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INTERNATIONAL SURVEY OF PATIENTS WITH IBS:

SYMPTOM FEATURES AND THEIR SEVERITY, HEALTH STATUS, TREATMENTS, AND RISK TAKING TO ACHIEVE CLINICAL BENEFIT

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Abstract

Background—While clinicians generally make treatment decisions in IBS related to the type of symptoms, other factors such as the perceived severity and the risks patients are willing to tolerate for effective treatment are also important to consider. These factors are not fully understood.

Objective—To describe among patients with IBS their symptoms and severity, quality of life and health status, medications taken, and the risk that they would take to continue medications for optimal relief.

Methods—Adult patients diagnosed with IBS who accessed the websites of the International Foundation for Functional GI Disorders (IFFGD) or the UNC Center for Functional GI Disorders filled out questionnaires to address the study aims.

Results—The 1,966 respondents (83% female, 91% Caucasian, 78% USA/Canada) reported impaired health status: restricting on average 73 days of activity in a year, having poor HRQOL particularly with dietary restrictions, mood disturbance and interference with daily activity, and 35% reported their symptoms as severe defined primarily as pain, bowel difficulties, bloating and eating/ dietary restrictions). These symptoms were reported in some combination by over 90%, and 35.1% endorsed all 4 items. To receive a treatment that would make them symptom free, patients would give up 25% of their remaining life (average 15 years) and 14% would risk a 1/1000 chance of death. Most of the medications being taken were for pain relief and 18% were taking narcotics. Complementary and alternative treatments were used by 37%.

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Study Highlights:

- Patients with IBS accessing the internet have considerable impairment in health status.
- Severity of IBS is determined by several factors including pain, bowel difficulties, bloating and eating/dietary restrictions.
- When taking a new medication patients are willing to take considerable risk to achieve treatment benefit.
- Regulatory agencies might consider raising risk - benefit ratios when approving new medications for IBS.

Conclusions—Patients accessing IBS informational websites report moderate to severe impairments in health status, and would take considerable risk to obtain symptom benefit. There is an unmet need to find effective treatments for patients with IBS and regulatory agencies might consider raising risk-benefit ratios when approving new medications for IBS.

Introduction

The irritable bowel syndrome (IBS) is the most recognized and studied functional GI disorder but has no specific treatment to encompass the breadth of the symptom experience. Traditionally clinicians make treatment decisions based on the nature and severity of the symptoms, the impact of the disorder on quality of life and overall health status, and the risks versus the benefits of the treatments. In the absence of "gold standard" treatments, consensus guidelines have been developed (1);(2); (3);(4). In recent years, the Food and Drug Administration (FDA) has attempted to address two important issues. First is the question of developing an acceptable endpoint to determine efficacy for investigational drugs in IBS, and there has been debate as to whether this endpoint should be symptom related or a global measure of change, e.g., adequate or satisfactory relief. In addition, the FDA seeks new treatments for IBS that have very low risk-benefit ratios primarily for safety concerns. While in part treatments are based on severity (2), very little is known about what actually determines severity (5), and missing from this formula are the patient's self-perceptions of severity, and their judgments relating to choosing medications based on the risks they would be willing to take to achieve symptom benefit.

Recently, more and more patients are preferring to obtain internet-based information about their condition and those who do are found to be more knowledgeable about IBS(6);(7). Given these factors, it would be helpful to characterize the health status of patients with IBS who access the internet: to understand the nature and severity of their IBS, and their treatment choices. This type of information may help determine proper treatments and permit regulatory agents to develop proper guidelines for approval of medications that are targeted to the needs of patients with IBS. Accordingly we conducted an international web-based survey to characterize the following factors among patients with IBS: 1) What are the demographic, clinical, and health status profiles of these patients?, 2) How severe do they perceive their IBS compared to standardized measures?, 3) What factors contribute to severity and can that information help identify endpoints in clinical trials?, 4) What types of medications and other treatments are being taken and what are their side effects? 5) How much risk would patients take to achieve clinical improvement?, and 6) How satisfied are patients with their care?

Methods

Population Sample and Selection Criteria

Between June 6th and October, 24, 2007, the UNC Center for Functional GI and Motility Disorders and the International Foundation for Functional GI Disorders (IFFGD) used their respective patient databases and also placed ads in their respective websites (www.med.unc.edu/ibs for UNC and www.iffgd.org and www.aboutibs.org for IFFGD) that directed potential subjects to the IFFGD website. At the website, potential respondents identified if they were 18 years or older, were diagnosed by a physician with IBS, and were able to complete an online questionnaire. Those who responded affirmatively were sent an email containing a unique subject ID number, password, and instructions for logging into the survey.

Of the 8,682 who responded to the website initially expressing interest, 2,413 were excluded because of no IBS diagnosis. Of the remaining 6,269 eligible subjects, 2,523 individuals started the study, 1,971 completed the study and 5 were excluded because of questionable diagnoses

(not diagnosed by a medical doctor). Thus, the study was analyzed using the 1,966 evaluable participants (**31.4% of those eligible** and 78% of those starting the survey). Those that completed the survey were more likely than those who started but did not complete the study to be younger (37.1 vs. 40.4 years, $p<0.0001$), Caucasian ($p<0.0001$), had greater educational attainment (15.2 vs. 14.7, $p<0.0001$), were from the USA (71.7% vs. 59.2%, $p<0.0001$) and were more likely to be restricting their activities (73.2 vs. 57.1 days, $p<0.0003$), be jobless due to their health (12.8% vs. 8.4%, $p<0.002$), and have a longer duration of symptoms 14.7 yrs. vs. 11.8 yrs, $p<0.0001$). Thus the reported data may over-represent the degree of impairment in the internet population.

