Ther 2008; 27:561-571.
14. Keohane J, Quigley EMM. Functional dyspepsia and non-erosive reflux disease: clinical interactions and their implications. Med Gen Med 2007; 9:31-36.
15. Vakil N, van Zanten SV, Kahrilas P, *et al*. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006; 101:1900-1920.
16. El-Serag HB, Talley NJ. Systematic review: the prevalence and clinical course of functional dyspepsia. Aliment Pharmacol Ther 2004; 19:643-654.
17. Conchillo JM, Selimah M, Bredenoord AJ, *et al*. Air swallowing, belching, acid and nonacid reflux in patients with functional dyspepsia. Aliment Pharmacol Ther 2007; 25:965-971.
18. Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. Gastroenterology 2004; 127:1239-1255.
19. van den Elzen BD, van den Wijngaard RM, Tytgat GN, Boeckxstaens GE. Influence of corticotropin-releasing hormone on gastric sensitivity and motor function in healthy volunteers. Eur J Gastroenterol Hepatol 2007; 19:401-407.
20. Hiyama T, Yoshihara M, Matsuo K, *et al*. Meta-analysis of the effects of prokinetic agents in patients with functional dyspepsia. J Gastroenterol Hepatol 2007; 22:304-310.
    •• This study nicely summarizes the frustrations of prokinetic studies in functional dyspepsia; overall there is no benefit for prokinetics; some individual drugs show some modest benefits.
21. Takamori K, Mizuta Y, Takeshima F, *et al*. Relation among plasma ghrelin level, gastric emptying, and psychologic condition in patients with functional dyspepsia. J Clin Gastroenterol 2007; 41:477-483.
22. Akamizu T, Iwakura H, Ariyasu H, *et al*, FD Clinical Study Team. Repeated administration of ghrelin to patients with functional dyspepsia: its effects on food intake and appetite. Eur J Endocrinol 2008; 158:491-498.
23. Lawal A, Barboi A, Krasnow A, *et al*. Rapid gastric emptying is more common than gastroparesis in patients with autonomic dysfunction. Am J Gastroenterol 2007; 102:618-623.
24. van den Elzen BD, Bennink RJ, Holman R, *et al*. Impaired drinking capacity in patients with functional dyspepsia: intragastric distribution and distal stomach volume. Neurogastroenterol Motil 2007; 19:968-976.
25. Choung RS, Cremonini F, Thapa P, *et al*. The effect of short-term, low-dose tricyclic and tetracyclic antidepressant treatment on satiation, postnutrient load gastrointestinal symptoms and gastric emptying: a double-blind, randomized, placebo-controlled trial. Neurogastroenterol Motil 2008; 20:220-227.
26. Vandenberghe J, Dupont P, Van Oudenhove L, *et al*. Regional cerebral blood flow during gastric balloon distension in functional dyspepsia. Gastroenterology 2007; 132:1684-1693.
    •• This study extends observations made with advanced imaging techniques in IBS to functional dyspepsia.
27. Lembo A, Zaman M, Jones M, Talley NJ. Influence of genetics on irritable bowel syndrome, gastro-oesophageal reflux and dyspepsia: a twin study. Aliment Pharmacol Ther 2007; 25:1343-1350.
28. Arisawa T, Tahara T, Shibata T, *et al*. Genetic polymorphisms of molecules associated with inflammation and immune response in Japanese subjects with functional dyspepsia. Int J Mol Med 2007; 20:717-723.
29. Gargala G, Lecleire S, François A, *et al*. Duodenal intraepithelial T lymphocytes in patients with

