

## EVALUATION AND MANAGEMENT OF DYSPEPSIA – CURRENT PERSPECTIVES

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### Key points

- o Spend time taking a good history and performing a physical examination even though the majority of patients have “functional” symptoms. Exclude “non-dyspepsia” conditions and be careful in excluding a “surgical” abdomen.
- o Consider gastroscopy or an ultrasound or CT scan of the abdomen, if alarm symptoms are present. The threshold to investigate should be lower with older male patients as there is a higher chance of organic disease.
- o When patients’ symptoms are unclear, a close follow-up and review is useful. Symptoms persisting over many months or years are unlikely to have an organic basis.
- o Explore, understand and address patients’ concerns including psychological problems. Patients need to be reassured.
- o Sensible advice on food/meal and lifestyle modifications is useful. Antacids often give immediate relief to acute dyspeptic symptoms. Gastroesophageal reflux symptoms may be atypical – a trial of PPI therapy may be useful. Patients with wind, bloating and discomfort often benefit from a course of prokinetic agents.

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## INTRODUCTION

Dyspepsia is a common yet poorly understood problem. In the majority of cases, no underlying structural abnormality can be identified and it then becomes a frustrating problem for both patients, who expect an explanation for their discomfort and doctors, who do not know what to do for these patients. Symptoms can be severe and occasionally incapacitating and it cannot be dismissed as a trivial problem. Taking into account the costs of doctor consultations, medications and utilization of healthcare services, impairment of work performance and absenteeism from work, dyspepsia is indeed a burden to society.<sup>1</sup>

### How prevalent is dyspepsia?

Dyspepsia is one of the most common complaints of patients attending a primary care clinic and constitutes at least 40% of cases in a gastroenterology practice.<sup>2</sup> Consultants however form a small proportion of the total; a large proportion, perhaps 70% of dyspeptics do not consult doctors but self-medicate with antacids or other medications that can be purchased “over the counter”.<sup>3</sup> Cross-sectional surveys performed on a Western population show that approximately 25% of the general population have recurrent dyspepsia over a 12-month period.<sup>3-9</sup> Data on Asians although sparse, show similar figures.<sup>10-13</sup>

### Definition of dyspepsia

There are numerous definitions of dyspepsia and patients and doctors often use it to mean different things. Many refer to any discomfort or pain in the abdomen as dyspepsia. The best definition is probably that of an International Working Party in 1991 who defined dyspepsia broadly as pain or discomfort centered in the upper abdomen.<sup>14</sup>

Dyspepsia can be divided into organic and functional dyspepsia (FD). Organic dyspepsia refers to peptic ulcer disease, gastric cancer, oesophagitis or other structural abnormalities in the upper gastrointestinal tract. The great majority of patients varying from 50-90% of patients suffer from what is termed as functional or non-ulcer dyspepsia. Functional dyspepsia is a clinical syndrome that encompasses several heterogeneous disorders where no definite structural cause can be found to explain the symptoms.

Dyspepsia connotes a relationship to the upper gastrointestinal tract and symptoms should be related to meals. Many symptoms constitute the clinical syndrome of dyspepsia; these symptoms are as shown in Box 1. These symptoms may occur singly but usually multiple symptoms occur together. The description of symptoms and terminology vary geographically and reflect the local cultural and social background of the population studied (Box 2).

**Box 1. Dyspeptic symptoms**

- o Abdominal distension
- o Anorexia
- o Early satiety
- o Epigastric pain
- o Nausea
- o Post-prandial fullness
- o Wind

**Box 2. Dyspepsia terminology**

- o "Gastric"
- o Gastritis
- o Indigestion
- o Stomach flu

excluded reflux-like symptoms which was categorised under gastroesophageal reflux disease.<sup>15</sup> The Rome III working party recently presented their deliberations at the American Digestive Disease Week in May 2006 and, in their attempt to streamline terminology for research,<sup>16</sup> has added more confusion to the terminology. Functional Dyspepsia which is now referred to as "Dyspepsia Symptom Complex" is defined as the presence of one or more dyspepsia symptoms that are considered to originate from the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms.<sup>12</sup> These symptoms are listed in Box 1. In addition, the group recognised the relationship of symptoms and meals and have now sub-categorised dyspepsia into 2 groups which may overlap: (a) *Postprandial Distress Syndrome*, and (b) *Epigastric Pain Syndrome* (Figure 1). Although similar to the dysmotility-like and ulcer-like dyspepsia of Rome II, there are now several items for the criteria derived from factor analytic studies and physiological support instead of being based on the single symptom of epigastric discomfort or pain. Further studies will be needed to validate the usefulness of this change.

