

# Medication Risk-Taking Behavior in Functional Dyspepsia Patients

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**OBJECTIVES:** No medication is approved for the treatment of functional dyspepsia (FD). The risks that patients would be willing to take to cure their FD symptoms are unknown.

**METHODS:** FD patients (Rome III criteria) were mailed a questionnaire that assessed demographics, medication use, and prior medication adverse events. Scales to measure FD severity, quality of life, anxiety, depression, impulsiveness, and risk-taking behavior were included. A standard gamble (SG) evaluated willingness to take risks associated with a theoretical FD medication. Data were analyzed using simple descriptive statistics.

**RESULTS:** One hundred and fourteen responses were analyzed (54.5% response rate). The mean age of the patients was 49.2 years; 84% were women and 96% were white. The mean duration of symptoms was 8.2 years (range 1–38 years). The most bothersome symptom was upper abdominal discomfort (25%), followed by upper abdominal pain (22%) and bloating (15%). Forty percent of respondents rated their FD symptoms as moderate and 31% as mild. Forty-six percent reported a side effect from a prescription medication used to treat FD. When asked about a hypothetical medication that could cure their FD symptoms, 49% of respondents reported that they would accept a mean 12.7% risk of sudden death for a 99% chance of cure.

**CONCLUSIONS:** This prospective study suggests that FD patients are surprisingly willing to take significant risks with a hypothetical medication to cure their symptoms. To counsel patients effectively and assist in the development of informed, preference-based decisions regarding medication therapy, physicians need to elicit and understand FD patients' risk adversity.

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**Subject Category:** Functional GI Disorders

## INTRODUCTION

Functional dyspepsia (FD) is defined as symptoms thought to arise in the gastroduodenal region in the absence of any organic, systemic, or metabolic disease thought to explain the symptoms.<sup>1</sup> Patients can be categorized into either postprandial distress syndrome (PDS) or epigastric pain syndrome (EPS) based on their predominant symptom; these subcategories appear to reflect accurately patients in clinical practice.<sup>2,3</sup> Other common symptoms include epigastric fullness, early satiation, postprandial nausea, and abdominal bloating.<sup>4–6</sup>

FD is a highly prevalent disorder that affects ~10% of United States adults.<sup>7–9</sup> The impact of FD on patients and society is impressive as it reduces quality of life<sup>10–12</sup> and imposes a significant negative economic impact to the health-care system. The Leeds UK HELP study determined that the costs of evaluating and treating dyspepsia were ~1 billion pounds per year.<sup>12</sup> A retrospective analysis of health insurance claims determined that FD patients incurred costs that were US \$5,138 greater than employees without FD,<sup>13</sup> whereas a second US study analyzing patient-reported costs and claims found that FD patients incurred additional expenses of more than US\$2,000/year.<sup>14</sup>

Surprisingly, despite the significant impact of FD on patients and society, no medication is currently approved for the treatment of FD. This results in patients and providers using a variety of medication trials to treat the multiple symptoms of FD.<sup>4,5,8,15</sup> However, both prescription and OTC medications are associated with adverse effects and some level of risk. FD patients' willingness to accept risks associated with the use of medications to treat their chronic symptoms has not been studied.

We designed this prospective study with the aim of identifying and describing FD patients' medication risk-taking behavior. We hypothesized that: (1) patients with more severe FD symptoms would be more willing to take greater risks for a hypothetical medication used to cure FD symptoms compared with patients with mild FD symptoms; and (2) that FD patients with impulsive behavior and those who engage in risk-taking behavior would be more willing to take risks associated with medication use. Secondary goals included analyzing self-reported medical side effects, evaluating anxiety and depression using the well-validated Hospital Anxiety and Depression (HAD) questionnaire, and determining the relationship of self-reported FD severity to anxiety, depression, and willingness to take medication risks.

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## METHODS

**Survey development.** We conducted this study at the Dartmouth-Hitchcock Medical Center (DHMC; Lebanon NH), which provides both primary care and tertiary care. As no survey existed to assess FD patients' willingness to accept risks associated with the use of medications, we developed one *de novo*. Specifically, we sought to describe quantitatively patients' risk-taking behavior, knowledge of risks associated with the use of medications, and, ultimately, their willingness to accept risks associated with medications used to treat FD symptoms. To ensure that our survey adequately addressed these domains, we asked the faculty and staff of the Division of Gastroenterology and Hepatology at DHMC to evaluate critically the content and clarity of the initial instrument, which we then revised.

