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Is Functional Dyspepsia of Particular Concern in Women? A Review of Gender Differences in Epidemiology, Pathophysiologic Mechanisms, Clinical Presentation, and Management

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Dyspepsia is a remarkably common symptom in the general population. Although multiple definitions have been used to describe the symptom, the most common explanation is that of chronic or recurrent pain or discomfort (a subjective negative feeling that may be associated with early satiety, fullness, bloating, or nausea) centered in the upper abdomen. When a thorough evaluation of a dyspeptic patient fails to identify a cause for her symptoms, the label of nonulcer or functional dyspepsia is applied. Functional dyspepsia is a heterogeneous disorder characterized by relapsing and remitting symptoms. Treatment strategies should focus on alleviating the most bothersome symptom and can be based on the proposed underlying pathophysiology. The effect of gender on mechanisms of disease, symptom presentation, and treatment response is an area of increasing interest and study. As with other functional gastrointestinal disorders, there appear to be some gender-specific features of functional dyspepsia. Specifically, gender-related differences have been observed in some studies of both the prevalence of individual dyspepsia symptoms, and in gastric emptying and proximal gastric motor function. There also appear to be gender differences in the psychosocial realm, with dyspeptic women experiencing a lesser sense of well-being than dyspeptic men, as well as an association of an abuse history with functional dyspepsia. This review will highlight specific gender differences related to the symptom presentation, pathophysiology, and approach to treatment of functional dyspepsia, while noting where differences have not been found and where further investigation is warranted.

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INTRODUCTION AND BACKGROUND

The term dyspepsia is often used imprecisely in clinical practice. Many definitions have been proposed, but the commonly accepted clinical definition is that of chronic or recurrent pain or discomfort (a subjective negative feeling that may be associated with early satiety, fullness, bloating, or nausea) centered in the upper abdomen (1–3). Part of the confusion related to the definition of dyspepsia relates to the broad differential diagnosis for the symptom. Although the focus here is on the gastrointestinal system, a complaint of pain or discomfort in the upper abdomen could be indicative of indigestion, angina, anxiety, or even a musculoskeletal disturbance. In some cases, a thorough clinical evaluation may reveal an underlying organic disturbance; however, many patients will have no identifiable structural or biochemical cause for symptoms and will be diagnosed with functional dyspepsia.

There is a growing literature related to this topic and several comprehensive reviews have been published in the past year (2, 4). Lack of consistent terminology has made it difficult to compare studies. In order to more precisely define dyspepsia, both clinically and for research purposes, the Rome III committee reconvened and, in April 2006, published new diagnostic criteria for functional dyspepsia (5). As defined by this committee, an individual must have one or more of the following symptoms *and* no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms: bothersome postprandial fullness, early satiety, epigastric pain, or epigastric burning. These symptoms must be present for the last 3 months with symptom onset at least 6 months before the diagnosis. Because of the confusion in nomenclature, new diagnostic categories of meal-induced dyspeptic symptoms, postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS), have been created with discreet criteria (Table 1) (5).

The purpose of this review is to evaluate gender differences in dyspepsia. The approach was via a MEDLINE search using the terms nonulcer dyspepsia or functional dyspepsia or functional bowel disorders and gender (differences), sex, or women. A separate search was performed for various medications referred to in the treatment section along with the terms for gender differences. Articles were retrieved and data reviewed in the areas of epidemiology, pathophysiology, clinical presentation, and treatment. It should be noted that, in

Table 1. Rome III Diagnostic Criteria* for Functional Dyspepsia

For *Clinical* Purposes the Following Criteria Must be Met:
1. The patient must experience at least one of the following symptoms: • Bothersome postprandial fullness • Early satiety • Epigastric pain • Epigastric burning and
2. There must be no evidence of structural disease (including at upper endoscopy) that could explain the symptoms
For *Research* Purposes the Following New Entities Have Been Described:
1. Postprandial distress syndrome, which must include at least one of the following: • Bothersome postprandial fullness, occurring after ordinary sized meals, at least several times a week • Early satiety that prevents finishing a regular meal, at least several times a week
2. Epigastric pain syndrome, which must include all of the following: • Pain or burning localized to the epigastrium of at least moderate severity at least once per week • The pain must be intermittent • The pain must be generalized or localized to other abdominal or chest regions • The pain must not be relieved by defecation or passage of flatus • Criteria must not be met for gallbladder and sphincter of Oddi disorders

*Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

the literature, there can be an overlap when the term "dyspepsia" is employed, even with the additional word "nonulcer" preceding it. As a result of this overlap, some of the retrieved articles included esophagitis, gastroesophageal reflux disease (GERD), and Barrett's esophagus. Particular overlap is seen in studies where there is no endoscopic evaluation to evaluate mucosal disease. This review will not address the gender issues related to esophagitis or upper gastrointestinal mucosal disease but will focus on functional dyspepsia.