functional dyspepsia. World J Gastroenterol 2007; 13:2333-2338.
30. Talley NJ, Walker MM, Aro P, *et al*. Nonulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. Clin Gastroenterol Hepatol 2007; 5:1175-1183.
•• From data generated in a population study in Sweden, the authors report a significant association between duodenal mucosal eosinophilia and dyspepsia.
31. Moayyedi P, Soo S, Deeks J, *et al*. Pharmacological interventions for nonulcer dyspepsia. Cochrane Database Syst Rev 2006:CD001960.
32. Moayyedi P, Soo S, Deeks J, *et al*. Eradication of *Helicobacter pylori* for nonulcer dyspepsia. Cochrane Database Syst Rev 2006:CD002096.
33. Ford AC, Qume M, Moayyedi P, *et al*. *Helicobacter pylori* 'test and treat' or endoscopy for managing dyspepsia: an individual patient data meta-analysis. Gastroenterology 2005; 128:1838-1844.
34. Barton PM, Moayyedi P, Talley NJ, *et al*. A second-order simulation model of the cost-effectiveness of managing dyspepsia in the United States. Med Decis Making 2008; 28:44-55.
35. van Kerkhoven LA, van Rossum LG, van Oijen MG, *et al*. Upper gastrointestinal endoscopy does not reassure patients with functional dyspepsia. Endoscopy 2006; 38:879-885.
36. Ford AC, Forman D, Nathan J, *et al*. Clinical trial: knowledge of negative *Helicobacter pylori* status reduces subsequent dyspepsia-related resource use. Aliment Pharmacol Ther 2007; 26:1267-1275.
37. Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology 2006; 131:390-401.
38. Wang WH, Huang JQ, Zheng GF, *et al*. Effects of proton-pump inhibitors on functional dyspepsia: a meta-analysis of randomized placebo-controlled trials. Clin Gastroenterol Hepatol 2007; 5:178-185.
39. Gwee KA, Hwang JE, Ho KY, *et al*. In-practice predictors of response to proton pump inhibitor therapy in primary care patients with dyspepsia in an Asian population. J Clin Gastroenterol 2008; 42:134-138.
40. Delaney BC, Qume M, Moayyedi P, *et al*. *Helicobacter pylori* test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). BMJ 2008; 336:651-654.
41. Talley NJ, Vakil N, Lauritsen K, *et al*, STARS I Study Group. Randomized-controlled trial of esomeprazole in functional dyspepsia patients with epigastric pain or burning: does a 1-week trial of acid suppression predict symptom response? Aliment Pharmacol Ther 2007; 26:673-682.
42. van Zanten SV, Flook N, Talley NJ, *et al*, STARS II Study Group. One-week acid suppression trial in uninvestigated dyspepsia patients with epigastric pain or burning to predict response to 8 weeks' treatment with esomeprazole: a randomized, placebo-controlled study. Aliment Pharmacol Ther 2007; 26:665-672.
43. Holtmann G, Talley NJ, Liebregts T, *et al*. A placebo-controlled trial of itopride in functional dyspepsia. N Engl J Med 2006; 354:832-840.
44. Boeckxstaens GE, Tytgat GN, Wajs E, *et al*. The influence of the novel 5-HT1A agonist R137696 on the proximal stomach function in healthy volunteers. Neurogastroenterol Motil 2006; 18:919-926.
45. Jin X, Li YM. Systematic review and meta-analysis from Chinese literature: the association between *Helicobacter pylori* eradication and improvement of functional dyspepsia. Helicobacter 2007; 12:541-546.
46. Talley NJ. How to manage the difficult-to-treat dyspeptic patient. Nat Clin Pract Gastroenterol Hepatol 2007; 4:35-42.
47. Klupin'ska G, Poplawski T, Drzewoski J, *et al*. Therapeutic effect of melatonin in patients with functional dyspepsia. J Clin Gastroenterol 2007; 41:270-274.
48. Hojo M, Miwa H, Yokoyama T, *et al*. Treatment of functional dyspepsia with antianxiety or antidepressive agents: systematic review. J Gastroenterol 2005; 40:1036-1042.
49. Soo S, Moayyedi P, Deeks J, *et al*. Psychological interventions for nonulcer dyspepsia. Cochrane Database Syst Rev 2005:CD002301.
50. von Arnim U, Peitz U, Vinson B, *et al*. STW 5, a phytopharmacon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. Am J Gastroenterol 2007; 102:1268-1275.
51. Melzer J, Rösch W, Reichling J, *et al*. Meta-analysis: phytotherapy of functional dyspepsia with the herbal drug preparation STW 5 (Iberogast). Aliment Pharmacol Ther 2004; 20:1279-1287.
52. Pilichiewicz AN, Horowitz M, Russo A, *et al*. Effects of Iberogast on proximal gastric volume,

antropyloroduodenal motility and gastric emptying in healthy men. Am J Gastroenterol 2007; 102:1276-1283.

Reprint Address
Eamonn M.M. Quigley, MD, FRCP, FACP, FACG, FRCPI, Department of Medicine, Clinical Sciences Building, Cork University Hospital, Cork, Ireland Tel: +353 21 490 1228; E-mail: e.quigley@ucc.ie

Curr Opin Gastroenterol. 2008;24(6):692-697.