Questionnaire Administration and Data Management

The survey was constructed by merging validated scales, selected questions from the 2002 IFFGD "IBS In the Real World" Survey (8) and research questionnaires developed at the UNC Center. Self-reported information was obtained on demographic variables, medical and health status, severity of symptoms and medication risk. The survey included the following validated scales: Functional Bowel Disorder Severity Index (FBDSI) (9) and the IBS Symptom Severity Score (IBS-SSS), (10)health related quality of life (IBS-QOL); (11); (12), Hospital Anxiety and Depression Scale - HADS (13), and a new health status instrument, the BEST(14). New questions included risk assessment using a modified time trade off method (15), as well as questions on the impact of FDA decisions related to withdrawal of IBS medications, and various treatments and their side effects. The checklist for items relating to severity (Table 2) were derived from patient reports obtained clinically that specifically elicited the items through open ended questioning. Questions were ordered, proofed, modified and implemented by consensus among members of the UNC Center and the implementation team at IFFGD.

After pilot testing among 8 patients and 6 members of the research team, the revised final draft was sent to the programming team (Red Anvil, Milwaukee, WI). The resulting first online draft was proofed by the IFFGD implementation and then moved to the live site and draft tested by 10 patients seen at UNC before live implementation.

All questionnaire responses were saved as numeric-coded values in an SQL database stored on the IFFGD secure server that contained no personal identifiers. Periodic monitoring was performed to review the data for completeness and adherence to protocol. Subjects who began but did not complete the survey were contacted again at 2-week with a reminder email.

Upon completion of data collection, the database was downloaded into a CSV file and sent to the UNC Center biometry core for data editing, cleaning and analysis. Personal identifiers were removed from the data sent to UNC. Quality assurance steps included range and consistency checks among the various questions; missing items were examined to see if missing at random (MAR). The online survey was designed with built-in checks that precluded respondents' entering inadmissible data. Users were also precluded from submitting the survey more than once under the same identifier. UNC converted the data into SAS data sets and added variable names and SAS formatting before final analysis.

Of the evaluable data on 1,966 patients, about 48% responded to an ad (40.4% IFFGD, 8.0% UNC), 34% were by direct email (31.8% IFFGD, 2.1% UNC) and 17.6% were from other sources (including mailings, printed materials, links from other websites and referrals from friends or health care providers). These data were combined for the analysis, since there were no demographic differences by site (IFFGD ads or emails, UNC ads or emails, and other sources) or *a prior*i reason to suspect the response groups would be different.

Data Analysis

Descriptive analyses were performed to summarize the distributions of all continuous and categorical variables with means and standard deviations for continuous variables and frequency distributions for categorical variables. Responses were stratified by gender, education, bowel subtype and severity of disease, to identify trends among particular subgroups. Three different severity measurements were analyzed to determine their association using Pearson's correlation (both measures continuous), Anova (one continuous/one categorical), or agreement using kappa (if both categorical). Demographics were tested between those who completed the survey versus those who did not using t-tests for continuous variables and chi-square tests for categorical variables. The primary measure for comparisons with other health status measures was the FBDSI since it is the most standardized measure (9) and had a more acceptable range of severity that is closer to self-report; Correlations were performed between the FBDSI and with the self report measure. However, an obstacle to comparing these measures was that the categories for degrees of severity varied, and agreement can only be measured when the number of categories is the same. Thus, we collapsed categories, and tried to preserve the range of severity for each category as best as possible. However, this can methodologically alter the level of the agreement. All analyses were performed using SAS version 9.

Results

Demographic and Diagnostic Features

The study sample was predominantly female (83%), Caucasian (91%) and from the USA or Canada (78%). The mean age was 40.4+14 years, and with an educational attainment of 15.2 +2.9 years and 59% were married or cohabiting. The symptoms were present for 14.7 +13.3years, and received a diagnosis of IBS 6.6+9.7 years after symptoms began; also 90.9% met Rome III criteria for IBS. The sub typing distribution was 61% IBS Mixed or Unspecified (IBS-M/U), 29.3% IBS with diarrhea (IBS-D) and 9.7% IBS with constipation (IBS-C).

Health Status, Perceptions, Behaviors and Health Care Utilization

While the majority (almost 80%) indicated their health to be "good (37.7%)," "very good (33.8%)," or "excellent (7.9%)," respondents had to restrict their usual activities on average 73.2±98.0 days (20% of the calendar year) and 12.8% were not working due to their health, presumably their IBS. When using the "BEST" question "How bad are your bowel symptoms?" 55% felt that their symptoms were so severe it was affecting their lifestyle (41.4% severe, 13.6% very severe) and an additional 39% reported that the symptoms were moderate and could not be ignored. When asked (BEST) "Do you feel your bowel symptoms mean something is seriously wrong with your body", over one third (33.7%) believed that quite a bit (21.5%) or a great deal (12.2%)(16). Participants consulted with 4.6±6.3 different healthcare providers about IBS in their lifetime, and saw their current provider 2.7±4.5 times in the previous 6 months, which compares to the US Householder study (a study that included a large proportion of individuals who were not seeking health care) of 1.6 visits in one year (17). They most often saw a primary care (89.3%) or GI physician (54.9%) over the last year followed by a gynecologist (34.2%), nurse practitioner/PA (27.4%), counselor/therapist (18.8%), a dietician nutritionist (8.7%) and others (28.2%). Only 3.5% had not seen a provider in the previous year. The respondents were hospitalized on average 3.0±1.9 times in the previous 2 years and had 2.5±3.1 major surgeries in their lifetime.