EPIDEMIOLOGY

Dyspepsia is a significantly common symptom in the general population, accounting for up to 5% of visits to a primary care physician (6–8). New onset dyspepsia has been reported to occur in up to 10% of the population annually (9). Although estimates from different studies show a considerable degree of variation (8–54%), the prevalence of dyspepsia is typically reported as 25% in industrialized countries (2, 6, 9–12). The difference in prevalence is at least in part related to the use of different definitions (6, 9, 13, 14). Of those patients seeking medical attention for dyspeptic symptoms, many will have no obvious structural explanation for their symptoms and will be labeled as having functional or nonulcer dyspepsia (2, 15, 16).

It is generally accepted that most functional gastrointestinal disorders are more common in women than in men. This difference in prevalence between the sexes has been particularly noted related to irritable bowel syndrome (IBS) in our western society. In both patient and nonpatient populations, more women have been shown to suffer from symptoms of IBS than men (17). Few studies have rigorously examined gender differences in the incidence of functional dyspepsia. In those studies that have investigated the relationship between gender and dyspepsia prevalence, many have failed to identify an association. The U.S. Householder Survey of Gastrointestinal Disorders, for example, published national data on the frequency and sociodemographic features of 20 functional gastrointestinal disorders. Although women were more likely to report some functional disorders such as IBS and globus, there was no difference in the prevalence of functional dyspepsia between men and women (18).

Some epidemiologic studies of dyspepsia do demonstrate that the symptom is more common in women than in men. Results from the Domestic/International Gastroenterology Surveillance Study (DIGEST) showed that women were more likely than men to report relevant upper gastrointestinal symptoms in all countries evaluated except Japan (11). This difference in prevalence may relate to differences in healthcare seeking behavior and reporting of medical ailments between the sexes. Far fewer studies have been done to explore the prevalence of functional dyspepsia, perhaps because this would require recruiting random members of the population for an evaluation that includes an invasive procedure. Most epidemiologic studies of functional dyspepsia are based on patients who have been referred for endoscopy by their primary care provider and are therefore not representative of the general population. Two population-based studies of functional dyspepsia found no significant gender-based difference in prevalence (12, 19).

A study of a random sample of the adult population from Sweden evaluating GERD and erosive esophagitis reported no significant difference in the prevalence of dyspepsia between the sexes except in the oldest age group where women were noted to have more symptoms (20). In an additional report from this study available in abstract only, male gender was shown to predict esophagitis (21). Using the same study population, Aro *et al.* published the population-based study results of upper gastrointestinal symptoms. A random sample of the population of two adjoining communities in northern Sweden was surveyed for symptoms of dyspepsia, with a random subsample of responders offered endoscopy (22). The investigators in these published reports succeeded in their goal of performing a complete upper endoscopy with biopsies in one third of the study population. In doing so, they concluded that it is possible to conduct endoscopy studies in adult patients representative of the population at large. Among the patients eligible for endoscopy, there was a significant difference in symptom prevalence between men and women. At 3 months, more women than men in the group undergoing endoscopy reported epigastric pain/discomfort, dyspepsia, and abdominal pain (22). These results are portrayed in table format only; this was not the focus of the study nor reviewed in the discussion of results. It appears as

if the same population was later evaluated for an association between obesity and GERD (23). While sampling bias is a concern in these types of studies, this one in particular had a remarkably high rate of response and no statistically significant bias of this kind. A randomized study with arms to endoscopy *versus* other diagnostic strategies of patients with presumed functional dyspepsia has not been performed in the United States or elsewhere to date.

It is possible that some studies failed to show gender differences in epidemiologic realms because of select populations in certain centers and perhaps other factors such as health-care seeking behaviors of the subjects, recruitment strategies, and demographics. It is difficult to compare the studies and therefore explain the discrepancy between them because the experimental design, recruitment efforts, numbers of patients, and populations differ. It should be noted, however, that where no gender association is found, men and women may differ with respect to individual dyspepsia symptoms.

