Impact of Irritable Bowel Syndrome with Diarrhea (IBS-D) Symptom Severity on HCP and Patient Behaviors: Results from Two Separate Surveys of HCPs and Patients with IBS-D

Short title: Impact of Symptom Severity in IBS-D

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scope, direction, and content of the manuscript and have approved the submitted manuscript. They received no compensation related to the development of the manuscript.

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Abstract

**BACKGROUND:** Management of diarrhea-predominant irritable bowel syndrome (IBS-D) is generally based on patient-reported symptoms, yet there is limited information about symptom severity.

**METHODS:** We conducted two web-based surveys of HCPs and patients from Australia, Canada, and Europe. We analyzed patient characteristics and attitudes by IBS-D severity using a composite of four variables: worst abdominal pain, IBS symptom frequency, Bristol Stool Form Scale, and quality of life (QoL).

**RESULTS:** Of 679 HCP respondents, one-third routinely classify patients by severity. The patient survey was completed by 513 patients with mild (26%), moderate (33%), and severe (41%) IBS-D, as classified using the composite scale. Age, sex, and treatment satisfaction did not change with severity. Nineteen percent of patients classified with severe IBS-D agreed with the statement: “When my IBS is bad, I wish I was dead” vs. 4% and 7% of patients with mild and moderate IBS-D, respectively ($P<0.05$). Significantly more patients classified with severe IBS-D reported use of both prescription and over-the-counter medications vs. mild IBS-D.

**CONCLUSIONS:** Compared with milder symptoms, severe IBS-D was associated with increased medication use and a negative perspective of IBS-D. This highlights the need for a validated severity scale for use in research and clinical practice, to inform treatment decisions.
KEY SUMMARY

SUMMARISE THE ESTABLISHED KNOWLEDGE ON THIS SUBJECT

- The management of irritable bowel syndrome with diarrhea (IBS-D) is generally informed by patient-reported symptoms.

- More severe IBS-D, based on patient-reported severity, is associated with worse health-related quality of life (QoL) and increased work and activity impairment, adverse food reactions, and healthcare resource use.

- Rome guidance advocates quantifying symptom severity, but there is limited data on the differences between mild and severe IBS.

- As more treatments become available for IBS, further guidance on severity is required to identify which patients are most likely to benefit from them.

WHAT ARE THE SIGNIFICANT AND/OR NEW FINDINGS OF THIS STUDY?

- Primary care physicians and gastroenterologists had a similar approach to the assessment of IBS-D severity, but specialists more often used worst abdominal pain and Bristol stool form scale.

- Patients with severe IBS-D were more likely to have continuous symptoms and higher medication use than those with moderate or mild IBS-D.

- Severe IBS-D was associated with an increase in negative emotions and a greater desire to find a treatment that significantly improves QoL.
Development of a comprehensively designed and validated scale is warranted for the assessment of severity in IBS-D
INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional bowel disorder with a global prevalence of around 11% [1]. IBS is characterized by abdominal pain with altered bowel habits, such as a predominance of constipation (IBS-C), diarrhea (IBS-D), or a mixed pattern of both (IBS-M), as well as urgency and bloating [2, 3]. Prevalence of the IBS-C, IBS-D, and IBS-M subtypes has been reported as 35%, 40%, and 23%, respectively [1]. Symptoms vary from mild to severe and intermittent to continuous, with incidence of mild IBS reported estimated to be ~40%, moderate ~35%, and severe ~25%, based on patients self-perceived severity [4]. Patients who self-report severe IBS-D have been described as experiencing greater impairments in health-related quality of life (QoL), increased work and activity impairment, more adverse food reactions, and increased healthcare resource use compared to patients who self-report mild or moderate IBS-D [5-9].

To date there is no established definition of severity for IBS. The Rome IV diagnostic criteria do not classify patients according to IBS severity, but set out a multifactorial approach for the diagnosis of IBS based on symptoms, primarily abdominal pain and diarrhea. [2]. The Rome IV criteria-state that IBS treatment should be dependent upon symptom type and severity [2] (for example, linaclotide is recommended for patients with moderate-to-severe IBS-C [10]); however, no validated scale is suggested to assess this, beyond those available for IBS as a whole, such as the Birmingham-IBS questionnaire, functional bowel disorder severity index, and the IBS symptom severity scale (IBS-SSS). These scales do not take into account the multifactorial diagnostic approach set out by the Rome IV criteria [4, 11-14] and are not specific to IBS-D or IBS-C. Therefore, classification of IBS-D severity is dependent upon the type of scale used and whether the patient or
physician makes the severity definition, as well as variables such as symptom intensity, time of assessment, and degree of disability or impairment [15].