The Rome II Working Party definition is essentially the same as the International Working Party definition but specifically

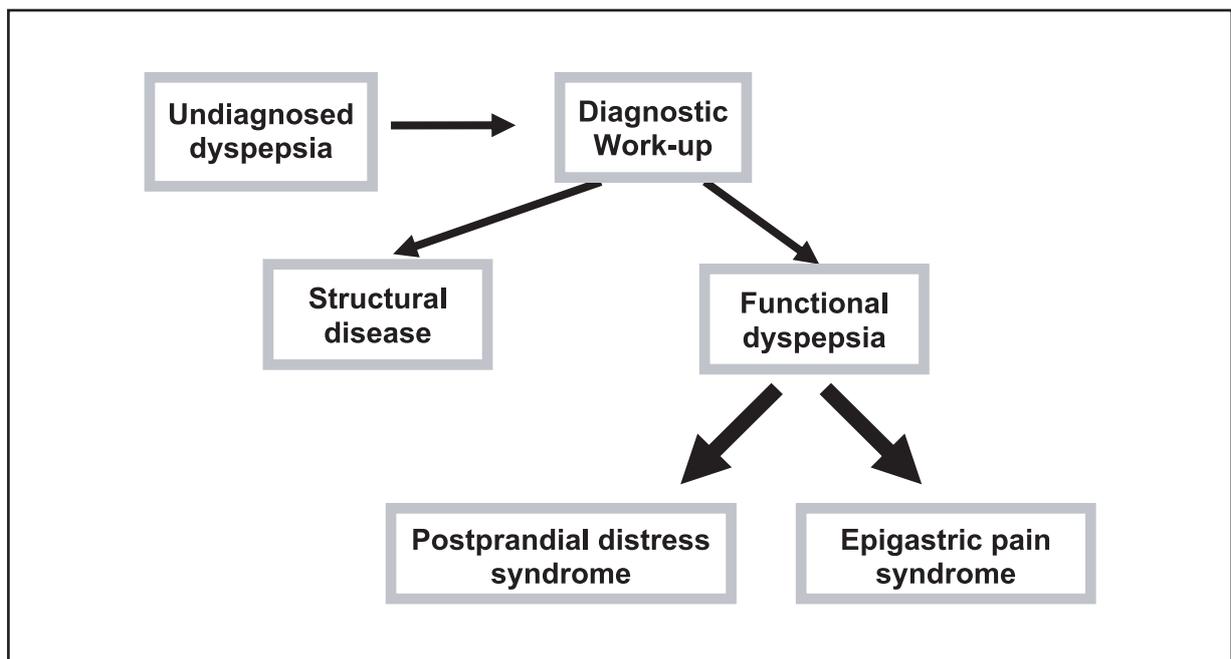


Figure 1. Dyspepsia and functional dyspepsia – Rome III definitions 2006

## CLINICAL EVALUATION OF DYSPEPSIA

Peptic ulcer pain is usually well localised and patients are able to point to the location of the pain in the epigastrium, the so-called finger-pointing sign. Nocturnal pains which wakes the patient up at night, when present, is characteristic of peptic ulcer disease. Classical symptoms may be masked because of the widespread use of acid-suppressing drugs. Nonetheless, a significant improvement in pain with H<sub>2</sub> antagonists and particularly proton pump inhibitors is highly indicative of peptic ulcer disease.

Symptoms suggesting cancer of the stomach include unrelenting, severe pain in the epigastrium, which is of recent onset. Concomitant loss of weight is usually a feature. It is important to note that elderly patients with cancer of stomach may present with minimal complaints or unexplained iron deficiency anemia. Cancer of the body of the pancreas also presents typically with persisting severe pain in the upper abdomen and may be completely missed on clinical examination. Pain radiating to the back and relief of pain when the patients assume knee-chest or a squatting position are characteristic of the disease. Up to 30% of patients may present with diarrhea as well.