PATHOPHYSIOLOGY

There are many proposed pathophysiologic mechanisms for the development of dyspepsia. Although a great deal of research has focused on the pathophysiology of functional dyspepsia, there is no consensus on the precise mechanism of disease. In fact, the evidence to date suggests that functional dyspepsia is a heterogeneous disorder (24, 25). Abnormalities in visceral hypersensitivity, gastric motor function, gastric accommodation, *Helicobacter pylori* (*H. pylori*) and other infections, as well as psychosocial factors are among the more common theories of pathogenesis (26).

Functional gastrointestinal disorders, which include dyspepsia, are considered to be complex biopsychosocial disorders that in some way reflect a dysregulation or an abnormality of the brain–gut interaction or axis (27). Most of the research examining gender-related differences in these pathophysiologic mechanisms has been explored in IBS. There is limited research in the specific area of dyspepsia and there were no papers retrieved where the objective of the study was an exploration of pathophysiologic mechanisms based on gender.

Perhaps the presentation of functional dyspepsia in women could be influenced by gender-based differences in pain perception. Whereas such gender-based differences have been definitively shown in studies of animal models, the data from human subjects is far from clear-cut (28). Studies of somatic pain have shown that women tend to have lower thresholds for certain stimuli such as pressure and electrical stimuli (29). When compared with men, women also tend to experience a given somatic pain as more intense, and they tend to be less tolerant of the stimuli than men (29). The results of visceral pain studies are mixed (28, 30–32), which is interesting because it is proposed that visceral hypersensitivity is a serious candidate for the pathophysiologic mechanism of IBS and, as noted above, it is clearly more prevalent in women.

On average, patients with functional dyspepsia exhibit lower sensory thresholds during intragastric balloon distension than their control counterparts (33). Although this hypersensitivity is by no means a universal feature of functional dyspepsia, it is interestingly not associated with organic dyspepsia (34). Tack *et al.* suggest that the most useful way to express the degree of sensitivity to gastric distension is with a measurement of the increase in intraballoon pressure over intra-abdominal pressure (35). In his study, 34% of patients with functional dyspepsia demonstrated hypersensitivity to gastric distension and there was no significant difference observed between men and women. There was also a significant association between hypersensitivity and symptoms of postprandial pain, belching, and weight loss (35). There is one study that measured duodenal perception thresholds in four groups of patients: functional dyspeptics, functional dyspeptics with IBS, IBS patients, and controls. When compared with healthy controls, patients with functional dyspepsia, IBS, or both exhibited lower thresholds both to first perception of distension and to pain, which was defined as the maximal tolerated pressure (36). There were no gender differences identified in any of the sensory thresholds examined (36). In a study examining the use of the water-loading test as a less invasive surrogate for the barostat in relating proximal gastric function to sensory thresholds, the impact of gender was evaluated as a secondary outcome (37). In patients with functional dyspepsia but not controls, female gender was associated with lower tolerance (37). Whether this difference relates to anatomical or physiologic differences in the sexes has yet to be determined.

The observation that some healthy, premenopausal women experience gastrointestinal symptoms such as bloating and abdominal cramping during menstruation has led some investigators to question the role of sex hormones in visceral sensitivity. Some suggest a role for hormone-dependent inhibitory pathways in visceral sensitivity (29). According to this theory, women will experience enhanced visceral sensitivity as estrogen and progesterone reach their nadir before menstruation. This perimenstrual hypersensitivity is even more pronounced in women with IBS. Heitkemper *et al.* showed that women with IBS rated abdominal symptoms such as pain, nausea, and diarrhea as higher during menses than did healthy controls (38). It should be noted that even healthy women without IBS experience more gastrointestinal symptoms during menses and that the increase in pain in healthy women and those with functional bowel syndromes parallels other complaints such as poor school performance, cramps, and backaches (38). The role of ovarian hormones as they relate to symptoms is not entirely clear.

Abnormalities implicated in gastric motor function include delayed gastric emptying, antral hypomotility, and impaired gastric accommodation. The evaluation of the role of gastric emptying delay and dyspepsia has revealed some gender differences in most studies and none in others. It should be noted that literature from 20 years ago did report slower gastric emptying in normal women compared with men (39, 40).