Health Related Quality of Life (HRQOL) and Psychosocial Features (Table 1)

The IBS-QOL is the standard disease-specific measure of HRQOL for IBS (11;12;18); (19), and is scored from 0-100 with a lower number being poorer HRQOL. The overall sum score

mean was 51.1, indicating a markedly impaired health related quality of life; this is similar to a cohort having moderate to severe symptoms in a treatment trial (20) but considerably more impaired when compared to values around 60-70 in other clinical populations globally (21); (22;23); (24). The subscale analysis indicates that the areas of greatest impairment (score<50) are Food avoidance (32), Dysphoria (46) and Interference with activity (49).

With regard to the impact of stress, pressure or tension affecting their health, 62% reported that to occur often (33.5%) or all the time (28.5%). The Hospital Anxiety and Depression Questionnaire (HADS) is a brief and frequently used measure of psychological distress used for a medical clinic or hospital population (13). The Anxiety and Depression scales range from 0-21 and a cutoff of ≥11 indicates a clinical diagnosis. Notably this population suffered primarily from anxiety; the average anxiety score was 10.1 and 47% of the sample had clinically meaningful anxiety. However, the average depression score was 6.2 and only 14% of the participants were clinically depressed. This compares to the higher affirmative responses of the BEST with 51.7% answering yes to: “Do you feel tense or wound up” as “a lot” (34.4%) or “most of the time” (17.4%) (Anxiety question) and a lower proportion for “Can you still enjoy things you used to enjoy with only 14.3% answering affirmatively to “only a little” (8.6%) or “hardly at all” (5.7%) (Depression question).

Severity

A major goal of this study was to assess the nature and correlates of severity in this population. Therefore, we evaluated the two standard severity measures, the FBDSI (9) and the IBS-SSS (10) along with the patient’s self report of severity “Rate how severe your IBS is” (not at all, somewhat, moderately, very, extremely). There was a statistically significant agreement between the 3 severity measure scores ($p<0.0001$). However, for methodological reasons (see Methods section) the agreement by κ scores was only modest. The correlation between the FBDSI and IBS-SS was $r=.38$ (continuous) and $\kappa=0.22$ (categorized), between the FBDSI and self-report $\kappa=0.25$, IBS-SSS and self-report $\kappa=0.30$. The majority of the study sample had moderate to severe ratings of severity. The proportion of participants rated as severe were 20% (FBDSI), 55% (IBS-SSS) and 35% (Patient self report) respectively.

We then used a check list of items (Table 2) to determine which factors contributed to severity and multiple factors were chosen, on average 7 of the 14 offered and less than 3% of participants reported only one item. This indicated the heterogeneity of factors contributing to patient perception of severity. The most frequently endorsed items (reported by at least 2/3 of the sample) were pain (80%), bowel difficulties (74%), bloating (69%) and limitations on diet or eating (69%). Additional items reported by at least 1/2 of the sample included limitations in social activities (62%) inability to leave the home (54%), and work and school limitations (50%). Most of the participants reported a clustering of the four most frequently endorsed items in their responses with 90.4% reporting at least 2 of the 4, 68.2% reporting 3 of the 4 items, 35.1% reporting all 4, and only 1.2% of patients reporting none of these items.

The patient’s level of severity affected the responses in the expected direction. The mean number of items endorsed increased with greater severity (mild 6.1, moderate 7.0, severe 8.9) and the proportion of each item endorsed was greater with greater severity (e.g., pain endorsed by 63.5% with mild, 84.5% moderate, and 92.3% with severe illness; data not shown). These data indicate that IBS is a complex syndrome, defined by a combination of symptoms: primarily pain, bowel difficulties, bloating and eating or dietary limitations. Furthermore, since the level of severity seems related to the number and intensity of these contributing factors, a reduction in these factors contributing to severity would be a reasonable way to assess a treatment response.

Relationship of Severity to Health Status Measures

To further explore the relationship of severity with health status impairment we display (Table 3) the health status measures of the study sample now categorized based on the 3 patient groups: mild, moderate or severe IBS (FBDSI). There is a consistent trend with greater severity associated with the poorer health status, thus providing some concurrent validity to the FBDSI. Notably for patients with severe IBS using the FBDSI: 30.3% are jobless due to their health, activity restriction was 139 days±118, there were 6.6±8.2 visits to MD in last 6 months, the amount of abdominal pain on a 0-100 VAS scale was 59±26 and the overall IBS-QOL score was 38±20. The proportion with clinical anxiety was 61% and depression 27%; this was reflected in the BEST individual questions as well. Similar trends were also seen with the patient's self report of severity (data not shown). Regarding demographic characteristics, no significant differences were seen between the severity subgroups for gender, race, country of origin, or IBS subtype. However, patients with severe illness were more likely to be younger in age (42.8±14.8 mild, 39.2±14.1 moderate, 39.8±13.8 severe, $p<.0001$), with less educational attainment (15.5±2.7 mild, 15.2±2.7 moderate, 14.9±2.7 severe, $p=0.006$), had fewer years with IBS disorder (16.1±14.3 mild, 14.5±13.0 moderate, 13.2±12.5 severe, $p=0.002$), and were diagnosed sooner (9.2±10.0 mild, 7.8±9.7 moderate, 7.4±8.9 severe, $p=0.006$) (data not shown in table).