Next, we convened a 90-min focus group with eight FD patients (Rome III criteria) to learn how to optimize the survey's inquiry into FD patients' illness experiences and risk adversity with the ease of its completion. First, patients carried on a free-flowing, open discussion about the use of medications for FD, their past experiences with medications, and their willingness to use medications for FD. Patients also discussed their use of medications in general and their willingness to take risks with medications. We dedicated the second half of the focus group to pilot testing the survey, at which time we asked focus group participants to review critically the clarity, format, and completeness of the questions, and ease and efficiency of taking the whole survey. We again revised the questionnaire to reflect solicited feedback.

Ultimately, the final survey (136 questions total) incorporated the following domains: demographics; FD symptoms; severity of FD symptoms; prior treatments sought to improve/cure them; comorbid conditions; side effects experienced from medication use; fears and concerns regarding a diagnosis of FD; knowledge of risks and risk-taking behavior (i.e., extreme sports, reckless driving); and risks of medications used to treat FD symptoms. Validated scales measured anxiety and depression (HAD; maximum score of 21 for either anxiety or depression; Zigmod and Snaith<sup>16</sup>) and impulsiveness.<sup>17</sup> Risk-taking behavior was assessed with a battery of questions and self-assessment. A standard gamble (SG) evaluated willingness to take risks associated with real and hypothetical irritable bowel syndrome (IBS) medications.<sup>18</sup>

**Design and sample.** After approval by the DHMC Institutional Review Board, we used the Dartmouth-Hitchcock Data Reporting System (HDRS) to identify patients diagnosed with FD (ICD-9 code 536.8) who had an office visit between January 2008 and June 2010; 291 patients met these initial inclusion criteria. From this patient population, we selected those who met several additional inclusion criteria, including those who: (1) were located in the geographic referral area for DHMC; (2) were age 18 years or over; and (3) who had current addresses on file. These files were then reviewed by one of the investigators (BEL) to verify that they met the Rome III criteria for FD.<sup>1</sup> Sixty-one patients were excluded because addresses could not be confirmed, they were outside of the mailing area, or an alternative diagnosis could be found. We collected demographic data, including gender,

age, income, and employment status, from all remaining survey participants (230). Although we numbered the initial wave of surveys for tracking purposes, the anonymity of responders was maintained. A small incentive (US\$2) was sent with the survey to thank patients for their time.

Data were manually entered and analyzed using the IBM SPSS Statistics Version 20.0 (SPSS, Chicago, IL, USA). Normality of data sets was determined using SPSS Explore and Descriptive functions. Stem-and-leaf plots and histograms were used to evaluate variable distributions and assess outliers. Normality plots were used to display normal probability and detrended normal probability plots as indicated. Where appropriate, the Kolmogorov–Smirnov statistic was used for testing normality. Frequency distributions were evaluated for all categorical variables (e.g., gender). Student's *t*-test and analyses of variance were performed to evaluate differences in demographic variable such as weight, height, or BMI among groups that were normally distributed. The Mann–Whitney test and Kruskal–Wallis one-way analysis of variance test were used to evaluate differences between groups when the assumptions of normality were not met. Tests for proportionality between groups were made using  $\chi^2$  tests with the Mantel–Haenszel odds ratios to quantify effects sizes between factors of interest. Summary statistics included point estimates and s.d.'s or 95% confidence intervals for all variables. All significance levels are set to  $P < 0.05$ .

## RESULTS

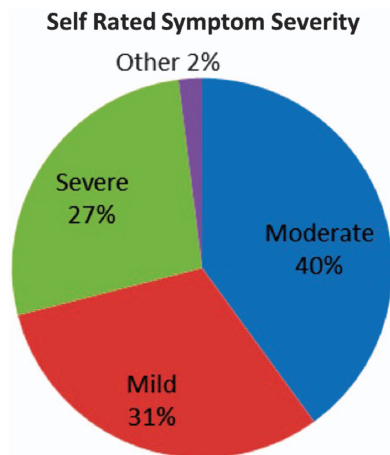
**Response rate and demographics.** We mailed questionnaires to 230 patients who met the inclusion and exclusion criteria for this study. Twenty-one envelopes were returned due to incorrect/outdated addresses, leaving 209 patients eligible for inclusion. One hundred and fourteen patients completed and returned the survey, yielding a response rate of 54.5%. The mean age of the patients was 49.2 years (s.d. = 15.8); 84% were women. Patients reported a mean of 3.8 (s.d. = 2.2) days per week with FD symptoms. The mean duration of symptoms was 8.2 years (range 1–38 years). Twenty-two percent of respondents were single, whereas 67% were married. Thirty-eight percent of patients had attended/completed high school and an additional 43% had attended/completed college. The criteria for PDS was present in 17.5%, EPS in 35.3%, and 31.0% were mixed. Additional patient demographics are shown in Table 1. Simple demographics (age, gender) of those with incorrect addresses and those who did not return the questionnaire were similar to those who returned the questionnaire.