There were no gender-related differences when assessing the rate of gastric emptying of both liquids and solids in patients with dyspepsia as reported in one study (41). Delayed gastric emptying, however, has been noted in women compared with men in most other studies (42, 43). One study of 343 patients with functional dyspepsia (43) did find that female sex is independently associated with delayed gastric emptying of solids. Another study showed that female gender was associated with delayed gastric emptying in both functional dyspeptics and in patients with diabetes (42).

In a study investigating the effect of gender and anxiety on gastric emptying in patients with functional dyspepsia, dyspeptic women were observed to have a significantly longer half-emptying time (119 $\pm$ 41 minutes) than dyspeptic men (78 $\pm$ 22 minutes) and female controls (96 $\pm$ 17 minutes) (44). Although not statistically significant, there was a trend toward greater distal gastric food retention in women with functional dyspepsia (44). The fact that gastric emptying in women with functional dyspepsia was delayed even in comparison with female controls suggests that this finding is not a normal gender variant. It is interesting to note that after correction for gender, the analysis showed that anxiety was associated with retention regardless of gender.

Delayed gastric emptying may be associated with complaints of postprandial fullness and vomiting (41, 43). Whether the relationship of gastric emptying with a sensation of fullness is causal or merely an association is unclear, because the studies to date have failed to show a definitive correlation (45, 46). Presumably, this mechanism alone is unlikely to explain functional dyspepsia.

A meta-analysis of 17 studies using scintigraphy to evaluate solid phase gastric emptying in functional dyspepsia showed that 40% of patients with functional dyspepsia exhibited delayed gastric emptying of solids (47). Specifically, the pooled data showed that it takes 1.5 times longer for half of a meal to empty the stomach (half-emptying time) in a patient with dyspepsia than it does in a control subject. The meta-analysis study (47) did note baseline differences in age and gender but linear regression analysis showed no significant influence of either age or gender on the $T\frac{1}{2}$ ratio (the ratio of the mean gastric half-emptying time of the patient group over that of the controls).

The discrepancies in the studies may be because of the selected populations, the differing study designs, or perhaps the heterogeneous etiology of the symptoms. It should be noted that many studies have shown there are no significant differences in gastric emptying during the menstrual cycle (48, 49), but others have shown some differences related to the cycle in either emptying (50) or the slow wave frequency as seen on electrogastrography (51). Whether the menstrual cycle could be a factor could not be ascertained by the studies discussed, as this was not evaluated.

Although some patients with functional dyspepsia have been shown to have gastric dysrhythmias, including but not limited to antral hypomotility, the significance of these abnormalities is also unclear (25, 46). A surprising number of control subjects in these studies have documented gastric dysrhythmias without dyspeptic symptoms. It is also unclear how many symptomatic patients actually display dysfunction and furthermore there is no clear benefit of prokinetic agents (25, 26, 46). There is no definitive study that has assessed gender differences with regard to gastric dysrhythmias.

Another problem of gastric motor function that has been implicated in functional dyspepsia is impaired accommodation of the proximal stomach. Under normal circumstances, the proximal stomach relaxes to accommodate food delivered from the esophagus. This relaxation permits the volume of the stomach to increase without substantially increasing the pressure in the stomach. The influence of gender on gastrointestinal motor function has been studied using the gastric barostat to quantify proximal gastric tone. In one such study, impaired gastric accommodation was demonstrated in 40% of patients with functional dyspepsia and was associated with symptoms of early satiety and weight loss (33). There were no significant differences in gender upon univariate analysis of the data (33).

However, in another study (52), healthy men and women exhibited no difference in either basal intragastric volume or proximal gastric relaxation until 30 minutes after a meal. From 30 to 90 minutes after a meal, however, women show significantly more gastric relaxation than male controls. This increase in proximal gastric relaxation was associated with higher ratings of abdominal pressure, nausea, and pain in women. Among patients with functional dyspepsia, the perception of sensation of stepwise pressure distensions is increased, although not statistically significant (52). This finding is likely related to a combination of disturbances in both accommodation and visceral sensitivity.

The role of *H. pylori* infection in functional dyspepsia is controversial. Infection with *H. pylori* commonly causes an inflammatory response and may lead to peptic ulcer formation, so it is not surprising that it can be associated with dyspepsia symptoms. Whether *H. pylori* infection can lead to dyspepsia in the absence of ulcer formation is yet to be demonstrated. In a study evaluating the role of *H. pylori* and dyspepsia in patients with IBS, female gender and *H. pylori* infection were found to be independent predictors of the presence of dyspepsia (53). The benefits of *H. pylori* eradication therapy in patients with functional dyspepsia are small but statistically significant in a systematic review of 12 trials, but there is no gender analysis in this paper (54).