Medications and Other Treatments

Participants reported currently taking an average of 2 drugs (ranging from 0 to 13 drugs with a mean of 1.6±1.6 for mild, 1.9±1.7 for moderate and 2.5±2.3 for severe IBS). Only 24.2% of the sample reported not currently taking any medication. Table 4 presents the proportion of subjects currently taking the major classes of medications used for their IBS and the proportion of moderate and severe side effects The proportions taken for the most common medication groups were 31.3% for non-narcotic analgesics (no difference by severity), 30.8% for antidepressants (28% mild, 30% moderate, 38% severe and no difference by stool subtype), 23.6% for antidiarrheals (38% IBS-D, 21% IBS M/U, 1.7% IBS-C and no difference by severity subtype), 18.5% antispasmodics (14% mild, 20% moderate 24% severe and no difference by stool subtype) and 18.1% narcotic medications for pain (12% mild, 18% moderate, 28% severe). This is consistent with the observation that pain is the predominant symptom reported by the participants and the proportion of medications taken for pain increase based on severity. Antidiarrheals were commonly taken by the subset with IBS-D (38%) when compared to IBS M/U (21%) or IBS-C (2%). Acid reducers were taken frequently (27.7%) but it is not possible to know if this was for GERD or IBS since both conditions are common. Antibiotics and anti-emetics were taken infrequently (<2% of participants).

In terms of side effects, for those medications taken currently (Table 4), the classes of medication with the greatest frequency of moderate to severe side effects (at least 10%, shaded in Table 4) were: antidepressants (10.9% moderate, 2.1% severe), narcotics (12.4% moderate, 0.8% severe), and anticonstipation medications (21.1% moderate, 2.2% severe).

With regard to Alosetron and Tegaserod, the serotonergic (5HT) medications currently under restricted use, only 35 patients (17 Tegaserod, 18 Alosetron) were currently taking the medication. In the past, 5% had taken Alosetron and 16% had taken Tegaserod.

The proportion of side effects for these IBS-targeted 5-HT medications was low, only 6% reporting moderate side effects for Alosetron. . However, when evaluating side effects in the past, 29% reported moderate to severe side effects ever with Alosetron (14.4% severe and 14.4% moderate; n=90) and 25% reported moderate to severe side effects ever with Tegaserod (13% severe, 12% moderate; n=322).

A substantial proportion (36.9%) at some time used complementary and alternative medical treatments, the most common being dietary supplements (30.5% ever, 15.9% currently) and probiotics (24.3% ever, 13.1% currently) followed by massage therapy (15.3% ever, 4.5% currently), meditation and relaxation therapy (each about 17% ever and 5% currently), homeopathy (12% ever, 3% currently), acupuncture (8.4% ever, 1.5% currently) Chinese herbal therapy (9.3% ever, 2.2% currently) and colonic irrigation (3.8% ever, 0.5% currently).

Risk Taking With Regard to New Treatments

To understand what risk patients would tolerate to receive new and effective treatments, we used a modified Time Trade-Off assessment originally developed by Torrance et al.(25), where an index is developed based on the individual trading of "X" years of his/her life in order to achieve perfect health. On average given their current perception of their health status, the participants would be willing to give up 15.1 years (about 25% of remaining years, given an index of 0.75) of their remaining life to achieve perfect health. We also asked participants what would be the minimal improvement they would accept given their current health status if they were to take a medication that cost $50. The mean symptom reduction was 66.4% in order to continue with the medication and this reduction amount was not different regardless of symptom type or severity. Finally we provided a list of options as to where they believed they could receive reliable information on medical risk. By far, the top resource was their personal physician, endorsed by 72.7 %, and this was followed by their pharmacist (49.3%), searching the internet (37.5%), from sites run by IBS professionals (34.9%) and patient organizations (31.8%), the FDA (30.7%), by personal decision (23.2%) and from news media reports (18.8%). The least trustworthy option was direct-to-consumer ads (10.4%). The single most reliable source was the physician in 44.4%.

Table 5 shows the risk that respondents would take for total IBS symptoms relief from a new medication with regard to death or potential adverse events. We created a series of questions that asked subjects to select the best choice from among 10 risk options (ranging from 1 in10 million down to 1 in 2), or to select "would not take") to assess the degree of risk for a given consequence (death, serious or permanent side effects, and mild side effects). Notably, 13.5% would accept at least a 1/1000 chance of death, a slightly lower proportion (10.1%) would accept at least a 1/1000 risk of serious or permanent side effects, and a large proportion (55.3%) would accept at least a 1/1000 chance of mild side effects (gray shading). The degree of risk for patients with severe IBS was always considerably greater as shown in Table 5.