We conducted a study which surveyed: (i) patients receiving treatment for IBS-D and (ii) treating gastroenterologists and primary care physicians, to assess the health burden of IBS-D on patients and the attitudes and perspectives of treating HCPs towards IBS-D. Our primary analysis found that many patients are dissatisfied with their current treatment and feel under supported by their HCPs, whilst the physicians themselves find IBS-D to be a challenging condition to manage. One surprising finding of the study was that faecal urgency was reported as the most troublesome symptom rather than the characteristic diarrhea and abdominal pain.[16]

The aim of this post hoc subanalysis was to evaluate HCPs’ attitudes towards the classification of severity in IBS-D based on the survey data and to evaluate symptom burden, medication consumption, and patients’ attitudes graded by severity, as defined using patient-reported variables.

**MATERIALS AND METHODS**

The study was comprised of two web-based, self-administered surveys of (1) treating HCPs and (2) patients with IBS-D. Detailed methodology of the surveys are described elsewhere.[16] Each structured questionnaire was administered via market research panels provided by Survey Sampling International and included individuals from Australia, Canada, France, Germany, Italy, Spain, and the UK.

The 40-minute HCP survey was completed between February and April 2016. Gastroenterologists and primary care physicians (PCPs) were included, with a target sample size of 45 of each HCP type per country. HCPs were paid honoraria of up to $150 for
participating in the survey. The analysis described here focuses on responses to questions around the assessment of IBS-D severity.

The 30-minute patient survey was completed between January and February 2016. The target sample size was 80 patients per country. Patients with IBS-D opted-in to complete the survey via an email link; they received a small monetary compensation for their time. The survey comprised 51 questions assessing patients’ attitudes towards their IBS and IBS treatments.

Sample population

For both surveys, individuals who were affiliated with a pharmaceutical company or who had participated in IBS market research within the 3 months prior to the study were excluded.

For the HCP survey, those who met the following screening criteria were included in the analysis: 3–35 years’ experience in their role; consultant grade or equivalent (gastroenterologists only); consultations with patients with diagnosed IBS-D within 3 months prior to the survey; and prescribed medication or recommended over-the-counter treatments for patients with IBS-D.

For the patient survey, those who met the following screening criteria were included: males and females aged 18–65 years; diagnosed with IBS-D by a doctor; symptoms of diarrhea and abdominal pain, discomfort, or spasm; symptoms present for >1 year and within the past 12 months; currently using prescription or over-the-counter medications for IBS-D; had not had their gallbladder removed; and not diagnosed with gastrointestinal comorbidities including chronic constipation, inflammatory bowel disease, celiac disease, stomach cancer, diverticulitis, ulcerative colitis, Crohn’s disease, pancreatitis, and small intestinal inflammation. Target maximum quotas were set for the proportion of female patients (70%) and the proportion of patients who had never seen a gastroenterologist for their IBS-D (40%).
Responses to statements

HCPs’ and patients’ attitudes to statements were scored using a 7-point Likert scale (1=completely disagree; 4=neither agree nor disagree; 7=completely agree). Participants who answered 6 (agree) or 7 were considered to agree with the statement; those who answered 1 or 2 (disagree) were considered to disagree with the statement. Participants with a score of 3–5 were classed as neither agreeing nor disagreeing with the statement.

Definition of IBS-D severity

For the HCP survey, definitions of severity (mild, moderate, and severe) were provided to survey participants, as defined by the 2011 Rome Foundation Working Team report [4]. Mild IBS-D was defined as mild or intermittent abdominal pain, little or no psychological distress, with occasional impact on activities. Moderate IBS-D was defined as moderate or frequent abdominal pain, more psychological distress, with more frequent impact on activities. Severe IBS-D was defined as very frequent or continuous abdominal pain, high psychological distress, with frequent or constant impact on activities. The survey also captured the criteria that HCPs were currently using to assess IBS-D symptom severity.