**FD patient symptoms, fears, and concerns.** Thirty-one percent of FD patients rated their symptoms as mild, whereas 40% rated their symptoms as moderate (see Figure 1). The most bothersome symptom was upper abdominal discomfort (25%), followed by upper abdominal pain (22%) and bloating (15%). When asked what aspect of abdominal pain and discomfort associated with dyspepsia was most bothersome, 35% reported that the unpredictability of the pain/discomfort was the most bothersome aspect, whereas frequency (24%), severity (24%), and duration (18%) were somewhat less

**Table 1** Patient demographics (n = 114)

Mean age	49.2 years (±15.7)
<b>Gender</b>	
Women	84%
Men	16%
<b>Race</b>	
Caucasian	96%
Hispanic	2%
Asian	1%
African-American	1%
BMI (kg/m <sup>2</sup> )	26 (±5.8)
Mean duration of symptoms	8.2 years (±6.9)
<b>FD subtype</b>	
PDS	17.5%
EPS	35.3%
Mixed	31%
<b>FD severity—self-rated</b>	
Mild	31%
Moderate	40%
Severe	27%
<b>Self-rated description of risk-taking behavior</b>	
Takes risks routinely	13.2%
Takes risks occasionally	25.4%
Takes risks rarely	30.7%
Never takes risks	25.4%
Percent with health insurance	95.6 (US national average: 85%)
Percent with life insurance	60.5 (US national average: 78%)

BMI, body mass index; EPS, epigastric pain syndrome; FD, functional dyspepsia; PDS, postprandial distress syndrome.



**Figure 1** Self-rated symptom severity.

bothersome aspects. Aspects of abdominal pain/discomfort associated with FD were objectively rated on a 0–100 mm visual analog scale. Unpredictability of symptoms was rated highest with a median (interquartile range (IQR)) of 66 (32–90) mm, whereas duration of pain (60 mm; 34–85), severity of abdominal pain (56 mm; 31–80), and frequency (54 mm; 21–78) were rated somewhat lower (see Figure 2).

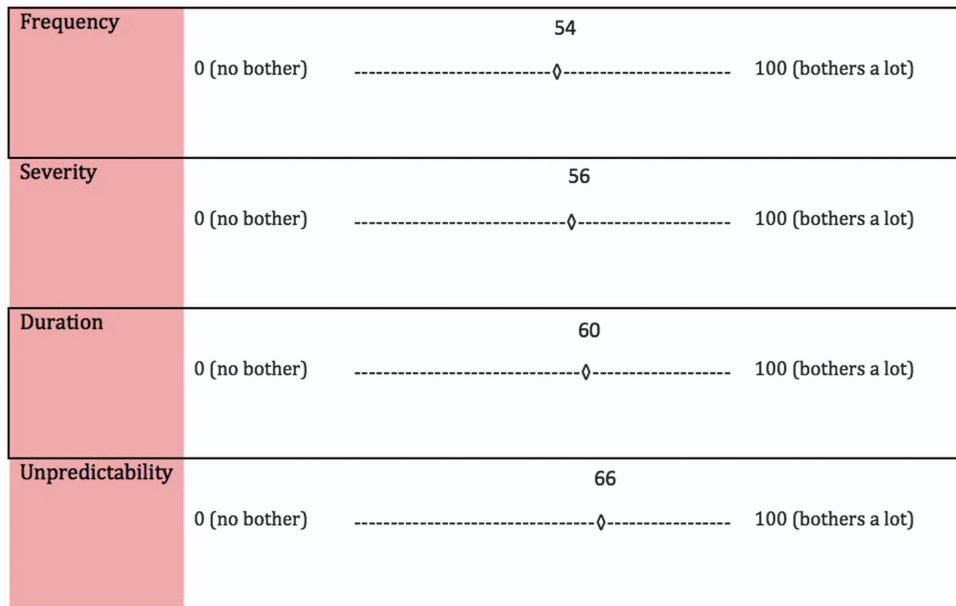
The concern that FD would adversely affect their lifespan was expressed by 11.5% of patients; 9.7% reported concern

that FD would increase their risk of developing stomach cancer. When asked to project the natural history of their FD symptoms, 40.7% reported that their FD symptoms will never go away, 7.1% believed that their FD symptoms would worsen with time, and 16.8% stated that their FD symptoms would stay the same. FD patients overestimated their median (IQR) lifetime risk of developing any cancer at 50% (50–73%), in contrast to reported lifetime estimates of developing cancer from the American Cancer Society of 45% in men and 38% in women (<http://www.cancer.org/cancer/cancerbasics/lifetime-probability-of-developing-or-dying-from-cancer>).