Attitudes and Perceptions Related to Safety Regulations

We then analyzed the USA subset of the study sample to evaluate the attitudes and perceptions related to safety regulations and the withdrawal of medications from the marketplace in the USA. The question was asked: "Let's assume you are taking a medication for over a year because it is helpful for your symptoms. The United States Food and Drug Administration (FDA) then decides that the medication may be harmful to others, for example to cause heart disease. There is some controversy as to whether this is truly the cause the FDA removed the drug from the market until the question of harm is resolved". Several questions revolving around this scenario were asked and responses were obtained using a 5-point Likert scale. Results for most, unless otherwise indicated, sum the highest 3 response items (shown in gray, Table 6).

Regarding the effect of the FDA's decision, 81.9% reported that they would be moderately, a great deal or completely affected. Nearly 68% reported that they would be moderately, a great deal or completely worried to continue to take the medication, and 55.8% reported that they would believe that the medication may have already caused harm to a moderate degree, a great

deal or completely. Notably, 84% were moderately, a great deal or completely appreciative with the FDA's decision to remove the drug from the market.

Almost 65% were moderately, a great deal or completely satisfied that the medication stay off the market, whereas 17.7% were not at all satisfied with the removal from the market. When asked their preference for drug to remain on or off market until the risk is established, the response was split: 45.1% preferred the medication stay off the market, 20.3% preferred it be placed back on the market and 34.6% were not sure.

Lastly, participants were asked about circumstances for the drug to stay on the market. A hierarchical list was created of increasing level of restriction so that each answer included all of the above listed restrictions as well as the selected one. A warning label was endorsed by 14.1% and a more severe restriction (warning label, plus MD and patient sign a form and the medication prescribed only by a GI specialist) was endorsed by 65.0%. An additional 9.2% wanted to require that the patient would need to get a new prescription each month, and finally an additional 25.8% endorsed the most restrictive guideline, which in addition to all of the above would require a gastroenterologist to apply for use of the medication.

Satisfaction with Care

When asked: "How satisfied are you with ALL types of treatments", only 37% of the respondents were at least somewhat satisfied, and only 8% were very or extremely satisfied. Notably 34% were not at all satisfied. However, when asked about their overall satisfaction with medications currently being taken, 73% are somewhat, very or extremely satisfied. When asked about the physician's care they received over previous year the results were intermediate: about (53.3%) were somewhat, very or extremely satisfied. Thus there is room for improvement with physician and other types of care compared to that of medications.

Discussion

Over the last several decades our concept of the IBS has moved from reductionistc views of single causality to that of a a syndrome having multiple pathophysiological determinants. For this reason, diagnosis is currently symptom based and treatments must be decided based upon the type of symptoms and their severity, the patient's quality of life, and the nature of the treatments and their risks.

Notably, while we ask all patients about symptoms to make a diagnosis, we may not as often assess patient views on treatment choices and we rarely obtain their opinions about risk preferences. In fact very little is known about how patients appraise their health status and what treatment preferences and risks they will take. Thus it would be helpful to obtain normative information on the health status of patients with IBS and a profile of their preferences and concerns relating to treatments for IBS, which can be of value to clinicians, clinical investigators and regulatory agencies.

What is the best group to study? A population-based epidemiological study includes individuals who may only be mildly symptomatic and about half have never seen a physician for the disorder (17). Conversely IBS patients are often obtained from medical centers or GI practices which may over-represent the patient's severity relative to other clinical populations. Recent data from Halpert (6); (7) indicates that more and more patients are searching the internet for information about their condition and for potential treatments and these individuals are more knowledgeable about their IBS. Thus a population of IBS patients accessed from the internet is, and will continue to be, an important group for clinicians, investigators and regulatory agencies to understand. Over time the internet may become a standard resource for patients to gain information about medical conditions and their treatments.

This survey was conducted to achieve several goals: 1) to identify the symptoms, and health status of an international sample of patients with IBS who actively seek information from the internet, 2) to understand the perceived severity of their IBS, and what factors contribute to severity (5), 3) to determine what medications patients are taking for IBS and the degree of side effects, 4) based on FDA interests, to understand what risks patients would take to achieve treatment benefit in addition to identifying patient views on FDA guidelines related to the withdrawal of certain IBS medications, and 5) to assess overall patient satisfaction with their care and specifically for their medical treatments.

Demographically, the respondents were not unlike those in clinical studies, predominantly middle aged, Caucasian, married or cohabiting women, who had their IBS for about 15 years. Notably, it took almost 7 years to make the diagnosis of IBS. The high educational attainment (15 years) likely reflects sampling of an internet savvy population. Their report of a physician diagnosis of IBS was a sound one: over 90% fulfilled Rome III criteria for IBS. Respondents having IBS-C seemed disproportionately low (10 %) compared to other studies where the figures for this subtype of IBS usually approach one-third (26).