In the patient survey IBS-D severity was calculated using an algorithm comprising four variables chosen retrospectively to reflect the Rome IV diagnostic criteria [2], recent clinical trial data, and clinical experience. Worst abdominal pain (WAP) scored from 0 (no pain) to 10 (worst pain imaginable), frequency of IBS symptoms measured in days/month, stool consistency scored from BSFS 3 (stools which are like a sausage but with cracks on its surface) to 7 (watery stool with no solid pieces, entirely liquid), and a measure of QoL assessed according to patient responses to the single statement: “Having IBS stops me enjoying life”, scored on a 7-point Likert scale. A-symptom frequency score was created by taking the maximum number of days from four questions on average monthly frequency of
stomach pain and/or diarrhea symptoms. The questions and response choices are listed in 

**Supplementary Table 1.**

Symptom frequency, WAP, BSFS and QoL scores were grouped into high or low categories (and medium for QoL) selected on the judgement of the lead investigators and informed by prior experience in the therapeutic area. These categories were the basis of the algorithm used to stratify patients into groups of mild, moderate, or severe IBS-D as per **Figure 1.**

**Statistical analysis**

Anonymized patient responses were analyzed at the respondent record level and stratified by the mild/moderate/severe classification. Statistical analyses were performed on the differences between the three severity groups. Two-tailed t-tests were performed for the means and proportions from independent groups (mild, moderate, severe IBS-D; HCPs and PCPs) to compare demographics, characteristics, and attitudes data at a 5% risk level, with $P<0.05$ denoting significance. Analyses were completed in Microsoft Excel (Microsoft, Redmond, WA, USA).

**RESULTS**

**HCP survey**

Of the 1,460 HCPs screened, 313 gastroenterologists and 366 PCPs were eligible for inclusion and completed the survey. The demographics and caseloads of these HCPs are described elsewhere [17].

**HCP classification of IBS-D severity**

Approximately one third each of PCPs (30%) and gastroenterologists (31%) reported that they routinely classify their IBS-D patients by severity (**Table 1**). Using the severity
definitions provided, gastroenterologists estimated that 42% of their diagnosed or suspected IBS-D patients have mild, 41% have moderate, and 18% have severe IBS-D. Similarly, PCPs estimated that 46%, 40%, and 14% of their diagnosed or suspected IBS-D patients have mild, moderate, and severe IBS-D, respectively.

Very few of the HCPs who routinely assessed IBS-D severity reported using guidelines to make this classification (3% and 8% of PCPs and gastroenterologists, respectively). In general, around half of the HCPs who classified patients by IBS-D severity reported that this was based on the frequency/duration of symptoms, type of symptoms, and/or impact on daily life (Table 1). Of those HCPs who did not routinely classify their patients by severity in their day-to-day practice, impact on QoL, level of abdominal pain, number of symptomatic days in an average month, and frequency of diarrhea were the factors most likely to be used for this purpose (Figure 2 Supplementary Figure 1). Compared to PCPs, gastroenterologists were more likely to use frequency of diarrhea, whether a patient responds to treatment, and stool consistency to make a severity assessment (Figure 2 Supplementary Figure 1).

Use and awareness of the BSFS and WAP scale varied widely between the groups of HCPs: 61% of PCPs reported a lack of awareness/use of the BSFS, compared to 28% of gastroenterologists (Figure 3). Similarly, 63% of PCPs reported a lack of awareness/use of the WAP scale, compared to 48% of gastroenterologists (Figure 3).

Patient survey

Demographics and healthcare characteristics

Overall, 8,627 patients were screened, of whom 513 were eligible and completed the survey; the mean age was 40.9 years and 70% were female [17]. All 513 patient responses were anonymized and assessed for severity, 193 patients (38%) had severe IBS-D, 158 (31%) had
moderate IBS-D, and 124 (24%) had mild IBS-D (Table 2). In total, 38 patients (7%) did not meet the severity criteria and were excluded from the severity analysis, including patients who answered “prefer not to answer” on BSFS score and “0—no pain” for WAP score. Comorbidities were generally evenly distributed across all severity groups, although a significantly greater proportion of patients with severe IBS-D reported depression and fibromyalgia compared to patients with mild or moderate IBS-D (P<0.05 for both comparisons; Table 2). Patients tended to have undergone several prior diagnostic tests, with a greater proportion of patients with severe IBS-D having had an endoscopy/colonoscopy (69%) compared to patients with mild (48%) or moderate (58%) IBS-D (P<0.05 for both comparisons; Table 2). Age and sex were not associated with IBS-D severity.