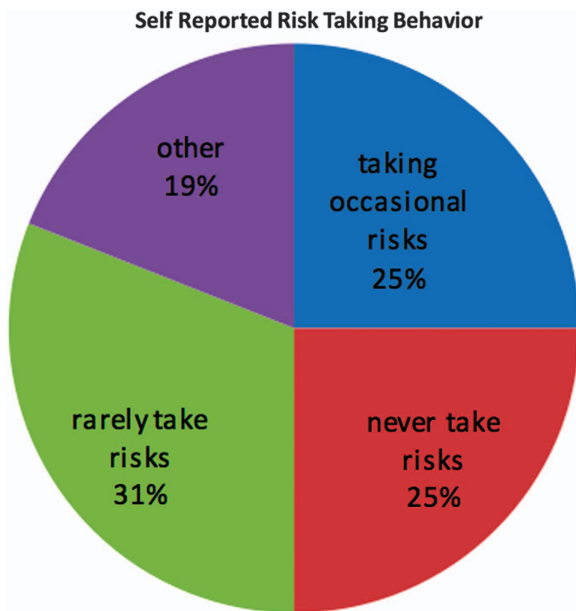
**Risk-taking behavior and impulsivity.** Life and health insurance rates, in addition to self-reported risk-taking behavior, are noted in Table 1. Occasional risk taking was reported by 25% of patients, whereas another 25% reported never taking risks (see Figure 3). Most FD patients reported having health insurance (96%), whereas only 61% reported having life insurance. Patients with life insurance did not show an increased tendency for taking risks with a hypothetical medication designed to cure FD compared with those without life insurance (2 (0–9.25) vs. 0 (0–6);  $P=0.236$ ). No association was found between those with and without health insurance and medication risk-taking behavior ( $P=0.955$ ). FD patients who reported taking risks routinely or occasionally were no more likely to take risks with a hypothetical medication designed to cure FD than were those FD patients who rarely or never take risks (2 (0–10) vs. 0 (0–5);  $P=0.191$ ).

All FD patients were queried about the use of a hypothetical medication that could permanently cure their FD symptoms, defined *a priori* as symptom resolution without the need for further medications for FD symptoms. Using an SG, 49% of respondents reported that they would accept a mean 12.7% risk of sudden death (range 1–90%) for a 99% chance of cure. A significant linear increase was noted in SG scores by FD subtypes. Patients with PDS alone had a significantly lower median (IQR) rating compared with those with mixed PDS/ EPS symptoms (0 (0–2) vs. 4 (0–10);  $P=0.025$ ). Patients with EPS had intermediate ratings and were not statistically different from the other two groups (2 (0–7)). Patients self-rated their FD symptoms as severe (27%), moderate (40%), and mild (31%). Patients with severe FD symptoms (median (IQR) 5 (0–10)) were willing to take more risks with a hypothetical medication to cure FD compared with those with self-rated moderate (1 (0–5)) and mild (0 (0–4.5)) symptoms, although the differences failed to reach statistical significance ( $P=0.099$ ).

Males were more often willing to take risks associated with a hypothetical medication to cure FD compared with females (65% vs. 37%;  $P=0.033$ ). However, age (younger or older than 45 years of age;  $P=0.781$ ), duration of FD symptoms ( $P=0.330$ ), current use of medications ( $P=0.518$ ), the number of medications used on a daily basis (<3/day vs. ≥3/day;  $P=0.627$ ), fear of developing stomach cancer ( $P=0.917$ ), or concerns that FD symptoms will worsen with time ( $P=0.717$ ) were not associated with an increased willingness to take medication risks. Overall impulsivity scores, or impulsivity scores by FD subtype, did not correlate with willingness to take medication risks.