With regard to health status, the patients had greater impairments in HRQOL and poorer health status than anticipated, and the results are similar to or worse than patients with moderate to severe IBS in clinical trials. About 20% of the days were restricted due to health problems, and work absenteeism and high health care utilization were common. Impairments in health related quality of life were most manifest in terms of dietary restrictions, emotional distress and activity limitations. The high levels of anxiety likely reflect the psychological impact of the disorder. When the psychological instruments standardized to normal or psychiatric populations are used in medical patients, the scores may become elevated due to the medical illness rather than any evident “psychopathology” (27). Paradoxically the patients generally reported “good health” despite these impairments. Perhaps the concept of good health “rides above” the patient’s sense of impairment. For example, an individual with a broken leg may be in pain and have limited activity but not necessarily perceive herself or himself to be in poor health. Conversely, patients with inflammatory bowel or HIV disease who are in remission with no symptoms or limitations may still see themselves in poor health.

When assessing severity, all measures indicated a larger proportion of severe IBS than previously assumed (28) as has been suggested by a recent review of this literature (5), and the two standardized measures were significantly correlated with the self-report measure. Furthermore, we confirm that the concept of severity is complex and multi-determined, and in fact multiple items (mean 7) were identified as contributing to IBS severity. All four of the most common items (Pain, bowel dysfunction, bloating, dietary restrictions) were endorsed by over one-third, 3 items by over two-thirds and some combination of these four items was endorsed by over 90%; only 1% endorsing none of the 4. Not unexpectedly, the number of total items endorsed and the proportion endorsed for each item increased with severity. These data indicate that clinical endpoints for IBS must encompass a variety of symptoms, primarily pain, bowel difficulties, bloating and eating or dietary limitations, rather than a single symptom like diarrhea or constipation. Furthermore since the level of severity seems related to the number and intensity of these contributing factors, a clinical response to treatment could be assessed by a reduction in these particular factors that contribute to severity. Therefore, we believe that a reasonable primary endpoint for a clinical trial in IBS could be: “How would you rate your IBS when considering all factors contributing to it (may include pain, bowel difficulties, bloating, and the need to restrict your diet)?” Scoring can be based on any prevailing rating scale.

The relatively high severity may help explain the high proportion of medications taken, primarily to obtain pain relief: antidepressants for central analgesia, non-narcotic analgesics

presumably for visceral pain and the inappropriate use of narcotics in almost one-fifth of the patients, and patients with more severe symptoms took more. In our experience, a certain proportion may also be suffering from narcotic bowel syndrome, and proper recognition and withdrawal of the narcotics may enhance clinical improvement (29). Given the small number of patients taking the two serotonergic medications targeted for IBS, we are unable to make judgments regarding their value.

The study provides some messages for pharmaceutical companies and regulatory agencies: 1) there is evidence that patients are willing to accept high levels of risk to achieve benefit, 2) future treatments need to target the multiplicity of symptoms presumably by addressing the underlying pathophysiology rather than specific single symptoms, and 3) when facing the reality of FDA decisions to withdraw medications because of potential risk, patient responses are mixed. Although they were concerned (and feared) that the medication might be adversely affecting them, and they approved the FDA decision, at the same time they were reluctant to have the medication off the market, and some would choose to continue the treatment if they could. Most all were agreeable to there being guidelines for return of the medication under restricted use.

Satisfaction with treatment was also mixed - notably there was a variable response to patient satisfaction with clinicians and surprisingly, satisfaction with medication was higher. Perhaps these patients had reached a level of accommodation with their medications. Clearly more work is needed to train clinicians on how to collaborate with patients in their care.

There are limitations to this study. First, there is the risk of selection bias and lack of generalizability to a non-internet population. In fact, the 20% who did not complete the survey did have slightly better functioning with their IBS, so our results may over-represent the severity of health status impairment **even** among internet users with diagnosed IBS. In addition, the study sample had high educational attainment consisting primarily of Caucasians from North America who are likely fluent in English. This limits the generalizability of the findings to other countries those with lower educational attainment or ethnic and socioeconomic groups. In fact recent data indicate that the interests and needs of patients not accessing the internet are quite different (7). Therefore further studies are needed to compare these findings to a non-internet and socially and culturally diverse population. Nevertheless, it is important to recognize that over time, more and more of the world population may be accessing the internet. Second, we acknowledge that the findings relating to high risk taking are hypothetical situations. Very possibly patients may be very agreeable to take accept greater risk with treatments based on a survey than in an actual clinical situation. Third, the proportion of IBS-C is lower than other studies and the reasons are unclear, although the proportion with IBS-M was larger than seen elsewhere; this group may at other times report symptoms more consistent with IBS-C; we know that the IBS-C and IBS-M groups tend to shift back and forth in their bowel pattern over time (26). Finally we recognize that there was a missed opportunity to study medical co-morbidities in this population sample; if this was done we would hypothesize a higher proportion of co-morbid conditions among those with more severe symptoms, though this has yet to be tested.

Despite these limitations, the study provides a first look into how patients appraise their IBS symptoms, the nature of its impact and the risk patients might take to obtain relief. From these data, we believe that there is an unmet need to find effective treatments for patients with IBS; regulatory agencies might consider raising risk-benefit ratios for approval of new medications in IBS.