**IBS symptom characteristics**

The mean duration of IBS symptoms for was 9.8 years without any significant difference in duration across severity groups (Supplementary Table 2). The two most common reasons for patients having a first visit to an HCP were increasing frequency of symptoms and large impact on QoL for all severity groups (Supplementary Table 2).

A greater proportion of patients with severe IBS-D reported continual symptoms over the 3 months prior to the survey compared to those with mild or moderate IBS-D (P<0.05 for both comparisons; Figure 3a). For individual IBS symptoms, a larger proportion of patients with severe IBS-D listed urgency as common, compared to patients with mild or moderate IBS-D (47% vs. 35% for mild and moderate; P<0.05 for both comparisons) and a larger proportion with severe IBS-D listed fecal incontinence as common, compared to mild or moderate IBS-D (22% vs. 16% and 13%, respectively; P<0.05 for severe vs. moderate groups; Supplementary Table 2). Finally, patients with severe IBS-D were more likely to
report fecal urgency as the most troublesome symptom, compared to patients with mild or moderate IBS-D (34% vs. 23% and 20%, respectively; $P<0.05$ each; Figure 53b).

**Medication use**

Of the different types of medications used, patients with severe IBS-D were more likely to use antidiarrheals compared to patients with mild or moderate IBS-D (87% vs. 76% and 78%, respectively; $P<0.05$ each; Table 3). A proportion of patients in all groups reported the use of codeine-based painkillers, analgesics, and antidepressants, including patients with only mild IBS-D (Table 3); however, antidepressant use was reported by a greater proportion of patients with severe vs. mild or moderate IBS-D (20% vs. 11% or 16%, respectively; $P<0.05$ as compared to mild only). Concurrent use of prescription and over-the-counter medications was reported in a greater proportion of patients with severe IBS-D compared to patients with mild or moderate IBS-D (36% vs. 24% or 29%, respectively; $P<0.05$ as compared to mild only; Table 3). Patients with severe IBS-D were also more likely to take three or more types of treatment intermittently or every day compared to those with mild IBS-D (69% vs. 56%; $P<0.05$). Treatment satisfaction for all medications considered was not found to be associated with IBS-D severity (data not shown).

**Patient attitudes**

Overall patient attitudes towards IBS-D are described in the initial overall report [17]. Response frequencies on negative emotions were significantly higher in patients with severe IBS-D for all emotions, compared to mild or moderate IBS-D, whereas response frequencies on positive emotions such as feeling “in control” or “accepting” were generally lower for patients with severe IBS-D compared to mild or moderate IBS-D (10% vs. 40% and 20%; 23% vs. 35% and 34%, respectively; Figure 4).
Compared to patients with mild or moderate IBS-D, there was a tendency for a significantly greater proportion of patients with severe IBS-D to report agreement with negative statements related to their IBS; over half of patients with severe IBS-D were constantly worried about when their symptoms would return, compared to patients with mild or moderate IBS-D (55% vs. 19% and 30%, respectively; \( P < 0.05 \) each) (Supplementary Figure 2A). Further, 19% of patients with severe IBS-D agreed with the statement: “When my IBS is bad, I wish I was dead”, compared to 4% of patients with mild IBS-D and 7% of patients with moderate IBS-D (\( P < 0.05 \) for both comparisons).

Similar severity associations were observed in terms of patients’ attitudes towards HCPs and services (Supplementary Figure 2B). A significantly greater proportion of patients with severe IBS-D agreed with statements that there should be more services and education available for patients with IBS, compared to patients with mild or moderate IBS-D (59% vs. 27% and 35%, respectively; \( P < 0.05 \) each), and that IBS is a “last resort” diagnosis (31% vs. 15% and 18%, respectively; \( P < 0.05 \) each).