**Figure 2** Median patient self-reported severity of functional dyspepsia (FD) symptoms.



**Figure 3** Self-reported risk-taking behavior.

**Impact of anxiety and depression on FD symptoms and medication risk-taking behavior.** The mean anxiety and depression subscores using the HAD questionnaire was 7.8 (s.d. ± 4.7) and 4.5 (s.d. ± 4.1), respectively. Total HAD scores were higher in patients who had symptoms of both bothersome fullness and upper abdominal pain (15.94; s.d. = 7.95) compared with those who only had bothersome fullness (11.35; s.d. = 8.58) or upper abdominal burning (12.39; s.d. = 8.63;  $P=0.040$ ). Similar results were found when just the

**Table 2** Medication use for FD symptoms ( $n=114$ )

Proton pump inhibitors	77%
Over-the-counter antacids	71%
Histamine type 2 receptor antagonists	43%
Tricyclic antidepressants	38%
Selective serotonin reuptake inhibitors	36%
Prokinetic agents	28%
Treatment for <i>Helicobacter pylori</i>	20%
Pregabalin	20%
Others	30%

FD, functional dyspepsia.

Note: The % adds up to > 100% as most patients had used several medications in an attempt to treat their FD symptoms.

depression subscore of the HAD was analyzed (6.28 (s.d. = 4.58) vs. 4.40 (s.d. = 4.23) vs. 4.51 (s.d. = 4.33;  $P=0.019$ )). Differences were not significant between these three groups when anxiety subscores of the HAD were analyzed ( $P=0.083$ ). When total HAD scores and HAD subscores for anxiety and depression were analyzed with respect to risk-taking behavior (never, occasionally, or rarely), no differences were found.

**Medication use and side effects.** Patients reported that they took some kind of medication (i.e., vitamins, OTC agents, herbal supplements, prescription medications), a median (IQR) of 7 (7–7) days per week and a median of 4 (2–7) (range 0–23) prescription and non-prescription medications per day. Seventy-seven percent of patients had been treated with a proton pump inhibitor for their FD symptoms, 38% had been treated with a tricyclic antidepressant, and 36% with a selective serotonin reuptake inhibitor. Other treatments reported by FD patients for their FD symptoms are listed in Table 2.



The survey queried patients about their experiences with side effects to medications. Side effects were defined *a priori* as any unintended symptom that developed after taking a medication, and a list of common side effects was provided. During the past 5 years, 68% reported developing a side effect from a prescription medication, whereas 46% reported developing a side effect from a prescription medication used to treat FD. FD patients who reported experiencing a side effect to an OTC medication or a prescription medication used to treat FD symptoms in the past were slightly less likely to take risks with a hypothetical medication to cure FD, although this was not statistically significant ( $P=0.358$  for any OTC medication and  $P=0.322$  for an OTC medication used to treat FD symptoms). FD patients who had a prior side effect to a prescription medication for FD were just as likely to take medication risks compared with those FD patients who had suffered a side effect to any prescription medication ( $P=0.634$ ) and to those patients who had not suffered an adverse effect from an FD medication ( $P=0.699$ ).

## DISCUSSION

FD is a highly prevalent disorder that markedly reduces patients' quality of life and imposes a significant economic burden to patients and society<sup>7-14</sup>. In clinical practice, a wide array of medications are used in an attempt to ameliorate symptoms and improve patients' quality of life. However, these medications are frequently associated with risks. In this study, we found that FD patients claim to be willing to take significant medication risks to cure their FD symptoms. Using an SG, a validated and well-accepted measure of utility that quantifies health-related quality of life,<sup>18</sup> 49% of FD patients reported that they would accept a median 12.9% risk of sudden death to cure their IBS symptoms for a 99% chance of cure. This remarkable willingness to risk sudden death illustrates how significantly the burden of FD symptoms compromises the quality of patients' lives.

These novel results extend recent findings that patients with functional gastrointestinal disorders such as IBS consider their symptoms severe enough that they would be willing to exchange a longer lifespan for better health and quality of life. For example, an internet-based study determined that IBS patients would be willing to give up 15.1 years of life to have an effective treatment for their IBS symptoms and achieve "perfect health",<sup>19</sup> whereas another study found that IBS patients would accept a 1% risk of sudden death to cure their IBS symptoms with a hypothetical medication.<sup>20</sup> Regulatory agencies should thus consider patients' demonstrated willingness to accept abnormally high medication risks when evaluating medications to treat functional gastrointestinal disorders.

This study lends credence to our hypothesis that patients who report severe FD symptoms would be more willing to accept risks associated with medications meant to treat FD, compared with those FD patients with self-rated mild or moderate symptoms. Although this did not quite meet statistical significance, a clear trend was realized. To treat patients effectively, clinicians may want to incorporate patients' risk adversity into their treatment plans and this may vary for different FD patients based on symptom severity.