The phenomenon of functional bowel disorders occurring after an infectious illness is recognized. In a study of 400 patients evaluated by a gastroenterologist because of meal-related epigastric pain, 17% were diagnosed with functional dyspepsia in the setting of probable acute infection (55). There was no significant difference in the prevalence of *H. pylori* infection in the patients with suspected postinfectious and unspecified-onset functional dyspepsia, suggesting that *H. pylori* is not the only pathogen involved (55). Although the mechanism has yet to be elucidated, an acute infection of the gastrointestinal tract may result in changes in visceral motor

and sensory function. There may be evidence of gastritis as well as increased mast cells in the lamina propria of patients with certain functional gastrointestinal disorders (56). In this study, there were no gender differences discussed; however, it should be noted that only 28 patients were studied and most were women.

The role of diet and food intake in the pathophysiology of functional dyspepsia is controversial. Functional dyspeptics commonly relate symptoms to food intake. Foods such as onions, peppers, citrus fruits, spices, fat, nuts, and chocolate have been shown to exacerbate symptoms, and anecdotal evidence suggests that functional dyspeptics snack more and are less likely to eat three meals a day than control subjects (57). Dietary modifications have some gender-specific features, with women having lower fat and carbohydrate intake than controls (57).

CLINICAL FEATURES

Symptom-Based Differences

Dyspepsia is typically considered a chronic syndrome; however, it is not uncommon for patients to report intermittent symptoms. When symptoms relapse and remit, individuals frequently return to their original symptom profile (58, 59). The most prevalent symptoms reported among functional dyspeptics at a tertiary care center were postprandial fullness and bloating followed by epigastric pain, early satiety, nausea, and belching (35).

Many investigators and clinicians have suggested dividing dyspepsia into symptom-based subgroups to aid in clinically identifying patients and possibly to help guide treatment (3, 13, 60–62). Initially these subgroups were based on symptom clusters, but the evidence to date suggests that this method is of limited utility (59, 63–65). Many of the studies have utilized the Rome II criteria (62), which suggested grouping patients with functional dyspepsia according to their predominant or most bothersome symptom (Table 2). As noted above, this set of criteria is now being replaced with the newer schema outlined by Rome III (Table 1). In order to understand the literature, it is important to understand that many studies separated dyspepsia into ulcer-like dyspepsia and dysmotility-like dyspepsia, and these subgroups were characterized by different clinical and pathophysiologic features (66). Whereas patients with ulcer-like dyspepsia typically complain of nocturnal pain, localized epigastric burning, and symptom improvement with food, those with dysmotility-like dyspepsia are more likely to report nausea, bloating, early satiety, abdominal fullness, and symptom aggravation with food (62, 65). Although not endorsed by the Rome II working committee, a third subgroup—reflux-like dyspepsia—has been used in some studies. Those who oppose this third subgroup argued that patients with reflux or heartburn have GERD until proven otherwise. The Rome III working group similarly acknowledges this overlap and notes that overlap of GERD with PDS or EPS likely occurs with significant frequency. The current recommendations suggest that patients with typical or frequent reflux should, at least provisionally, be diagnosed with GERD. The following section reviews the gender differences in symptom subgroups found in studies that are based largely on the older Rome II criteria.

Table 2. Predominant Symptom Subgroups

Ulcer-Like Dyspepsia	Dysmotility-Like Dyspepsia
Nocturnal pain	Nausea and bloating
Localized epigastric burning	Early satiety
Symptoms improve with food	Symptoms worsen with food

A 1993 study by Talley *et al.* concluded that identifying the dyspepsia subgroups before endoscopy—ulcer-like, dysmotility-like, reflux-like, and nonspecific—has little clinical utility (65). This study did note some gender differences. The following factors were all predictive of functional dyspepsia *versus* other diagnoses: being a woman, of younger age, experiencing frequent abdominal pain, having no relief with antacid therapy, and infrequent vomiting (65).

In the DIGEST study published by Stanghellini, women were more likely than men to exhibit dysmotility-like symptoms and to report ulcer-like symptoms as their most bothersome symptom (11). In another study by the same author, dyspepsia was shown to be more prevalent in women who were also more likely to have delayed gastric emptying than men regardless of symptom severity (43). Delivery of care and patterns of management have been shown to be similar across the various symptom subgroups as well as between male and female patients (67).