Regarding current therapies, 62% of patients with severe IBS-D agreed with the statement: “I would use a daily treatment for the rest of my life if it prevented IBS symptoms”, compared to 26% of patients with mild IBS-D (\( P < 0.05 \)) and 49% of patients with moderate IBS-D (\( P < 0.05 \); Supplementary Figure 2C). Overall, 60% of patients with severe IBS-D would be willing to try anything to help manage their IBS, compared to 28% of patients with mild IBS-D and 43% with moderate IBS-D (\( P < 0.05 \) each).

**DISCUSSION**
This post hoc analysis indicates that increasing severity of IBS-D was associated with increased medication use and a negative impact on patients’ attitudes towards the condition itself and HCPs, services, and available treatments. In addition, we found that the majority of HCPs surveyed did not routinely assess severity in their patients with IBS. There is therefore a need for a standardized, multidimensional scale to assess severity in IBS-D, including measures of self-reported outcomes covering health-related QoL, psychosocial factors, and burden of illness associated with IBS-D, particularly as new treatments emerge that are specific for this condition. A more complete understanding of symptom severity could not only improve the management and treatment of IBS-D, but could also inform patient stratification during future clinical trials to assess efficacy and safety across severity subgroups. One available method which could assist clinicians in monitoring symptoms is, the IBS-D daily symptom diary and event log, a patient-reported outcome measure designed to measure treatment benefit, which includes measures of patient impression of severity and change over time.[18-20]

In those HCPs who did routinely assess severity, this was largely based on the frequency/duration of symptoms, type of symptom, and perceived impact on patients’ daily lives. When directly questioned, similar criteria including abdominal pain, number of symptomatic days, and frequency of diarrhea were likely to be used by those HCPs who did not routinely assess severity in their day-to-day practice, factors which are included in the Rome IV diagnostic criteria for IBS [2]. It is particularly noteworthy, given that most IBS patients are managed in the community, that a large proportion of PCPs were found to be unaware of the BSFS and WAP scale. Among PCPs and gastroenterologists, only half of those surveyed used either scale in their clinical practice, despite the inclusion of the BSFS in the Rome IV criteria [2]. Further, very few respondents indicated that they used guidelines in the assessment of severity, indicating that current IBS-D guidelines are inadequate in this
respect. While various scales for the assessment of severity in IBS have been reported previously, such as the Birmingham-IBS questionnaire and IBS-SSS, these assessments are not specific to IBS-D [11-13].

In the current analysis, we used a composite severity scale to define subgroups of patients with IBS-D. This algorithm, although limited by the data already collected in the primary survey, was retrospectively designed to reflect the latest Rome IV diagnostic criteria [2], capturing information related to four key variables (abdominal pain, frequency of IBS symptoms, stool form, and QoL). As such, this work was not powered to present a definitive research-oriented severity index, but rather to assess differences in physical symptoms, attitudes and behaviors in order to inform clinicians’ future management strategies according to IBS severity. A prospectively developed severity index for IBS-D will require external validation for use in clinical practice [21, 22]. This validation should include validation of the content, construct, and criteria, as well as an assessment of the reliability and responsiveness of the index, with consideration given to the target sample numbers required a priori [23, 24].

IBS-D imposes a substantial burden on patients with the condition, who can experience troublesome symptoms, such as urgency, for long periods of time. Patients also express high levels of dissatisfaction with available treatments, which demonstrates an unmet need for the satisfactory management of these patients. This is important to note, as patient education has been shown to reduce IBS symptom severity [25, 26] and to improve QoL [26], suggesting that management of patients’ attitudes towards IBS will also help them manage their symptoms. Indeed, we found that a greater proportion of patients classified with severe IBS-D agreed that more education should be available.
Rome IV criteria state that IBS treatment should be dependent upon symptom type and severity, with initial treatment involving reassurance and diet and lifestyle modifications [2]. Other treatment options include opioid antagonists, bile acid sequestrants, probiotics, antibiotics, and 5-HT3 antagonists, yet prescription medications appear to be underutilized [27]. We observed in this study that while the majority of patients had received antidiarrheals, around 40% of patients with severe IBS-D were not taking any prescription medications but were relying on over-the-counter medications, despite over 60% of patients with severe IBS-D being willing to receive regular treatment.