Patients with chronic medical disorders are more likely to suffer from symptoms of anxiety and depression than the general population.<sup>21</sup> Patients with functional gastrointestinal disorders, such as IBS and FD, are no different. Using the well-validated HAD questionnaire to assess anxiety and depression, we found that HAD scores were higher in FD respondents compared with the general population, which confirms earlier data from a separate group of FD patients.<sup>22</sup> Although an increase in the severity of symptoms was associated with a concomitant increase in HAD scores (data not shown), it was interesting to find that elevated HAD scores did not translate into an increased willingness to take medication risks. As well, impulsivity scores, general risk-taking behavior, age, purchase of life or health insurance, duration of FD symptoms, current medication use, and prior side effects from medications did not appear to influence medication risk-taking behavior.

Interestingly, FD subtype influenced willingness to take medication risks. The mixed PDS/EPS group was more willing to take risks with a hypothetical medication than the PDS group ( $P=0.025$ ). Patients with EPS were more willing to take medication risks than the PDS group, although this was not statistically different. Future medication trials will need to determine accurately FD subgroups, as this may affect patients' willingness to take medication risks.

Research studies involving IBS patients often use the IBS severity scale<sup>23</sup> and patient self-ratings for IBS symptom severity correlate well with this scale.<sup>20</sup> At present, no validated symptom severity scale exists for FD patients. In this study, FD patients were asked to self-rate their symptoms as mild, moderate, or severe. These ratings were then compared with visual analog scale (VAS) scores assessing four separate pain parameters—frequency, severity, duration, and unpredictability. We found a strong correlation between self-rated FD symptom severity and visual analog scale scores for all four parameters in patients with severe FD symptoms compared with those with mild symptoms ( $P<0.001$ ). In a comparison of those FD patients with self-rated moderate pain and those with mild pain, the duration and frequency of pain using the visual analog scale scores were still significantly significant ( $P=0.001$  and  $0.002$ , respectively), although unpredictability of pain and severity of pain were no longer statistically significant for these two groups. These novel data highlights the need to develop a validated patient-centric severity scale for FD patients.

There are several limitations to this study. First, the results of this study reflect a predominantly Caucasian population in New England. Second, future studies to confirm these results should use a larger sample size to help tease out willingness to take medication risks in different FD subgroups and in those who experienced side effects with prior medications. Third, this study focused on a hypothetical medication that could "cure" FD. The current questionnaire could be easily modified and incorporated into future medication research studies in an attempt to quantitate willingness to take medication risks associated with symptom reduction. Finally, this study focused on FD patients but did not evaluate other coexisting medical disorders. Stratifying FD patients based on the presence and number of coexisting medical conditions could alter the magnitude or direction of our results.

In conclusion, this study is the first to assess the fears, concerns, and medication risk-taking behavior in FD patients. Although FD patients do not appear to engage in abnormally risky behavior and are not generally impulsive, they are, as a patient population, willing to take extraordinary risks (i.e., sudden death) to cure their FD symptoms. Further studies into FD patients' risk-taking behavior are required as this behavior may directly influence drug development, the drug approval process, and individual treatment plans offered to FD patients by their physicians.

## CONFLICT OF INTEREST

**Guarantor of the article:** Brian E. Lacy, PhD, MD.

**Specific author contributions:** The study was designed and implemented by Lacy, Crowell and Yu. Mailing of the survey and data collection and data input were performed by Lacy and Yu. Statistical analysis was performed by Crowell. The manuscript was written by Lacy, Crowell and Yu. All authors contributed to the editing and final approval of the manuscript.

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**Potential competing interests:** No author has any conflict of interest to disclose with regard to this study.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Functional dyspepsia (FD) is a highly prevalent functional gastrointestinal disorder.
- ✓ FD reduces patients quality of life and imposes a significant economic impact to the health-care system.
- ✓ No medication is approved for the treatment of FD.
- ✓ The willingness of FD patients to take risks to cure their symptoms is unknown.

### WHAT IS NEW HERE

- ✓ FD patients are willing to take significant risks with medications to cure their symptoms.
- ✓ FD patients with more severe symptoms were willing to take greater risks than those with mild symptoms.
- ✓ FD patients with postprandial distress syndrome (PDS) subtype were less likely to take medication risks than those with mixed PDS/EPS subtype.
- ✓ Anxiety and depression did not increase medication risk-taking behavior.

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