Gender-related differences in functional gastrointestinal disorders have been explored in a review by Mayer *et al.* When compared with men, women were found to be more likely both to note persistent episodic or chronic pain and to report multiple or recurrent pain symptoms, particularly in the abdomen and pelvis (29).

In addition to the gender differences in the subgroups noted above, a population-based study of symptoms and well-being has revealed that bloating, nausea, and early satiety are more commonly reported by women dyspeptics, whereas men are more likely to experience food regurgitation and heartburn (14). One might speculate that these men have true GERD rather than functional dyspepsia, yet people who only reported symptoms of heartburn, food regurgitation, or acid regurgitation were excluded from the dyspepsia group in this study.

Psychological Aspects and Sexuality

The psychosocial aspects of functional gastrointestinal disorders have long been debated. Emotional and environmental stresses affect not only gastrointestinal physiology but also symptom experience, illness behavior, and decisions regarding therapy (68). Likewise, the experience of chronic gastrointestinal symptoms can produce psychological distress (68). In comparison with people with chronic illnesses such

as diabetes, cancer, and hypertension, dyspeptics have been shown in at least one study to have poorer mental well-being (14). In fact, people with dyspepsia exhibited poorer mental well-being than all people with other comparison illnesses except for clinical depression in this study. Interestingly, it was also noted that, overall, women with dyspepsia had poorer physical and mental well-being than men with dyspepsia. The experience of nausea, which has previously been shown to have a negative impact on quality of life, strongly correlated with negative mental well-being (14). Studies have suggested that psychological factors are implicated in health-seeking behaviors of patients with IBS (69). In one study evaluating the role of psychological factors in consultation patterns in patients with dyspepsia, patients who sought medical attention reported greater severity of pain and longer duration of symptoms (70). Unlike the case with IBS, psychological factors were not significant predictors of health-care seeking behavior among patients with dyspepsia in this study. This study also concluded that women were at greater risk of seeking care.

In a survey of nearly 800 dyspeptic Australians, women suffered more damage to their mental well-being than men did (14). Why should women be more psychologically affected by dyspepsia than men? Although admittedly stereotypical, societal expectations have led men and women to perceive and therefore react differently to certain bodily functions (17). Some cultural or societal issues may lead to teaching girls and women to keep their bodily functions private, and they may therefore be more likely than men to be embarrassed by the need to belch or pass flatus. Whereas men and women might find bloating to be of equal discomfort, women may additionally be distressed by its effect on appearance. In one study of healthy volunteers, however, gender had no significant influence on frequency of flatus (71). Although there have been no studies specifically investigating the influence of culture or societal pressures on the psychological distress associated with functional dyspepsia, many authors have postulated a relationship (17, 72).

In one study assessing the association of functional gastrointestinal problems with patients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV diagnostic criteria for panic disorder, the prevalence of IBS and other functional gastrointestinal disorders including dyspepsia was found to be higher than found in the U.S. Household Survey (73). There were no gender differences found related to panic disorder and functional dyspepsia in this paper.

The correlation of sexual abuse with functional gastrointestinal disorders and particularly with IBS and functional dyspepsia has been noted. Sexual abuse is the most common abuse reported by patients with functional dyspepsia, with more women reporting abuse than men (74). In one study of 207 patients who met the Rome I criteria for IBS and/or dyspepsia (74), adulthood abuse was seen more commonly in these disorders; however, abuse was not an independent predictor of either disorder when psychological factors were controlled for during the analysis. In another study, frequency of rape or incest was 31% for patients who had functional gastrointestinal disorders (of which functional dyspepsia was considered) compared with 18% for those with organic gastrointestinal disorders (75). It has also been shown that, when compared with normals, patients who had a history of sexual abuse did demonstrate an increased risk for both IBS and functional dyspepsia (76). A more recent study of functional gastrointestinal disorders in women who reported domestic violence to the police found that most women who suffer such trauma have functional dyspepsia and/or IBS (77).

Sexual dysfunction has been reported to be higher in patients with functional bowel disorder *versus* controls (43.4% *vs* 16.1%). A decrease in sexual drive is most common. Dyspareunia has been reported in 16.4% of IBS patients but is rarely seen in patients with functional dyspepsia. Reports of sexual dysfunction appear to be associated with perceived severity of the gastrointestinal symptoms (78).