Classification of IBS-D severity is also crucial to understanding the natural history of the condition, and whether patients with mild IBS go on to develop more severe IBS or whether patients may fluctuate between severity grades. A reliable method to classify IBS-D severity will also be of value for payers and regulatory agencies in order to indicate drugs based on IBS-D severity, such as alosetron, which is indicated by the FDA only for female patients with severe IBS-D [28].

These results should be interpreted in light of the study limitations. As 60% of patients were required to have previously seen a gastroenterologist for their IBS-D, this patient population may have been skewed, leading to a higher estimate of patients suffering from severe IBS-D symptoms. Likewise, the requirement for gastroenterologists to be consultant grade may have excluded the perspectives of younger HCPs. In addition, the limitations of the survey itself include the use of a single question to assess troublesome symptoms (patients may have several highly troublesome symptoms), and also the lack of appropriate response options for certain questions. Indeed, a proportion of patients with severe IBS-D selected their most troublesome symptom as “other” (i.e. not listed in this questionnaire). In particular, the troublesome symptom question did not take into account the severity of individual symptoms.
Further, there may be inherent biases introduced by the use of the Likert format, such as acquiesce bias (the tendency for respondents to agree with statements) [29]. Finally, there are limitations to the severity algorithm utilized in this analysis. We feel that the categories we selected to assess severity WAP, BSFS, symptom frequency and QoL adequately reflect the key factors we use to assess IBS-D in the clinic, however the depth of information available to us particularly within the QoL and symptom frequency categories was limited due to the retrospective development of the severity scale. This scale does not assess certain factors reported as important drivers of reduced QoL, such as abdominal distension or urgency [30]; this is also true of the IBS-SSS, which does not assess urgency and incontinence. However, this scale was able to demonstrate some clear differences in-patient characteristics and attitudes according to the level of IBS-D severity and therefore highlights the need for a validated scale.

CONCLUSIONS

This post hoc analysis demonstrated that patient characteristics and attitudes differ substantially according to the severity of their IBS-D symptoms. This indicates a need for the development of a symptom severity index. Further attention is warranted by the Rome IV Committees as part of their multi-axial work-up of patients with functional disorders [4]. We also identified a distinct need for improved pharmacological and supportive management of patients with IBS-D in order to reduce symptom burden, particularly in those with more severe IBS-D.

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REFERENCES


## Tables

### Table 1. Factors used by PCPs and gastroenterologists to classify patients with IBS-D by severity

<table>
<thead>
<tr>
<th>HCPs, n (%)</th>
<th>PCPs (n=366)</th>
<th>Gastroenterologists (n=313)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classifying patients by severity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>110 (30)</td>
<td>98 (31)</td>
</tr>
<tr>
<td>Classification based on:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency/duration of symptoms</td>
<td>59 (54)</td>
<td>48 (49)</td>
</tr>
<tr>
<td>Impact on daily life</td>
<td>52 (47)</td>
<td>50 (51)</td>
</tr>
<tr>
<td>Type of symptoms</td>
<td>51 (46)</td>
<td>46 (47)</td>
</tr>
<tr>
<td>Intensity of symptoms</td>
<td>21 (19)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Abdominal pain intensity scale</td>
<td>19 (17)</td>
<td>21 (21)</td>
</tr>
<tr>
<td>Guidelines</td>
<td>3 (3)</td>
<td>8 (8)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on responses to the question: “Do you classify or group your diagnosed IBS-D patients by severity in your day-to-day practice?”

<sup>b</sup>Based on responses to the question: “Please describe below how you classify or group your diagnosed IBS-D patients by severity in your day-to-day practice”, (select all that apply) expressed as a proportion of those HCPs answering “yes” to the previous question.