Biliary pain is quite characteristic with severe sharp pains usually localised to the right hypochondrium and occurring intermittently for several hours at a time. Patients may have jaundice and may also complain of tea-colored urine and fever as well. Gallstones by themselves do not cause flatulence, abdominal discomfort or epigastric pain.<sup>17,18</sup>

Up to 20% of patients with irritable bowel syndrome suffer from dyspepsia as both conditions are not uncommon.<sup>19</sup> In fact, a generalized bloating sensation in the abdomen is a classical feature of irritable bowel syndrome together with bowel changes and lower abdominal pains. Functional dyspeptic symptoms are often less well described by patients and are usually poorly localised. The patients are constantly aware of their symptoms and the severity of symptoms is often disproportionate to the patient's well being. Symptoms however, are characteristically absent during sleep. Extra gastrointestinal complaints are common in patients with functional dyspepsia and include myalgia, headaches, poor sleep, dysuria, dysmenorrhoea and dyspareunia.

## PATHOPHYSIOLOGY OF FUNCTIONAL DYSPEPSIA

There is no single pathophysiological mechanism for FD. Several pathological processes occur alone or in combination. Pathophysiology of FD continues to be a confusing area to discuss.

Excessive acid secretion was believed to be responsible but several studies have failed to demonstrate an increased basal

or peak acid secretion.<sup>20,21</sup> One study however has shown an increase in acid secretion in response to intravenous gastrin releasing peptide in dyspeptic patients who were *Helicobacter pylori* positive.<sup>22</sup> Furthermore, if symptoms were due to acid, potent acid suppression would result in relief of symptoms. Symptom response to acid suppression in functional dyspeptic patients has been suboptimal. There is no evidence that direct instillation of acid into the stomach provoke symptoms.<sup>23</sup>

The relationship between *H. pylori* and functional dyspepsia remains tenuous.<sup>24</sup> *H. pylori* has not been consistently shown to be more prevalent in dyspeptic patients compared to normal controls. No consistent *H. pylori* specific symptomatology has been described and no specific underlying pathophysiological mechanism has been identified. Finally, response to treatment trials of *H. pylori* have not consistently resulted in improved symptoms. It is likely that *H. pylori* may be responsible for symptoms in a subset of patients and eradicating the bacterium in these patients would result in marked amelioration of symptoms. Gastric motility disorders have been described in up to 50% of patients with functional dyspepsia.<sup>25-27</sup> Delayed gastric emptying has been most frequently studied and has been shown to be very common. However the correlation of symptoms and motility disorders has not been consistent.

There has been recent interest in the role of visceral hypersensitivity. About half of all patients with functional dyspepsia have abdominal discomfort in response to gastric balloon distension and at lower pressures compared with healthy controls.<sup>28</sup> The mechanisms as to how patients develop gastric perception abnormalities are unclear. Gastric reflex relaxation or accommodation has been shown to be impaired but it is unclear if spinal or central processing pathways are abnormal in patients with functional dyspepsia.

Psychological factors including personality traits and psychiatric disorders in functional dyspepsia remain unclear. Whether psychiatric disease is a cause or a result of chronic functional dyspepsia and whether certain personality traits predispose a person to develop chronic symptoms are unclear.<sup>29-31</sup> Studies carried out so far have focused on consultants; it may be that underlying psychological factors or personality disorders drive patients to seek medical help for dyspepsia. The role of stress in provoking symptoms is also unclear.<sup>32-34</sup> Dyspeptic patients have a more negative perception of life events. This could of course be a result of chronic illness than a cause of the dyspepsia.

The role of various foods also remains controversial particularly in Asia. There is widespread belief that chili containing foods for example would provoke symptoms. This has not been proven. However it seems reasonable that patients should avoid foods that are known to provoke dyspepsia and this can vary from patient to patient. On the other hand, many patients report an aggravation of symptoms when they miss meals.