APPROACH TO TREATMENT

It has been more than 10 years since the FDA published guidelines on the inclusion of women and minorities in the design of studies of clinical research strengthening policies that were previously created (79). Those earlier guidelines required the inclusion of women and minorities in studies; however, the newer guidelines additionally required that the NIH (National Institutes of Health) make certain that women and minorities would be included in all human research, that in Phase III trials women and minorities must be included with valid numbers and mechanisms to detect differences in treatment effects, that cost would not be a reason for excluding these study subjects, and that outreach efforts would recruit subjects into studies. With these new guidelines the pharmaceutical companies have been required to do very careful analyses of any gender differences that have resulted in several motility medications being restricted to one gender or to certain age groups. In 2000 a new rule called the Clinical Hold Rule was adopted by the FDA. This rule allows the FDA to stop continuation of a clinical trial if the study sponsor plans to exclude women based on reproductive issues (80).

There are pharmacokinetic differences that exist between men and women. Pharmacodynamic differences are not well studied but it has been observed that women are more susceptible to torsades de pointes and QT prolongation (80). This is an interesting finding as cisapride, which was taken off the market for this side effect, was a promotility medication that may have been used in some patients with dyspepsia in the past.

There are a few interesting general facts that have been established about treatment in men *versus* women: women are greater utilizers of all medications (about 60% of total) and women report adverse events more often than men (80). It is also known that liver failure, although rare, occurs more frequently in women. In terms of specific gender differences in the treatment of dyspepsia, little is published or described.

In one study of gender differences in GERD (81), women were found to have a similar prevalence and symptom features as men; however, they had more severe symptoms but less Barrett's. Whether or not the higher severity of symptoms led to differences in treatment was not examined.

The most recent review of gender differences in medications for gastrointestinal problems resulted in restrictions of the approval of both alosetron, a 5-HT3 antagonist, and tegaserod, a partial 5-HT4 agonist. The former medication was developed for diarrhea-predominant irritable bowel patients and a greater female responsiveness was found with the initial FDA approval for women only. It is hypothesized that gender may contribute to differences in the serotonergic control of intestinal transit in these patients. This medication is currently available on a limited access basis because of the side effect issues. Tegaserod now has two FDA indications: (a) female patients with constipation-dominant IBS and (b) patients with chronic constipation under the age of 65. The restriction to women IBS patients is because of a gender difference in response to the medication. It should be noted that there are trials of tegaserod in progress for GERD and dyspepsia currently in Phase III (82).

Regardless of sex, patients who seek medical attention for dyspepsia symptoms require a careful evaluation with particular attention to the history of presentation. Symptoms of acid reflux should be considered carefully and, if after treatment, dyspepsia persists, a diagnosis of PDS or EPS could be concurrent (5, 62). Patients who are predominantly affected by heartburn should, therefore, undergo typical GERD evaluation and management. There are no gender restrictions for FDA approval of any of the H2 blockers or PPIs (proton pump inhibitors).

When a patient presents with true dyspepsia symptoms, the first step in the management algorithm is to identify any alarm symptoms. Weight loss, recurrent vomiting, jaundice, and anemia should direct the clinician toward early endoscopy regardless of gender. In the absence of alarm symptoms or the use of aspirin or nonsteroidal anti-inflammatory drugs, most gastroenterologists will employ the "test and treat" strategy which was recommended in a position statement and technical review by the American Gastroenterological Association (AGA) in 2005 (1, 2) and re-endorsed by the authors of the Rome III Criteria (5). According to this algorithm, patients are tested for *H. pylori* and treated if positive. The practice guidelines for the management of dyspepsia published in 2005 in the *American Journal of Gastroenterology* also endorse this strategy and suggest that using the test and treat option is best implemented in populations with a moderate-to-high prevalence of *H. pylori* (4). There are very little gender data in *H. pylori* treatment differences. There is one study from Turkey that found that age in men and smoking in women may decrease the efficacy of treatment (83). Those who test negative or who have persistent symptoms after *H. pylori* eradication should be treated empirically based on their most bothersome symptom (Table 2).