HCP, healthcare professional; IBS-D, irritable bowel syndrome with diarrhea; PCP, primary care physician.
<table>
<thead>
<tr>
<th></th>
<th>Mild IBS-D</th>
<th>Moderate IBS-D</th>
<th>Severe IBS-D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>((n=124))</td>
<td>((n=158))</td>
<td>((n=193))</td>
</tr>
<tr>
<td>Female, (n (%))</td>
<td>81 (65)</td>
<td>109 (69)</td>
<td>143 (74)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>40.4 (10.9)</td>
<td>40.5 (11.2)</td>
<td>42.0 (12.1)</td>
</tr>
<tr>
<td>Most common comorbidities, (n) (%)(^{a,b})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>42 (34)</td>
<td>60 (38)</td>
<td>73 (38)</td>
</tr>
<tr>
<td>Depression</td>
<td>26 (21)</td>
<td>35 (22)</td>
<td>65 (34)(^{*})(^{†})</td>
</tr>
<tr>
<td>Migraine</td>
<td>31 (25)</td>
<td>41 (26)</td>
<td>55 (28)</td>
</tr>
<tr>
<td>Gastric reflux</td>
<td>23 (19)</td>
<td>38 (24)</td>
<td>39 (20)</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>11 (9)</td>
<td>23 (15)</td>
<td>30 (16)</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>3 (2)</td>
<td>5 (3)</td>
<td>22 (11)(^{*})(^{†})</td>
</tr>
<tr>
<td>Diarrhea due to bacterial infection</td>
<td>13 (10)</td>
<td>9 (6)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Diagnostic testing history, (n) (%)(^{c,d})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood tests</td>
<td>94 (76)</td>
<td>121 (77)</td>
<td>158 (82)</td>
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<tr>
<td>Stool test</td>
<td>72 (58)</td>
<td>95 (60)</td>
<td>128 (66)</td>
</tr>
<tr>
<td>Endoscopy/colonoscopy</td>
<td>59 (48)</td>
<td>91 (58)</td>
<td>134 (69)(^{*})(^{†})</td>
</tr>
<tr>
<td>Food allergy tests</td>
<td>42 (34)</td>
<td>56 (35)</td>
<td>88 (46)</td>
</tr>
</tbody>
</table>

\(^{*}\)\(P<0.05\) vs. patients with mild IBS-D; \(^{†}\)\(P<0.05\) vs. patients with moderate IBS-D.

\(^a\)Based on responses to the question: “Which of the following conditions, if any, have you...
been diagnosed with by a doctor?”  bReported in ≥10% of patients.  cBased on responses to the question: “Which of the following tests have been carried out since you first experienced symptoms of IBS?”  dReported in ≥20% of patients.

IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; SD, standard deviation.
Table 4.3. Medication use by IBS-D severity

<table>
<thead>
<tr>
<th></th>
<th>Mild IBS-D (n=124)</th>
<th>Moderate IBS-D (n=158)</th>
<th>Severe IBS-D (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of medication used over the past 12 months&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidiarrheal</td>
<td>94 (76)</td>
<td>124 (78)</td>
<td>167 (87)&lt;sup&gt;*&lt;/sup&gt;†</td>
</tr>
<tr>
<td>Antispasmodic</td>
<td>71 (57)</td>
<td>99 (63)</td>
<td>112 (58)</td>
</tr>
<tr>
<td>Analgesic</td>
<td>17 (14)</td>
<td>27 (17)</td>
<td>33 (17)</td>
</tr>
<tr>
<td>Codeine-based painkiller</td>
<td>18 (15)</td>
<td>28 (18)</td>
<td>43 (22)</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>14 (11)</td>
<td>25 (16)</td>
<td>38 (20)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other</td>
<td>9 (7)</td>
<td>11 (7)</td>
<td>15 (8)</td>
</tr>
</tbody>
</table>

| Current medication use<sup>b</sup> |                    |                        |                      |
|------------------------------------|                    |                        |                      |
| OTC medication only                | 59 (48)            | 66 (42)                | 75 (39)              |
| Prescription and OTC medication    | 30 (24)            | 46 (29)                | 69 (36)<sup>*</sup>  |
| Prescription medication only       | 35 (28)            | 46 (29)                | 49 (25)              |

<sup>*</sup>P<0.05 vs. patients with mild IBS-D; †P<0.05 vs. patients with moderate IBS-D.

<sup>a</sup>Based on responses to the question: “Which of the following have you taken in the past 12 months for your IBS?”

<sup>b</sup>Based on responses to the question: “Do you take either of the following to help manage your IBS?”

IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; OTC, over-the-counter.
**Figure legends**

**Figure 1.** Criteria for the determination of IBS-D severity by worst abdominal pain, frequency of symptoms, Bristol Stool Form Scale, and quality of life. Cut-offs for severity levels were arbitrary and based on clinical experience; frequency was based on the number of days with IBS symptoms. BSFS, Bristol Stool Form Scale; IBS-D, irritable bowel syndrome with diarrhea; QoL, quality of life; WAP, worst abdominal pain.

