American Gastroenterological Association Technical Review on the Evaluation of Dyspepsia

This literature review and the recommendations therein were prepared for the American Gastroenterological Association Clinical Practice and Economics Committee. The paper was approved by the Committee on April 22, 2005, and by the AGA Governing Board on October 6, 2005.

Since the publication of the initial technical review on evaluation of dyspepsia in 1998,[1] test and treat for *Helicobacter pylori* has become very widely accepted as the approach of choice in those with chronic dyspepsia but no alarm features.[2–6] However, this choice was based predominantly on the results of decision analyses, because limited management trial evidence was available 7 years ago. Indeed, in primary care, empirical antisecretory therapy continues to be often prescribed, but whether this is the most cost-effective and safest approach remains debated.[7–9] Further, gastroenterologists often still elect to undertake prompt esophagogastroduodenoscopy (EGD) in all cases to reassure both patient and physician and treat specific disease (eg, peptic ulcer, esophagitis, Barrett's esophagus, or malignancy) rather than rely on any kind of empirical approach.[9] However, it is known that the prevalence of *H pylori* infection has continued to dramatically decline, as has the identification of peptic ulcer disease and gastric (but not cardia or esophageal) adenocarcinoma at EGD.[9] Moreover, the prevalence of *H pylori* infection varies widely across the United States and is different by age and race.[10] The use of cyclooxygenase-2–selective nonsteroidal anti-inflammatory drugs (NSAIDs) was common but has declined whereas prophylactic use of low-dose aspirin is increasing, also variably affecting ulcer rates.[11,12] On the other hand, the prevalence of esophagitis detected at EGD may be increasing despite more rigorous and reliable classification (eg, the LA classification) for the presence of this condition.[13] Over-the-counter H_2 blockers and proton pump inhibitors (PPIs) mean that many patients end up on antisecretory therapy first anyway, regardless of what physicians recommend,[14] and their use may impair the ability of EGD to detect esophagitis or peptic ulceration.

Our aim was to review all the available management strategies in the literature and critically evaluate them to help develop practice recommendations for dyspepsia and functional (nonulcer) dyspepsia. To do this, MEDLINE and Current Contents searches were performed from April 1997 (the date of completion of the previous report) to July 2004 using the Medical Subject Heading (MeSH) terms dyspepsia, nonulcer dyspepsia, functional dyspepsia, and *H pylori*. In addition, specific searches were performed with the support of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group, and these will be highlighted in the appropriate sections. The reports that considered management of dyspepsia and functional dyspepsia were retrieved and reviewed, and their reference lists were checked for additional citations. The authors met to review the available data in order to produce currently applicable recommendations for the United States.

Definitions

The definition of dyspepsia remains controversial.[15] Guidelines from the United Kingdom[16] and Canada[4] use the term to mean all (or almost all) symptoms referable to the upper gastrointestinal tract, whereas the Rome II definition[17] excludes patients with predominant reflux symptoms. The rationale for the Rome II definition is that when classic heartburn or regurgitation are the only or predominant symptoms or occur frequently (more than once a week), objective evidence of gastroesophageal reflux disease (GERD) can often be identified. The problem is that there is no gold standard for diagnosing GERD; patients often find it difficult to describe a predominant symptom, and even when this is possible, the predominant symptom may change over time.[18] Furthermore, in clinical practice, there is considerable overlap among reflux and dyspeptic symptoms; in a Canadian study in primary care, the mean number of symptoms reported in patients labeled broadly as having dyspepsia was 6 and often included typical heartburn.[13] It is therefore difficult to establish the accuracy of predominant

Abbreviations used in this paper: CI, confidence interval; DOR, diagnostic odds ratio; EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; H_2RA, H_2-receptor antagonist; IBS, irritable bowel syndrome; NNT, number needed to treat; PPI, proton pump inhibitor; RR, relative risk.

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reflux symptoms for diagnosing GERD in the uninvestigated patient in primary care.