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Table 1

Health Related Quality of Life and Psychosocial Features (N=1966)

	TOTAL	
	Mean ± SD	
QOL Total Score	51.1 ± 21.9	
Relationship	62.86 ± 26.7	
Sexual	60.2 ± 32.9	
Body image	56.8 ± 26.7	
Health worry	53.7 ± 24.3	
Social reaction	53.4 ± 27.5	
Interfere w/ activity	48.8 ± 26.0	
Dysphoria	45.6 ±28.4	
Food avoidance	32.0 ± 27.4	
Stress/pressure/tension affect your health	**N (%)**	
Never	48 (2.4)	
Occasionally	698 (35.5)	
Often	659 (33.5)	
All time	561 (28.5)	
HADS	**Score**	**Clinical Diagnosis**
	Mean ± SD	**N (%)**
Anxiety	10.1 ± 4.4	925 (47.0)
Depression	6.2 ± 4.0	270 (13.7)
BEST Individual Questions	**N (%)**	
Do you feel tense or wound up		
Not at all	127 (6.5)	
From time to time, occasionally	823 (41.9)	
A lot of the time	674 (34.3)	
Most of the time	342 (17.4)	
Can you still enjoy things you used to enjoy		
Definitely as much	506 (25.7)	
Not quite as much	1177 (59.9)	
Only a little	170 (8.6)	
Hardly at all	113 (5.7)	

Table 2

Factors that Contribute to Severity* (N=1966)

Factors that make your IBS severe	Answering all that apply*
	N (%)
Pain	1563 (79.5)
Bowel difficulties	1463 (74.4)
Bloating	1365 (69.4)
Limits eating/diet	1360 (69.2)
Limits socials	1209 (61.5)
Cannot leave home	1051 (53.5)
Limits work/school	987 (50.2)
Limits thinking	975 (49.6)
Trouble sleeping	892 (45.4)
Nausea	830 (42.2)
Limits home acts	771 (39.2)
Poor QOL	766 (39.0)
Incontinence	537 (27.3)
Other troubles	212 (10.8)

*Average response was 7 items and 4 items (shaded) overlapped the most; <3% endorsed one item

Table 3
HRQOL and Psychosocial Features by FBDSI Severity

	FBDSIC:FBD SEVERITY INDEX		
	Mild:<36 (n=617)	**Moderate:36 - <110 (n=949)**	**Severe:>=110 (N=400)**
	N (%)	**N (%)**	**N (%)**
Out of work due to health problems			
Jobless due to health	33 (5.3)	98 (10.3)	121 (30.3)
Jobless, but NOT due to health	126 (20.4)	164 (17.3)	51 (12.8)
Currently working	458 (74.2)	687 (72.4)	228 (57)
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
Days restricting usual/social activities	44.0 ± 80.4	64.3 ± 86.0	139.1 ± 117.9
Times seen MD for IBS in past 6 months	1.0 ± 1.5	2.3 ± 1.8	6.6 ± 8.2
Total physicians and healthcare providers consulted about your IBS symptoms in your lifetime	3.4 ± 3.0	4.4 ± 5.9	6.6 ± 9.7
Amount of Abdominal Pain None=0 through 100=Very Severe	13.0 ± 13.7	44.2 ± 21.6	59.2 ± 26.0
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
QOL Total Score	59.8 ± 21.8	51.0 ± 20.1	38.1 ± 19.7
Relationship	68.9 ± 25.6	64.0 ± 25.1	50.8 ± 28.2
Sexual	70.4 ± 30.2	61.1 ± 31.2	42.4 ± 33.7
Body image	65.8 ± 26.1	56.0 ± 25.4	45.1 ± 25.8
Health worry	62.6 ± 24.1	53.2 ± 22.4	41.2 ± 23.5
Social reaction	62.6 ± 26.8	52.7 ± 26.4	41.1 ± 25.9
Interfere w/ activity	57.2 ± 26.4	48.6 ± 24.5	36.5 ± 23.8
Dysphoria	54.8 ± 28.9	46.2 ± 26.9	30.3 ± 24.5
Food avoidance	41.6 ± 28.8	30.3 ± 25.8	21.4 ± 23.9
	N (%)	**N (%)**	**N (%)**
Stress/pressure/tension affect your health			
Never	21 (3.4)	14 (1.5)	13 (3.3)
Occasionally	240 (38.9)	331 (34.9)	127 (31.8)
Often	218 (35.3)	324 (34.1)	117 (29.3)
All time	138 (22.4)	280 (29.5)	143 (35.8)
HADS	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Score			
Anxiety	8.9 ± 4.4	10.3 ± 4.2	11.4 ± 4.4
Depression	5.0 ± 3.8	5.9 ± 3.6	8.5 ± 4.1
	N (%)	**N (%)**	**N (%)**
Proportion with Clinical Diagnosis			
Anxiety	217 (35.2)	463 (48.8)	245 (61.3)
Depression	63 (10.2)	101 (10.6)	106 (26.5)
BEST Individual Questions	**N (%)**	**N (%)**	**N (%)**
Do you feel tense or wound up?			