Tricyclic antidepressants (TCAs) may reduce gastric sensitivity and therefore be appropriate in patients with hypersensitivity to gastric distension (26). Patients with impaired gastric accommodation may benefit from a serotonin reuptake inhibitor (SSRI) or $5HT_1$ receptor antagonist, as both medications relax the proximal stomach in healthy controls (26). A meta-analysis study of the use of antidepressant medications showed these therapies to be effective in reducing the symptoms of functional gastrointestinal disorders; however, these conclusions were not specific to functional dyspepsia (84). It is unclear what the contribution of depressive symptoms and their treatment is to the effects observed (84). There are no studies to evaluate gender differences in the use of these medications specifically for dyspepsia. There are limited data in patients with depression. One study suggested that depressed women were more likely to respond to SSRIs than TCAs with the converse being true for men (85). There were also age differences with women over 40 having comparable responses to TCAs and SSRIs, but women under 40 showing a superior response to the SSRIs. Another study (86) showed that men had a superior response rate with imipramine (a TCA). Yet another study showed that the SSRI fluoxetine was not more effective than TCAs in women (87). These inconsistencies led to a subsequent study in 2003 that failed to find either that women had a preferential response to SSRIs or that men had a better response to TCAs (88). It is unclear if these findings can be applied to the treatment of dyspepsia that may be targeting a change in visceral sensitivity rather than depression. Further analysis and study of gender differences would be required in the future.

In a population-based study of patients seeking medical attention for dyspepsia symptoms, Ahlawat *et al.* reported a significant difference in the choice of initial management between male and female subjects. Men were significantly more likely than women to be treated with a PPI and there was a tendency for women to be treated with psychotropic agents even after adjusting for age and somatization scores (67).

In addition to the use of antidepressants, trials evaluating psychological therapies *versus* supportive care in the treatment of functional dyspepsia were highlighted in the AGA technical review. Although all four of the studies reviewed reported an improvement in symptoms with psychological intervention, the data could not be pooled and the overall quality of the evidence was insufficient to support these therapies (2). There were no gender analyses done.

If symptoms persist after empiric therapy, investigation with endoscopy is recommended. The timing of endoscopy should take into consideration the presence of any alarm factors as well as the age of the patient. Patients with refractory dyspepsia and negative endoscopic exams may benefit from dietary modifications, psychotherapy, or newer investigational drugs (7, 26, 89).

CONCLUSION

Gender-specific features of functional dyspepsia have been observed both in clinical practice and through the analysis of multiple studies. In particular, some studies have demonstrated gender-related differences in the prevalence of individual dyspeptic symptoms as well as in gastric emptying and motor function. Despite these observations, studies dedicated to the evaluation of gender-based differences are lacking. Some studies have attempted to analyze subgroups for gender differences as one factor but these data are difficult to pool for review. Some of the challenges in comparing studies include the lack of consistency of definitions, evaluation strategies, and management plans. A recent review cited these difficulties in addition to proposing a need for studies related to abuse and psychiatric diagnoses in men and women to appreciate the influence of gender roles and psychosocial issues (90).

The evidence to date suggests that functional dyspepsia is a heterogeneous disorder whereby multiple pathophysiologic mechanisms may be involved. Hormonal, environmental, and psychological factors are likely to play a role in both the manifestation and progression of the disorder. Despite the prevalence of dyspepsia symptoms among the general population, many people never approach a physician for further evaluation. Part of the problem is that many of these symptoms are not taken seriously by practitioners—especially once they have been labeled as being functional. The manner in which women with dyspeptic symptoms present to physicians and the subsequent assessment of the woman's symptoms by that physician would be of value to study. Physicians' attitudes toward women with dyspeptic symptoms have not been studied directly, but a study from 1983 investigating sex bias in the assessment of patient complaints in general by primary care doctors noted that physicians found female patients to be more emotional but no less ill than their male counterparts (91).

Although functional dyspepsia may not have an impact on patient mortality, the effect on quality of life can be dramatic. Successful management of these patients requires close follow-up, ample patient education, and support. Additional studies assessing gender-based differences should be encouraged in an effort to elucidate any information that will lead to an improved understanding of these issues and ultimately to an enhancement of patient care.

STUDY HIGHLIGHTS

- Dyspepsia is a common symptom.
- Many studies show that dyspepsia is more common in women.
- Dyspepsia appears to be a heterogeneous disorder with several hypothesized mechanisms of pathophysiology.
- Gender differences have been observed related to prevalence, gastric emptying, and psychosocial factors.
- There is an association of a history of abuse with dyspepsia.

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CONFLICT OF INTEREST

Suzanne Rose has acted as a speaker and consultant for Novartis and Takeda.