Excessive consumption of food at one meal has also been reported to cause symptoms as have consumption of specific foods particularly spicy or "oily" foods. Coffee, smoking and alcohol intake have not been clearly shown to be associated with dyspepsia.<sup>34</sup> Non-steroidal anti-inflammatory drugs particularly in higher doses have been shown to cause dyspepsia.<sup>35</sup> Numerous drugs, including metformin and various antibiotics, have been thought to cause dyspepsia although the mechanism of symptom generation is unclear (Box 3).

#### Box 3. Medications that can cause dyspepsia

- o Acarbose
- o Alendronate (Fosamax)
- o Antibiotics (e.g. erythromycin, metronidazole)
- o Aspirin
- o Herbal remedies
- o Iron
- o Metformin
- o NSAIDs
- o Orlistat
- o Potassium chloride
- o Theophylline
- o Vitamins

### THERAPEUTIC APPROACH TO UNINVESTIGATED DYSPEPSIA

In clinical practice where patients (and doctors) loosely label any patient with abdominal discomfort or pain as "dyspepsia", it is important firstly to exclude non-dyspepsia conditions. A careful history and physical examination would exclude muscular pain, costochondritis, herpes zoster infection of the abdominal wall and even acute coronary insufficiency. Once the patient is established to have dyspepsia, the overriding concern for the doctor is not to miss any serious underlying disease. Symptom patterns are insufficiently specific to allow a doctor to adequately discriminate between organic and functional dyspepsia. Patients with well-defined history of biliary pain, irritable bowel syndrome and gastro-esophageal reflux should be investigated and treated appropriately. Many patients with irritable bowel syndrome have symptoms of dyspepsia as well and it may be necessary to treat the predominant syndrome first. An acute surgical abdomen has to be excluded. Usually these patients present with pain acutely (as opposed to discomfort) and have abdominal tenderness and guarding. Atypical location of pain, for example in the epigastric region, in acute appendicitis has been observed.

Patients with alarm features including loss of weight, jaundice, and the findings of an abdominal mass and unexplained anemia should be investigated immediately (Box 4). In the absence of these symptoms, consideration of age and gender and the recent onset of symptoms may make a doctor order a

gastroscopy or abdominal scan. Patients with symptoms persisting over many months or years are unlikely to have any organic disease and need to be firmly reassured. Patients who have cancer phobia particularly those with a close family member suffering from a gastrointestinal malignancy deserve consideration for an early investigation.

#### Box 4. Indications for investigation of dyspepsia

- o Age over 45 years and recent onset of new symptoms
- o Clinical suspicion of ulcer, cancer or other organic disease
- o Unexplained anemia
- o Abdominal mass
- o Jaundice
- o Gastrointestinal bleeding
- o Fear of serious disease
- o Failure to respond to a therapeutic trial or rapid recurrence after cessation of therapy

### Investigations

Endoscopy is the first-line investigation for upper gastrointestinal symptoms. Where appropriate, an abdominal ultrasound is carried out to exclude biliary and pancreatic disease. With the advent of reliable and convenient non-invasive testing for *H. pylori* and the availability of effective, safe and tolerable treatment regimens, doctors have increasingly adopted a "Test and Treat approach" for the management of dyspepsia. This approach is most useful in areas of low to moderate prevalence of *H. pylori*; in areas of high prevalence this treatment strategy is probably limited. How does this help with upper gastrointestinal disease? In a young, low-risk individual, a negative test excludes with a high level of confidence, ulcer disease. On the other hand, the finding of a positive test and elimination of the bacteria in those tested positive removes the ulcer diathesis. In areas with high prevalence of cancer, this approach may result in missed diagnosis and endoscopy in patients with symptoms and alarm features should instead be performed. Where endoscopy is not available as in many parts of Asia, it may be reasonable to perform a Hp test as a cancer-screening test.<sup>36</sup> The "Test and Treat" approach results in decreased utilization of upper gastrointestinal endoscopy but the implications of this approach in general use and in different health systems and populations is not clearly known at the present moment. Clearly this approach is not targeted at treating dyspepsia and many patients will continue to have dyspepsia despite having *H. pylori* eliminated but the chance of missing ulcer disease without performing an endoscopy is virtually eliminated.

### Management of functional dyspepsia

Management can be divided broadly into non-drug measures and specific drug therapy.