	FBDSIC:FBD SEVERITY INDEX		
	Mild:<36 (n=617)	**Moderate:36 - <110 (n=949)**	**Severe:>=110 (N=400)**
	N (%)	**N (%)**	**N (%)**
Not at all	46 (7.5)	53 (5.6)	28 (7.0)
From time to time, occasionally	308 (49.9)	392 (41.3)	123 (30.8)
A lot of the time	184 (29.8)	344 (36.2)	146 (36.5)
Most of the time	79 (12.8)	160 (16.9)	103 (25.8)
Can you still enjoy things you used to enjoy?			
Definitely as much	230 (37.3)	236 (24.9)	40 (10.0)
Not quite as much	334 (54.1)	598 (63.0)	245 (61.3)
Only a little	35 (5.7)	73 (7.7)	62 (15.5)
Hardly at all	18 (2.9)	42 (4.4)	53 (13.3)

Table 4

Medication Use and Side Effects for Drugs Currently Used

Medication Type	Medication Use	Side Effects	
		Moderate	Severe
	N (%)	N (%)	N (%)
Non Narcotic Medications for Pain	616 (31.3)	11 (1.8)	2 (0.3)
Antidepressants	606 (30.8)	66 (10.9)	13 (2.1)
Acid Reducers	544 (27.7)	7 (1.3)	1 (0.2)
Antidiarrheals	464 (23.6)	29 (6.3)	2 (0.4)
Antispasmodics	363 (18.5)	32 (8.8)	2 (0.6)
Narcotic Pain Killers	355 (18.1)	44 (12.4)	3 (0.8)
Anti-Anxiety Medications	246 (12.5)	12 (4.9)	1 (0.4)
Anticonstipation Medications	90 (4.6)	19 (21.1)	2 (2.2)
Anti Nausea and Vomiting Medications	37 (1.9)	2 (5.4)	0 (0)
IBS Targeted Drugs	35 (1.8)	1 (2.9)	0 (0)
Tegaserod	17 (0.9)	0 (0)	0 (0)
Alosetron	18 (0.9)	1 (5.6)	0 (0)
Antibiotics	20 (1.0)	1 (5.0)	1 (5.0)

Shaded area denotes >10% moderate to severe side effects reported.

Table 5

Risk for Total IBS Symptom Relief

If given new medication	Death		Serious or permanent side effects		Mild side effects	
	All (N=1966)	Severe IBS (N=400)	All (N=1966)	Severe IBS (N=400)	All (N=1966)	Severe IBS (N=400)
Risk to take for total IBS symptom relief:	%	%	%	%	%	%
would not take	30.2	21.3	39.6	32.8	8.8	5
1/10million	15.4	13.5	16.3	14	7.3	9
1/1million	17.6	15.8	17.2	15.3	7.3	4
1/100,000	14.5	14.5	9.9	12	9.5	6.3
1 in 10,000	8.9	10.3	6.9	7.3	11.9	10.8
1 in 1,000	5.8	10	4.5	7.5	14.5	13.8
1 in 100	4.2	6.3	2.6	4.3	14.3	14.5
1 in 10	1.5	3	1.3	3	9.1	11
1 in 5	0.9	2	0.7	1.5	4.2	4.8
1 in 3	0.2	0.3	0.2	0.5	1.9	2
1 in 2	1.1	3.3	0.8	2	11.3	19

Table 6

FDA Influence

Let's assume you are taking a medication for over a year because it is helpful for your symptoms. The United States Food and Drug Administration (FDA) then decide that the medication may be harmful to others, for example to cause heart disease. There is some controversy as to whether this is truly the cause the FDA removed the drug from the market until the question of harm is resolved.	**US (N=1409)**	
	N	**(%)**
Considering that this keeps you from making an informed choice with your doctor and family, how much does this decision by the FDA affect you?		
Not at all	63	(4.5)
A little bit	192	(13.6)
A moderate amount	347	(24.6)
A great deal	630	(44.7)
Completely affected	177	(12.6)
Assuming it was helpful to your symptoms, how worried would you be to continue to take the medication with this information (assuming you still had a supply of your medication)?		
Not at all	99	(7.0)
A little bit	354	(25.1)
A moderate amount	420	(29.8)
A great deal	371	(26.3)
Completely worried	165	(11.7)
How much would you believe that this medication may have already done harm?		
Not at all	128	(9.1)
A little bit	495	(35.1)
A moderate amount	478	(33.9)
A great deal	255	(18.1)
Would believe it completely	53	(3.8)
How appreciative would you be that the FDA did its job of protecting the public from possible medical risk from this medication?		
Not at all	52	(3.7)
A little bit	174	(12.4)
A moderate amount	335	(23.8)
A great deal	482	(34.2)
Completely appreciative	366	(26.0)
How satisfied would you be with removal of the medication from the market as a precaution (and without evidence for harm) until the safety of the medication is established?		
Not at all	249	(17.7)
A little bit	247	(17.5)
A moderate amount	355	(25.2)
A great deal	297	(21.1)
Completely satisfied	261	(18.5)
Would you prefer that the medication remain off the market until the risk of the medication is established?		
Prefer the med remain off market	636	(45.1)
Prefer the med placed back on market	286	(20.3)
Not sure	487	(34.6)
If it were decided that the medication can stay on the market under restricted use, under what circumstances would you take this medication? (answer only once)		
Warning label /no other restrictions	198	(14.1)

Let's assume you are taking a medication for over a year because it is helpful for your symptoms. The United States Food and Drug Administration (FDA) then decide that the medication may be harmful to others, for example to cause heart disease. There is some controversy as to whether this is truly the cause the FDA removed the drug from the market until the question of harm is resolved.	**US (N=1409)**	
	N	**(%)**
Above plus: MD&I sign form /no other restrictions	255	(18.1)
All of the above plus: Med only prescribed by GI specialist	463	(32.9)
All of the above plus: Need get new prescription each month	130	(9.2)
All of the above plus: GI MD applies for use/pt files forms	363	(25.8)