Despite these caveats, this review will follow the Rome II definition and the term "dyspepsia" here will be restricted to mean chronic or recurrent pain or discomfort centered in the upper abdomen (ie, the epigastrium); symptoms of reflux as defined above and acute abdominal conditions will not be included.[17] We have taken this view because the Rome II criteria or modified criteria have been and continue to be most widely used in large randomized controlled trials of new drugs for functional dyspepsia.[19,20] There are data that heartburn often overlaps with epigastric pain[13]; however, based on expert opinion, where symptoms of reflux are prominent, GERD should be the diagnosis until proven otherwise in gastroenterology practice.

Because meal-related symptoms are not discriminating, the relationship to meals has not been considered part of the definition, although it is likely that a large subset will have meal-related complaints.[1,21–23] It has been proposed that weight loss is a specific symptom of dyspepsia associated with early satiety and reduced oral intake, but this is controversial.[24,25] Bloating is difficult to localize to a specific abdominal site and is more typically a symptom of irritable bowel syndrome (IBS),[26] so it may be best not to consider this a characteristic feature of dyspepsia. It has been suggested that if the upper abdominal pain or discomfort is relieved by defecation or associated with altered stool symptoms, the diagnosis of IBS should be strongly entertained,[17] but the importance of this distinction is not established. Nausea can be due to gastric, intestinal, or extraintestinal causes; alone it is not sufficient to identify dyspepsia, although it may cluster with these symptoms.[27] Recurrent belching is common but is most often attributable to air swallowing[28] and alone is not considered to constitute dyspepsia in the absence of upper abdominal discomfort.

It is assumed here when identifying dyspepsia that the physician evaluating the patient, after the history and physical examination, considers the symptoms to probably arise from the upper gastrointestinal tract and not from the abdominal wall muscles, chest, or elsewhere.[1] The Rome committees have previously endorsed similar criteria.[17] "Uninvestigated dyspepsia" refers here to patients with symptoms of dyspepsia who have not undergone testing to exclude peptic ulcer disease or upper gastrointestinal malignancy. "Investigated dyspepsia" is used to describe patients who have had a relevant structural evaluation. "Functional dyspepsia" is a clinical syndrome; no evidence of peptic ulcer, upper gastrointestinal malignancy, or GERD has been found by definition on routine testing.

Scope of the Review

Reflux symptoms and epigastric pain are both treated with acid suppression and investigated with endoscopy; as noted previously, there is often overlap among symptoms. The review will focus on patients presenting with predominant epigastric pain or discomfort and will not assess the management of GERD.[29] The optimum management of Barrett's esophagus is also not addressed for similar reasons.[30,31]

The management of dyspepsia related to NSAIDs, including aspirin, is a significant problem. The appropriate management of the risk of peptic ulcer complications associated with long-term use of NSAIDs is also an important issue, but this is beyond the scope of this document.[32–34]

Epidemiology

The annual prevalence of recurrent upper abdominal pain or discomfort in the United States and other Western countries is approximately 25%; if frequent heartburn (defined as rising retrosternal burning pain or discomfort weekly or more often) is also considered, the prevalence approaches 40%.[1,35] The incidence of dyspepsia (number of new disease cases per population at risk) is poorly documented; however, in Scandinavia over a 3-month period, dyspepsia developed in $<1\%$.[36] Notably, the number of subjects who develop dyspepsia appears to be matched by a similar number of subjects who lose their symptoms, so the prevalence remains stable from year to year.[37,38] The pattern of individual symptom cycling in dyspepsia has not yet been adequately documented, but symptom relapse is probably the rule.

Definitions of dyspepsia also impact on the prevalence.[15] For example, in the US householder study of volunteers, the prevalence of dyspepsia was 13%; one third of the population had heartburn.[39] However, if heartburn and symptoms of IBS were excluded from the dyspepsia category, only 3% of the population still had a diagnosis of dyspepsia.[39]

Dyspepsia remains a costly, chronic condition, and drug costs in particular continue to increase rapidly.[40,41] In many cases, the symptoms are of short duration or mild severity and are self-managed.[1,42,43] Less than half in the United States and Europe seek medical care for their dyspepsia.[1,35,44] Even so, the management of dyspepsia represents a major component of clinical practice; 2%–5% of family practice consultations are for dyspepsia.[1,45] The factors that determine whether a patient