### Non-drug measures

Patients with dyspepsia consult doctors for relief of their symptoms as well as to seek reassurance that they do not suffer from a serious illness such as cancer. Time and effort must be spent by the doctor on a clear explanation and a firm reassurance to the patient. The finding of a normal endoscopy is frequently helpful in allaying a patient's anxiety. Time should also be spent to explore any psychosocial issues and steps taken to remedy them where possible. Dietary and lifestyle modifications should be recommended where appropriate. Sensible advice as to timing of meals and avoidance of certain "aggravating" foods should be made. But care should be taken not to go "overboard" with advice on avoidance of foods because food aversion is highly individualised. Cessation of smoking and moderation of alcohol intake may be helpful and are in any case, good general medical advice. Reduction of stress particularly at the workplace and adequate rest and sleep may be important in the amelioration of symptoms and/or in helping patients cope with their discomfort.

### Specific drug treatment

Many patients expect or even demand specific drug treatment. This is particularly so in Asia where patients often perceived doctors as being better if they prescribe more medications. A large part of the efficacy of these drugs may be due to a placebo effect. In functional dyspepsia, placebo response rates of up to 40% have been reported.<sup>37</sup>

Treatment is prescribed on what doctors perceived as the possible underlying mechanism of functional dyspepsia. It is reasonable to prescribe antacids and acid-suppressing drugs for ulcer-like symptoms. In a systematic analysis of published studies, H<sub>2</sub> antagonists have been shown to be more effective than placebo. However many studies are of weak design and results are in actual fact difficult to interpret. Proton pump inhibitors have also been studied in FD. In the only Asian study, no improvement between PPI therapy compared to placebo was noted.<sup>38</sup> In other studies carried out in Western patients, potential misclassification of patients with GERD may have given a positive response compared to placebo.<sup>39,40</sup> For example in the study by Talley *et al*<sup>69</sup> improvement in symptoms were found in patients with ulcer and reflux-like symptoms. No improvement was seen in patients with dysmotility-like dyspepsia.

Prokinetic agents affect motility of the GIT by coordinating and promoting peristalsis throughout the whole GIT. Most practitioners would prescribe this agent when patients complain of bloating flatulence or abdominal distension as the main symptoms. Many clinical trials on prokinetic agents have been performed but many suffer from small sample size. Results from this individual studies show a beneficial effect compared to placebo and this is confirmed in a systematic analysis of the published data.<sup>41</sup> Many of these studies have used cisapride as the prokinetic agent. However, this drug is

no longer available for use in many countries. Newer agents have now been introduced including itopride hydrochloride which has shown good results in one international multinational study.<sup>42</sup> Other prokinetic agents which are also used include metoclopramide and domperidone but these agents have central nervous side-effects which are not present with cisapride or itopride. In an earlier meta-analysis, domperidone has been shown to have a beneficial effect on functional dyspepsia compared to placebo. Metoclopramide because of its sedative side-effects is mainly used for anti-emesis in clinical practice.

Other agents have also been tried and they include kappa receptor antagonists and other novel agents targeting at visceral hypersensitivity. None have however been used with adequate popularity. If therapy fails with one agent, it may be reasonable to try another class of drugs (*viz.* switching from H<sub>2</sub> antagonists to a prokinetic agent and vice versa). Generally, co-prescription with both types of drugs is not recommended. Patients seek relief from their symptoms and ultimately, treatment of FD is empirical.

Finally, patients with troublesome, persistent or recurrent symptoms should be closely followed-up, not just to determine treatment response but to look for onset of new symptoms and exclusion of organic disease which may not have been obvious in the first place.

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**Sung JJ, Lau JY, Goh KL, Leung WK, for the Asia Pacific Working Group on Colorectal Cancer. Increasing incidence of colorectal cancer in Asia: implications for screening. *Lancet Oncol.* 2005;6(11):871-6.**

This paper reviewed epidemiological data from several Asian countries and concluded that incidence of colorectal cancer has increased 2-4 times during the past few decades, especially in the more affluent societies. In Malaysia and Singapore, the Chinese have higher incidence of colorectal cancer than Malays and Indians. Changes in dietary habits and lifestyle, interacting with genetic factors, are postulated to be the reasons for the increased incidence.