**Figure 32.** Use of the Bristol Stool Form Scale and worst abdominal pain scale in the management of patients with IBS-D. Based on responses to the question: “At what point, if at all, do you use the following scales in managing your IBS-D patients?” (a) \( P<0.05 \) for PCPs vs. gastroenterologists unaware of the BSFS, only using the BSFS at initial assessment with patient, and using the BSFS at each consultation with patient before and after diagnosis. (b) \( P<0.05 \) for PCPs vs. gastroenterologists unaware of the WAP scale, aware of the WAP scale but not using, and using the WAP scale at each consultation with patient before and after diagnosis. BSFS, Bristol Stool Form Scale; Gastro, gastroenterologist; HCP, healthcare professional; IBS-D, irritable bowel syndrome with diarrhea; PCP, primary care physician; WAP, worst abdominal pain.

**Figure 43.** Symptom patterns and most troublesome symptoms by IBS-D severity.

a. Symptom patterns over the past 3 months by IBS-D severity. \( P<0.05 \) for all comparisons (mild vs. severe and moderate vs. severe; continual and intermittent). Based on responses to the question: “Which best describes the pattern of your IBS symptoms over the past 3 months?” aDefined as experiencing some IBS symptoms every day. bDefined as having some days without any IBS symptoms. IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea.
b. Most troublesome symptoms currently experienced by IBS-D severity. Based on the first selected response to the question: “Which of the symptoms you currently experience trouble you the most?” (bloating was not included as a potential response). *P<0.05. IBS-D, irritable bowel syndrome with diarrhea.

Figure 6.4. Patients’ feelings about having IBS by IBS-D severity. Based on responses to the question: “How do you currently feel about having IBS?” (a) Negative emotions associated with IBS. (b) Positive emotions associated with IBS. *P<0.05. IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea.
Figure 1. Criteria for the determination of IBS-D severity by worst abdominal pain, frequency of symptoms, Bristol Stool Form Scale, and quality of life. Cut-offs for severity levels were arbitrary and based on clinical experience; frequency was based on the number of days with IBS symptoms. BSFS, Bristol Stool Form Scale; IBS-D, irritable bowel syndrome with diarrhea; QoL, quality of life; WAP, worst abdominal pain.
**Figure 32.** Use of the Bristol Stool Form Scale and worst abdominal pain scale in the management of patients with IBS-D. Based on responses to the question: “At what point, if at all, do you use the following scales in managing your IBS-D patients?”

(a) $P<0.05$ for PCPs vs. gastroenterologists unaware of the BSFS, only using the BSFS at initial assessment with patient, and using the BSFS at each consultation with patient before and after diagnosis. 

(b) $P<0.05$ for PCPs vs. gastroenterologists unaware of the WAP scale, aware of the WAP scale but not using, and using the WAP scale at each consultation with patient before and after diagnosis. BSFS, Bristol Stool Form Scale; Gastro, gastroenterologist; HCP, healthcare professional; IBS-D, irritable bowel syndrome with diarrhea; PCP, primary care physician; WAP, worst abdominal pain.
**Figure 43** Symptom patterns and most troublesome symptoms by IBS-D severity.

**(a)** Symptom patterns over the past 3 months by IBS-D severity. \( P<0.05 \) for all comparisons (mild vs. severe and moderate vs. severe; continual and intermittent). Based on responses to the question: “Which best describes the pattern of your IBS symptoms over the past 3 months?” 

- Defined as experiencing some IBS symptoms every day.
- Defined as having some days without any IBS symptoms.

IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea.

**(b)** Most troublesome symptoms currently experienced by IBS-D severity. Based on the first selected response to the question: “Which of the symptoms you currently experience trouble you the most?” (bloating was not included as a potential response). \(*P<0.05\). IBS-D, irritable bowel syndrome with diarrhea.
Figure 6.4. Patients’ feelings about having IBS by IBS-D severity. Based on responses to the question: “How do you currently feel about having IBS?” (a) Negative emotions associated with IBS. (b) Positive emotions associated with IBS. *P<0.05. IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea.