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Willingness to accept risk with medication in return for cure of symptoms among patients with Rome IV irritable bowel syndrome

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Summary

Background: Some drugs for irritable bowel syndrome (IBS) have serious side effects.

Aims: To examine the willingness of individuals with IBS to accept risks with medication in return for symptom cure.

Methods: We collected demographic, gastrointestinal symptoms, psychological health, quality of life and impact on work and daily activities data from 752 adults with Rome IV-defined IBS. We examined median willingness to accept death in return for cure with a hypothetical medication using a standard gamble, according to these variables.

Results: Participants would accept a median 2.0% (IQR 0.0%-9.0%) risk of death in return for a 98.0% (IQR 91.0%-100.0%) chance of permanent symptom cure. The median accepted risk of death was higher in men (5.0% vs 2.0%, $P < 0.001$), those with continuous abdominal pain (4.0% vs 1.0%, $P < 0.001$), more severe symptoms ($P = 0.005$ for trend), abnormal depression scores ($P < 0.001$ for trend), higher gastrointestinal symptom-specific anxiety ($P < 0.001$ for trend), and lower IBS-related quality of life ($P < 0.001$ for trend). Those willing to accept above median risk of death were more likely to be male (17.1% vs 9.1%, $P < 0.001$), take higher levels of risks in their daily life ($P = 0.008$ for trend), and report continuous abdominal pain (53.1% vs 39.4%, $P < 0.001$), and had higher depression ($P = 0.004$ for trend) and lower quality of life ($P < 0.001$ for trend) scores.

Conclusion: Patients are willing to accept significant risks in return for cure of their IBS symptoms.

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1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction (DGBI) affecting 5% to 10% of the population,[1] characterised by recurrent abdominal pain in association with abnormal stool form or frequency. Although the diagnosis is made using symptom-based criteria proposed by the Rome Foundation,[2] the pathophysiology is complex and incompletely understood.[3] As a result, patients with IBS form a heterogenous group of individuals possibly suffering from different underlying pathophysiological dysregulations but presenting with similar symptoms of abdominal pain and altered bowel habit.

For most patients, IBS is a chronic condition, with a relapsing and remitting course.[4] Quality of life is affected to the same degree as organic gastrointestinal disorders, such as Crohn's disease.[5] The condition also impacts on other aspects of daily life, such as work productivity,[6,7] social functioning,[8,9] and psychological health.[10-12] As the cause of IBS remains unclear, current treatment approaches target predominant gastrointestinal symptoms, rather than addressing specific underlying mechanisms. Most treatment trials demonstrate high placebo response rates and modest efficacy.[13-18] Although novel drugs continue to be developed, over the last 20 years several have been either withdrawn or their use restricted, due to safety concerns. Examples include ischemic colitis with alosetron,[19] an excess of cardiovascular and cerebrovascular events with tegaserod,[20] and episodes of acute pancreatitis with eluxadoline.[21] Although regulatory bodies often have laypersons, including patients and carers, on their committee, they do not require formal consideration, review or quantification of the risks patients are willing to accept to relieve or cure their symptoms. In a chronic, incurable, condition like IBS, which has a huge impact on quality of life, and where most drugs have limited efficacy, it is important to determine these risks.

A previous survey established that individuals with IBS were, on average, willing to relinquish 15.1 years of their life to achieve perfect health with a new medication.[22] In one study patients were willing to accept a 2.65% risk of bowel impaction and a 1.34% risk of bowel perforation from medication, although the use of a discrete choice experiment only allowed the authors to examine a specific set of trade-offs for a drug for use in women with IBS with diarrhoea (IBS-D).[23] Two other studies reported that patients with IBS were willing to accept a median 1% risk of sudden death for a 99% chance of cure of their symptoms,[24] and that patients with IBS with predominant severe diarrhoea would accept a mean 10.2% risk of sudden death for a 99% chance of cure,[25] but these studies were relatively small and patients were recruited from referral populations. In addition, three of these previous studies used the Rome III criteria for IBS, but symptom severity appears worse with the current Rome IV criteria,[26] so their findings may no longer be applicable. Finally, none of these examined predictors of a higher acceptance of medication-related risk among individuals with IBS. We, therefore, examined willingness to accept risks with medications in return for cure of symptoms in a cohort of individuals with IBS defined according to the Rome IV criteria.

2 | MATERIALS AND METHODS

2.1 | Participants and Setting

We recruited individuals registered with ContactME-IBS, a national UK registry of 4280 members with IBS who have expressed an interest in volunteering for research. Individuals find out about the registry via numerous sources including their primary care practice, specialist hospital clinics, posters in pharmacies or social media. All registrants have a documented diagnosis of IBS, of whom 1455 (34%) have seen a gastroenterologist with IBS, and 2268 (53%) their primary care physician. They self-identify to the registry as having IBS and enrol online by completing a short questionnaire about their bowel symptoms. They are then asked to provide their contact details. The registry is run by County Durham and Darlington NHS Foundation Trust. There were no exclusion criteria apart from the inability to understand written English. We contacted all individuals registered with ContactME-IBS, via electronic mailshot, in July 2021. The correspondence directed them to a website where they were able to access further information about the study. Those willing to participate were able to complete an online questionnaire, with their responses stored in an online database. Non-responders received a reminder email in August 2021. Those who participated in the study were given a chance to win one of three gift cards (worth £200, £100 or £50) in return for completing the questionnaire. The University of Leeds research ethics committee approved the study in March 2021 (MREC 20-051).

2.2 | Data collection and synthesis

2.2.1 | Demographic and symptom data

We collected basic demographic data, including age, sex, lifestyle (tobacco and alcohol consumption), ethnicity, marital status, educational level and annual income. We defined the presence of IBS according to the Rome IV questionnaire,[27] via the scoring algorithm proposed for its use.[2] We categorised IBS subtype using the proportion of time stools were abnormal according to the Bristol stool form scale (BSFS), as recommended.[27] We asked all participants to report their most troublesome symptom from a list of five possibilities, including abdominal pain, constipation, diarrhoea, bloating or urgency. We also asked them about their willingness to take risks in their daily life, number of years since their diagnosis of IBS, and number of drugs taken for IBS in the last 12 months.

2.2.2 | IBS symptom severity

We assessed the severity of symptoms using the IBS severity scoring system (IBS-SSS),[28] which measures presence, severity and frequency of abdominal pain, presence and severity of abdominal distension, satisfaction with bowel habit and degree to which IBS

symptoms are affecting, or interfering with, the individual's life. The IBS-SSS carries a maximum score of 500 points, with <75 points indicating remission of symptoms, 75-174 points mild symptoms, 175-299 moderate symptoms and 300-500 severe symptoms.

2.2.3 | Mood and somatic symptoms

We used the hospital anxiety and depression scale (HADS) to collect anxiety and depression data.[29] The total HADS score ranges from 0 to 21 for either anxiety or depression. We categorised severity for each into normal (total HADS depression or anxiety score 0-7), borderline normal (8-10) or abnormal (≥11).[29] We collected somatic symptom data using the patient health questionnaire-12 (PHQ-12),[30] derived from the validated PHQ-15.[31] The total PHQ-12 score ranges from 0 to 24. We categorised severity into high (total PHQ-12 ≥ 13), medium (8-12), low (4-7) or minimal (≤3).

2.2.4 | Gastrointestinal symptom-specific anxiety

We used the visceral sensitivity index (VSI),[32] which measures gastrointestinal symptom-specific anxiety. Replies to each of the 15 items are provided on a 6-point scale from "strongly disagree" (score 0) to "strongly agree" (score 5). We divided these data into equally sized tertiles, as there are no validated cutoffs to define low, medium or high levels of gastrointestinal symptom-specific anxiety.

2.2.5 | IBS-specific quality of life

We used the irritable bowel syndrome quality of life (IBS-QOL), a validated IBS-specific questionnaire, to measure health-related quality of life in individuals with IBS.[33,34] This consists of 34 items, each ranked on a 5-point Likert scale ranging from 0 to 4, with a total possible score from 0 to 136, and lower scores indicating better quality of life. The 34 items are based on the following eight variables: dysphoria, interference with activity, body image, health worry, food avoidance, social reactions, sexual activity and relationships. Score was transformed to a 0 to 100-point scale with zero indicating worst and 100 indicating best quality of life. Again, we divided these data into equally sized tertiles, as there are no validated cutoffs to define low, medium or high levels of quality of life.

2.2.6 | Impact of IBS on productivity and ability to work

We used the work productivity and activity impairment questionnaire for irritable bowel syndrome (WPAI:IBS),[35] a validated questionnaire to assess the level of work productivity loss in people with IBS who are employed, as well as impairment in their activities of daily living. The WPAI:IBS consists of six questions related to current employment status, hours of work missed due to IBS, hours of work missed for other reasons, hours worked, the degree to which IBS has affected work productivity whilst working, and the degree to which IBS has affected other activities of daily living in the last 7 days. The WPAI:IBS measures four domains: absenteeism (percentage of work hours missed because of IBS); presenteeism (percentage of impairment experienced whilst working because of IBS); overall work impairment (percentage of work productivity loss because of IBS); and activity impairment (percentage impairment in activities of daily living because of IBS).

2.2.7 | Willingness to accept risk of death in return for cure of IBS symptoms

We used a standard gamble to evaluate the risk of death that participants were willing to accept in return for a permanent cure of their IBS symptoms.[36] Each question offered participants a choice of a chance of permanent cure of their IBS symptoms with a hypothetical pill or a risk of a painless death in their sleep from the same pill. As the participants move from one question to the next, the chance of cure is titrated down from 100% whilst the risk of death is titrated up from 0%. In doing so, we estimated the maximum risk of death that participants were willing to accept for the corresponding minimum chance of cure.

2.3 | Statistical analysis

All participants who met Rome IV criteria for IBS were included in the statistical analysis. We assessed for normality of data using histogram and normality plots. We used the Kolmogorov-Smirnov statistic to test normality. We calculated the frequency distributions for all categorical variables and used the Mann-Whitney *U* test and Kruskal-Wallis H test to assess differences between groups. We examined characteristics of patients willing to accept above the median risk of death compared with those willing to accept the median or below median risk of death in return for cure of their IBS in the standard gamble. Categorical variables such as sex, ethnicity, self-rated risk-taking behaviour, IBS subtype, IBS-SSS severity, presence or absence of abnormal anxiety or depression scores, levels of somatic symptom reporting, levels of gastrointestinal symptom-specific anxiety, and levels of quality of life were compared between individuals willing to accept above the median risk of death compared with the median or below median risk of death using a χ^2 test. Data such as age, and scores for absenteeism, presenteeism, overall work impairment or activity impairment were compared between these two groups using an independent samples *t* test or Mann-Whitney *U* test. Statistical significance was defined as a *P* value <0.01. We used a logistic regression model, controlling for all baseline data, to examine predictors of willingness to accept above the median risk of death, and reported the results with odds ratios (ORs) with 95% confidence intervals (CIs). We performed all analyses using SPSS for Windows (version 27.0 SPSS, Chicago, IL).

3 | RESULTS

In total, 1278 (29.9%) of 4280 registrants (mean age 47.2 years (range 18-89 years), 1086 (85.0%) female) responded and completed the questionnaire. Of these, 752 (58.8%) met Rome IV criteria for IBS. The mean age of these 752 individuals was 45.3 years (range 18-81 years), 655 (87.1%) were female and 729 (96.9%) were White. In total, 136 (18.1%) had IBS with constipation (IBS-C), 306 (40.7%) IBS-D and 301 (40.0%) IBS with mixed bowel habits (IBS-M). The mean IBS-SSS score was 293.1 (SD 95.1). When asked to rate their risk-taking behaviour in their daily life, 66 (8.8%) reported never taking risk, 343 (45.6%) rarely, 323 (43.0%) occasionally and 20 (2.7%) routinely.

3.1 | Willingness to accept risk of death in return for cure of IBS symptoms from a hypothetical medication

Using a standard gamble, participants reported that they would accept a median 2.0% (interquartile range [IQR], 0.0%-9.0%) risk of death from a hypothetical medication in return for a 98.0% (IQR, 91.0%-100.0%) chance of permanent cure of their IBS symptoms. Men with IBS were willing to accept a higher risk of death compared with women (median 5.0% vs 2.0%, $P < 0.001$) (Table 1). Willingness to accept risk was not associated with marital status, tobacco or alcohol use, level of education, annual income, IBS subtype, duration of IBS or most troublesome symptom, but increasing degree of risk taken in daily life was associated with willingness to accept a higher risk of death in return for cure ($P < 0.001$ for trend). Willingness to accept death also increased significantly with the number of medications taken for IBS in the 12 months prior to the study ($P = 0.005$ for trend) and with the presence of continuous abdominal pain (median 4.0% vs 1.0%, $P < 0.001$). We also observed a significantly higher median accepted the risk of death in those with severe IBS (severe, 3.0% vs moderate, 1.0% vs mild, 2.0%, $P = 0.005$ for trend), those with abnormal HADS depression scores (abnormal, 5.0% vs borderline, 2.0% vs normal, 2.0%, $P < 0.001$ for trend) and higher VSI scores (high, 3.0% vs medium, 2.0% vs low, 1.0%, $P < 0.001$ for trend), but not abnormal HADS anxiety scores or high somatization scores. Median accepted risk of death was also significantly higher with lower IBS-related quality of life (low, 4.0% vs medium, 2.0% vs high, 1.0%, $P < 0.001$ for trend).

3.2 | Characteristics of patients willing to accept above median risk of death in return for cure of IBS symptoms from a hypothetical medication

We also examined the characteristics of individuals willing to accept above median risk of death compared with those willing to accept median or below risk of death in return for a cure of their IBS (Table 2). There was a significantly lower proportion of female individuals (82.9% vs 90.9%, $P < 0.001$) and a higher proportion of individuals willing to take a higher degree of risk in their daily life ($P = 0.008$ for trend). There was also a significantly higher proportion of individuals with continuous abdominal pain (53.1% vs 39.4%, $P < 0.001$) in the above median risk of death group. A greater proportion of individuals willing to accept above median risk of death had more severe IBS, although this did not reach statistical significance ($P = 0.02$ for trend). There was a significantly higher proportion of individuals with abnormal depression scores ($P = 0.004$ for trend) in the group willing to accept above median risk of death, but not abnormal anxiety scores or high somatization scores. VSI scores were generally higher, although this did not reach statistical significance ($P = 0.02$ for trend) but IBS-related quality of life was significantly lower ($P < 0.001$ for trend). Finally, we examined the association between work productivity and activity impairment and willingness to accept the risk of death. Levels of presenteeism, overall work impairment (40.0% vs 30.0% for both, $P = 0.002$ and $P = 0.004$, respectively) and activity impairment (50.0% vs 40.0%, $P < 0.001$) were significantly higher among those willing to accept above median risk of death. Following logistic regression, those willing to accept above median risk of death were more likely to take higher risks in their daily life (OR = 3.64; 95% CI 1.19 to 11.2), to report continuous abdominal pain (OR = 1.50; 95% CI 1.03 to 2.18), to have IBS-M (OR = 1.75; 95% CI 1.05 to 2.91), and less likely to be female (OR = 0.52; 95% CI 0.30 to 0.89) or married (OR = 0.68; 95% CI 0.48 to 0.98).

4 | DISCUSSION

This cross-sectional study has recruited 752 individuals with Rome IV-defined IBS who, when presented with a standard gamble, were willing to accept a 2% risk of death from a hypothetical medication in return for a 98% chance of permanent cure of their IBS. However, this increased to 5% in some of our analyses. Men, individuals with continuous abdominal pain, those who took increased risks in their daily life, and who had taken more IBS medications in the last 12 months were willing to accept a significantly higher risk of death. Not surprisingly, those with more severe IBS symptoms and those with poorer quality of life were also willing to accept significantly higher risks. In terms of psychological comorbidities, higher depression and gastrointestinal symptom-specific anxiety scores were associated with a significantly higher willingness to accept risk. When we analysed the characteristics of those willing to accept above median risk of death, a significantly higher proportion of these individuals were male, they were more likely to report continuous abdominal pain, took higher levels of risks in their daily life, had higher depression scores and lower quality of life. Finally, those who were more likely to accept above median risk from a medication reported greater impairment at work and in their daily life.

A large number of individuals were recruited from the community in this study, all of whom self-identified as having IBS and met Rome IV criteria. This sample is likely to be representative of

TABLE 1 Median willingness to accept risk of death in return for cure of IBS symptoms from a hypothetical medication according to demographics, symptom characteristics and level of psychological comorbidity among 752 individuals with Rome IV IBS

	Median risk of death, % (IQR)	*P* value*
Sex		
Male (n = 97)	5.00 (1.00-10.00)	
Female (n = 655)	2.00 (0.00-8.00)	<0.001
Smoker		
Yes (n = 82)	3.5 (0.0-10.0)	
No (n = 670)	2.0 (0.0-9.0)	0.15
Alcohol use		
Yes (n = 439)	2.0 (0.0-8.0)	
No (n = 313)	2.0 (0.0-10.0)	0.48
Married		
Yes (n = 487)	2.0 (0.0-7.0)	
No (n = 265)	3.0 (0.0-10.0)	0.02
University or postgraduate level of education		
Yes (n = 314)	2.0 (0.0-6.0)	
No (n = 438)	2.0 (0.0-10.0)	0.15
Annual income of £30,000 or more		
Yes (n = 197)	3.0 (0.0-9.0)	
No (n = 483)	2.0 (0.0-9.0)	0.34
IBS subtype		
IBS-C (n = 136)	1.0 (0.0-5.0)	
IBS-D (n = 306)	2.0 (0.0-8.25)	
IBS-M (n = 301)	3.0 (0.0-10.0)	0.14
Most troublesome symptom		
Abdominal pain (n = 169)	3.0 (0.0-10.0)	
Constipation (n = 53)	2.0 (0.0-9.0)	
Diarrhoea (n = 117)	4.0 (0.0-10.0)	
Bloating/distension (n = 218)	2.0 (0.0-5.0)	
Urgency (n = 195)	2.0 (0.0-9.0)	0.11
Continuous abdominal pain		
Yes (n = 345)	4.0 (0.0-10.0)	
No (n = 407)	1.0 (0.0-5.0)	<0.001
Self-rated risk-taking behaviour		
Never (n = 66)	0.0 (0.0-4.0)	
Rarely (n = 343)	2.0 (0.0-6.0)	
Occasionally (n = 323)	3.0 (0.0-10.0)	
Routinely (n = 20)	3.5 (0.0-31.25)	<0.001
Duration of IBS diagnosis, year(s)		
1 (n = 25)	2.0 (0.0-5.0)	
2 (n = 41)	2.0 (0.0-6.5)	
3 (n = 54)	3.0 (0.0-11.25)	
4 (n = 33)	1.0 (0.0-9.0)	
5 (n = 38)	3.0 (0.0-9.25)	
>5 (n = 561)	2.0 (0.0-9.0)	0.56
Number of IBS drugs in the last 12 months		
0 (n = 96)	1.0 (0.0-5.0)	
1 (n = 189)	1.0 (0.0-7.0)	
2 (n = 196)	2.0 (0.0-9.0)	
3 (n = 129)	4.0 (0.0-10.0)	
4 (n = 76)	3.0 (0.0-10.0)	
≥5 (n = 66)	4.0 (0.0-10.0)	0.005
Severity on IBS-SSS		
Mild (n = 86)	2.0 (0.0-5.0)	
Moderate (n = 300)	1.0 (0.0-7.0)	
Severe (n = 359)	3.0 (0.0-10.0)	0.005
HADS anxiety categories		
Normal (n = 200)	2.0 (0.0-5.0)	
Borderline abnormal (n = 174)	2.0 (0.0-8.25)	
Abnormal (n = 378)	2.5 (0.0-10.0)	0.20
HADS depression categories		
Normal (n = 404)	2.0 (0.0-5.0)	
Borderline abnormal (n = 165)	2.0 (0.0-8.5)	
Abnormal (n = 183)	5.0 (0.0-15.0)	<0.001
PHQ-12 severity		
Low (n = 36)	2.0 (0.0-5.0)	
Mild (n = 176)	2.0 (0.0-9.0)	
Moderate (n = 307)	2.0 (0.0-6.0)	
Severe (n = 233)	4.0 (0.0-10.0)	0.14
VSI scores		
Low (n = 247)	1.0 (0.0-5.0)	
Medium (n = 247)	2.0 (0.0-9.0)	
High (n = 258)	3.0 (0.0-10.0)	<0.001
IBS-QOL scores		
Low (n = 239)	4.0 (0.0-10.0)	
Medium (n = 252)	2.0 (0.0-9.0)	
High (n = 261)	1.0 (1.0-5.0)	<0.001

*P value for Mann-Whitney *U* test for 2 groups and for Kruskal-Wallis test for 3 groups or more.

individuals with IBS in the United Kingdom because some had never seen a doctor for their IBS, some had seen a primary care physician, and some had seen a gastroenterologist. All the questionnaires used in our study were validated and have been used widely in studies of IBS and other chronic gastrointestinal diseases. Because we used an online questionnaire with mandatory fields, we obtained near-complete data for variables of interest.

Weaknesses of our study include the fact that, because we recruited participants with IBS from the community to better reflect the wide spectrum of patients with IBS, we were unable to check their medical records to rule out other organic diseases that present with similar symptoms such as celiac disease or inflammatory bowel disease.[37,38] However, IBS is more prevalent than

TABLE 2 Characteristics of individuals with Rome IV IBS willing to accept above median risk of death in return for cure of IBS symptoms from a hypothetical medication compared with median or below median risk of death

	Above median risk of death (n = 356)	Median or below median risk of death (n = 396)	*P* value*
Female (%)	295 (82.9)	360 (90.9)	0.001
Mean age (SD)	45.7 (14.7)	45.0 (14.9)	0.54
White ethnicity (%)	346 (97.2)	383 (96.7)	0.71
Married (%)	216 (60.7)	270 (68.4)	0.03
Smoker (%)	45 (12.6)	37 (9.3)	0.15
Alcohol user (%)	200 (56.2)	239 (60.4)	0.25
University or postgraduate level of education (%)	140 (39.3)	174 (43.9)	0.20
Annual income of £30,000 or more (%)	102 (31.1)	95 (27.0)	0.24
IBS subtype (%)			
IBS-C	55 (15.5)	81 (20.8)	
IBS-D	146 (41.2)	160 (41.1)	
IBS-M	153(43.2)	148 (38.0)	0.13
Most troublesome symptom (%)			
Abdominal pain	87 (24.4)	82 (20.7)	
Constipation	26 (7.3)	27 (6.8)	
Diarrhoea	62 (17.4)	55 (13.9)	
Bloating/distension	92 (25.8)	126 (31.8)	
Urgency	89 (25.0)	106 (26.8)	0.26
Continuous abdominal pain (%)	189 (53.1)	156 (39.4)	<0.001
Self-rated risk-taking behaviour (%)			
Never	21 (5.9)	45 (11.4)	
Rarely	153 (43.0)	190 (48.0)	
Occasionally	171 (48.0)	152 (38.4)	
Routinely	11 (3.1)	9 (2.3)	0.008
Duration of IBS diagnosis, year(s) (%)			
1	9 (2.5)	16 (4.0)	
2	16 (4.5)	25 (6.3)	
3	28 (7.9)	26 (6.6)	
4	13 (3.7)	20 (5.1)	
5	20 (5.6)	18 (4.5)	
>5	270 (75.8)	291 (73.5)	0.51
Number of IBS drugs in the last 12 months (%)			
0	40 (11.2)	56 (14.1)	
1	80 (22.5)	109 (27.5)	
2	90 (25.3)	106 (26.8)	
3	69 (19.4)	60 (15.2)	
4	41 (11.5)	35 (8.8)	
≥5	36 (10.1)	30 (7.6)	0.16
IBS-SSS severity (%)			
Mild	33 (9.3)	53 (13.4)	
Moderate	132 (37.1)	168 (42.4)	
Severe	189 (53.1)	170 (42.9)	0.02
HADS anxiety categories (%)			
Normal	84 (23.6)	116 (29.3)	
Borderline abnormal	83 (23.3)	91 (23.0)	
Abnormal	189 (53.1)	189 (47.7)	0.19
HADS depression categories (%)			
Normal	171 (48.0)	233 (58.8)	
Borderline abnormal	81 (22.8)	84 (21.2)	
Abnormal	104 (29.2)	79 (19.9)	0.004
PHQ-12 severity (%)			
Low	16 (4.5)	20 (5.1)	
Mild	81 (22.8)	95 (24.0)	
Moderate	132 (37.1)	175 (44.2)	
Severe	127 (35.7)	106 (26.8)	0.06
VSI scores (%)			
Low	101 (28.4)	146 (36.9)	
Medium	118 (33.1)	129 (32.6)	
High	137 (38.5)	121 (30.6)	0.02
IBS-QOL score (%)			
Low	133 (37.4)	106 (26.8)	
Medium	124 (34.8)	128 (32.3)	
High	99 (27.8)	162 (40.9)	<0.001
WPAI: IBS, median % (IQR)			
Absenteeism	0.0 (0.0-5.1)	0.0 (0.0-1.3)	0.10
Presenteeism	40.0 (20.0-60.0)	30.0 (10.0-60.0)	0.002
Overall work impairment	40.0 (15.9-65.3)	30.0 (10.0-57.1)	0.004
Activity impairment	50.0 (30.0-70.0)	40.0 (20.0-60.0)	<0.001

*P value for Pearson χ^2 for comparison of categorical data, independent samples t-test for age, and Mann-Whitney U test for all four dimensions of Work Productivity and Activity Impairment: Irritable Bowel Syndrome.

these conditions in the community and UK national guidance recommends ruling out celiac disease or inflammatory bowel disease in people with suspected IBS.[39,40] In addition, all members of the

ContactME-IBS registry need a documented diagnosis of IBS to register, and almost 90% of members have seen a primary care physician or a gastroenterologist for their IBS. Taken together with the fact that nearly 80% of the sample had a diagnosis of IBS for 5 years or longer, this suggests that our participants genuinely have IBS. Because the questionnaire was completed online, we were unable to assess how many individuals chose not to complete the questionnaire and whether those who responded are broadly representative of all individuals with IBS registered with ContactME-IBS. In addition, all participants were UK residents and nearly 97% of them were White, meaning the results may not be applicable to individuals with IBS outside the UK or from other ethnic groups. Finally, our inclusion of data from only the 752 individuals who met the Rome IV criteria, from the 1278 responders, may have affected our study results. We have previously shown that the Rome IV criteria select a group of individuals with IBS with more severe symptoms and higher levels of psychological comorbidity.[10,41] The Rome Foundation have acknowledged that the modifications made in moving from Rome III to IV identify a group of more severely affected individuals and have suggested modifications to these criteria, the Rome IV criteria for clinical practice,[42] to address this issue. Preliminary evidence suggests these modified criteria incorporate those with less severe symptoms.[43]

Although the standard gamble is a validated and well-established tool used widely in health economics to examine health utilities,[44] including studies in DGBI,[24,25,45] it has limitations. The choices given to the participants are hypothetical, given that there are currently no medications that can cure IBS. The choices that individuals were asked to make, although intended to simulate a clinical scenario, are unlikely to have captured the complex decision-making process involving health, emotional or financial consequences on both individuals and their relatives. Moreover, adverse effects for licensed medications used in IBS, when experienced by patients, are most likely to be mild rather than can causing death. However, the term "painless death", used in the standard gamble, may suggest to some people a pleasant death, which may have influenced our results. Previously, Johnson et al. attempted to minimise this hypothetical bias by using a discrete choice experiment, offering alternatives that mimicked the real world.[23] The limitation of such a design is that one can only investigate a specific set of trade-offs for a specific medication in a defined subset of patients, such as constipation or risk of perforated ischemic bowel requiring surgery with alosetron in women with IBS-D.[23] On the other hand, using standard gamble methodology allows for direct comparisons among subgroups of patients to identify those who are willing to accept higher levels of medication-related risks. This is important to inform drug development and approval processes for novel medications.

As discussed, there have been previous studies examining willingness to accept medication-related risks among IBS patients. One study using Rome III-defined IBS, recruiting 186 patients from a referral population, concluded that participants were willing to accept a median risk of 1% death in return for a 99% chance of cure.[24] However, there were no significant differences in willingness to accept risks according to various patient characteristics, other than self-reported symptom severity. In another study, recruiting 215 patients with Rome IV-defined IBS from a referral population, the severity of IBS did not appear to affect willingness to accept risk with medication significantly, other than among those reporting intensity or unpredictability of constipation as their most bothersome symptom.[25] Both studies had relatively small sample sizes, which may have hampered their ability to detect significant differences. In an international survey of almost 2000 individuals meeting Rome III criteria for IBS, participants were willing, on average, to forgo 15.1 years of their life to achieve perfect health.[22] Despite having a large sample size, the authors did not examine the associations between willingness to accept risk from medication and participants' demographics, IBS severity, anxiety or depression. Finally, none of these studies have examined the relationship between willingness to accept risk and other psychological comorbidities such as gastrointestinal symptom-specific anxiety or somatoform-type behaviour and did not examine characteristics of individuals with IBS who were willing to accept higher levels of risk. Although our finding that men and those who take more risk in their daily lives were willing to accept higher levels of risk is unsurprising, we did identify other potential predictors.

This study has demonstrated that individuals with IBS are willing to accept remarkable risks to achieve cure of their symptoms, even though IBS is not known to reduce life expectancy.[46,47] This serves to highlight the substantial impact that IBS has on individuals. It is, perhaps, not surprising that those with more severe symptoms and lower IBS-related quality of life are willing to accept greater risks to cure their symptoms. Interestingly, individuals with higher levels of depression, but not anxiety, were also willing to accept greater risks from medications. One possible explanation is that those with higher levels of anxiety may be equally worried about adverse events from medications. In fact, the HADS anxiety score measures generalised, rather than health-related, anxiety. This hypothesis is further supported by the fact that those with higher levels of gastrointestinal symptom-specific anxiety were willing to accept significantly higher levels of risk.

Our study has important implications. Clinicians should be mindful of the impact of IBS on patients' lives and the levels of risks they are willing to accept to relieve their symptoms. Careful discussion about various treatment options, and their relative risks and benefits, should take place to allow patients to make informed decisions about therapies. These results are also important for pharmaceutical companies to aid decisions regarding continued drug development when serious adverse events arise, as well as the regulatory agencies responsible for assessing the risk-benefit profile of new drugs prior to approval. As IBS is considered a benign condition, drugs with serious side effects are often withdrawn or their use restricted. Our results suggest this debate needs to be recalibrated, particularly in those with more severe, or refractory, symptoms. Of course, it will be crucial to develop treatment algorithms and tools to help clinicians and patients to make such complex decisions.

In summary, in this study individuals with Rome IV IBS were willing to accept a 2% risk of death from a hypothetical medication in return for a 98% chance of permanent cure of their IBS. This increased to 5% in some subgroups of patients, including men and individuals with abnormal depression scores. Men, those with continuous abdominal pain, those willing to take higher risks in their daily lives, those with higher levels of depression, those with lower quality of life, and those with greater impairments at work or in their daily life were significantly more likely to be willing to accept an above average increased risk of death from a medication. Although our study has important clinical, research and regulatory implications, whether the willingness to accept risk from medication fluctuates over time, and whether the changing clinical course of IBS influences this is unclear. Future studies should address these issues.

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AUTHORSHIP

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Author contributions: VCG, CEN, CJB and ACF conceived and drafted the study. VCG and CEN collected all data. VCG, CJB and ACF analysed and interpreted the data. VCG and ACF drafted the manuscript. All authors have approved the final draft of the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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REFERENCES

1. Oka P, Parr H, Barberio B, Black CJ, Savarino EV, Ford AC. Global prevalence of irritable bowel syndrome according to Rome III or IV criteria: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2020;5:908-917.
2. Mearin F, Lacy BE, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393-1407.
3. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. *Lancet Gastroenterol Hepatol*. 2016;1:133-146.
4. Ford AC, Forman D, Bailey AG, Axon AT, Moayyedi P. Irritable bowel syndrome: a 10-yr natural history of symptoms and factors that influence consultation behavior. *Am J Gastroenterol*. 2007;103:1229-1239.
5. Pace F, Molteni P, Bollani S, et al. Inflammatory bowel disease versus irritable bowel syndrome: a hospital-based, case-control study of disease impact on quality of life. *Scand J Gastroenterol*. 2003;38:1031-1038.
6. Frandemark A, Tornblom H, Jakobsson S, Simren M. Work productivity and activity impairment in irritable bowel syndrome (IBS): a multifaceted problem. *Am J Gastroenterol*. 2018;113:1540-1549.
7. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes*. 2017;15:35.
8. Corney RH, Stanton R. Physical symptom severity, psychological and social dysfunction in a series of outpatients with irritable bowel syndrome. *J Psychosom Res*. 1990;34(5):483-491.
9. Ballou S, McMahon C, Lee HN, et al. Effects of irritable bowel syndrome on daily activities vary among subtypes based on results from the IBS in America survey. *Clin Gastroenterol Hepatol*. 2019;17:2471-2478.e2473.
10. Black CJ, Yiannakou Y, Houghton LA, Ford AC. Epidemiological, clinical, and psychological characteristics of individuals with self-reported irritable bowel syndrome based on the Rome IV vs Rome III criteria. *Clin Gastroenterol Hepatol*. 2020;18:392-398.e392.
11. Patel P, Bercik P, Morgan DG, et al. Irritable bowel syndrome is significantly associated with somatisation in 840 patients, which may drive bloating. *Aliment Pharmacol Ther*. 2015;41:449-458.
12. Goodoory VC, Mikocka-Walus A, Yiannakou Y, Houghton LA, Black CJ, Ford AC. Impact of psychological comorbidity on the prognosis of irritable bowel syndrome. *Am J Gastroenterol*. 2021;116:1485-1494.
13. Black CJ, Burr NE, Camilleri M, et al. Efficacy of pharmacological therapies in patients with IBS with diarrhoea or mixed stool pattern: systematic review and network meta-analysis. *Gut*. 2020;69:74-82.
14. Black CJ, Burr NE, Quigley EMM, Moayyedi P, Houghton LA, Ford AC. Efficacy of secretagogues in patients with irritable bowel syndrome with constipation: systematic review and network meta-analysis. *Gastroenterology*. 2018;155:1753-1763.
15. Black CJ, Staudacher HM, Ford AC. Efficacy of a low FODMAP diet in irritable bowel syndrome: systematic review and network meta-analysis. *Gut* 2021:gutjnl-2021-325214; doi: 10.1136/gutjnl-2021-325214
16. Black CJ, Thakur ER, Houghton LA, Quigley EMM, Moayyedi P, Ford AC. Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis. *Gut*. 2020;69:1441-1451.
17. Black CJ, Yuan Y, Selinger CP, et al. Efficacy of soluble fibre, antispasmodic drugs, and gut-brain neuromodulators in irritable bowel syndrome: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. 2020;5:117-131.
18. Barberio B, Savarino EV, Black CJ, Ford AC. Placebo response rates in trials of licensed drugs for irritable bowel syndrome with constipation or diarrhea: meta-analysis. *Clin Gastroenterol Hepatol*. 2021. doi:10.1016/j.cgh.2021.08.025
19. US Food and Drug Administration. Lotronex (alosetron hydrochloride) Information [Internet]. [New Hampshire]: FDA; 2017 [cited December 22, 2021]. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/lotronex-alosetron-hydrochloride-information.
20. Tegaserod: withdrawal from the world market. A treatment for constipation with cardiovascular adverse effects. *Prescrire Int*. 2008;17:112-113.
21. US Food and Drug Administration. FDA drug safety communication: FDA warns about increased risk of serious pancreatitis with irritable bowel drug Viberzi (eluxadoline) in patients without a gallbladder [Internet]. [New Hampshire]: FDA; 2017 [cited December 22, 2021]. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-about-increased-risk-serious-pancreatitis-irritable-bowel.

22. Drossman DA, Morris CB, Schneck S, et al. International survey of patients with IBS: symptom features and their severity, health status, treatments, and risk taking to achieve clinical benefit. *J Clin Gastroenterol*. 2009;43:541-550.
23. Johnson FR, Hauber AB, Ozdemir S, Lynd L. Quantifying women's stated benefit-risk trade-off preferences for IBS treatment outcomes. *Value Health*. 2010;13:418-423.
24. Lacy BE, Everhart KK, Weiser KT, et al. IBS patients' willingness to take risks with medications. *Am J Gastroenterol*. 2012;107:804-809.
25. Shah SL, Janisch NH, Crowell M, Lacy BE. Patients with irritable bowel syndrome are willing to take substantial medication risks for symptom relief. *Clin Gastroenterol Hepatol*. 2021;19:80-86.
26. Goodoory VC, Yiannakou Y, Houghton LA, Black CJ, Ford AC. Natural history and disease impact of Rome IV versus Rome III irritable bowel syndrome: a longitudinal follow-up study. *Clin Gastroenterol Hepatol*. 2021. doi:10.1016/j.cgh.2021.04.043
27. Palsson O, Whitehead W, Van Tilburg M, et al. Development and validation of the Rome IV diagnostic questionnaire for adults. *Gastroenterology*. 2016;150:1481-1491.
28. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther*. 1997;11:395-402.
29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*. 1983;67:361-370.
30. Spiller RC, Humes DJ, Campbell E, et al. The Patient Health Questionnaire 12 Somatic Symptom scale as a predictor of symptom severity and consulting behaviour in patients with irritable bowel syndrome and symptomatic diverticular disease. *Aliment Pharmacol Ther*. 2010;32:811-820.
31. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosomatic Medicine*. 2002;64:258-266.
32. Labus JS, Bolus R, Chang L, et al. The Visceral sensitivity index: development and validation of a gastrointestinal symptom-specific anxiety scale. *Aliment Pharmacol Ther*. 2004;20:89-97.
33. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Dig Dis Sci*. 1998;43:400-411.
34. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. *Am J Gastroenterol*. 2000;95:999-1007.
35. Reilly MC, Bracco A, Ricci JF, Santoro J, Stevens T. The validity and accuracy of the Work Productivity and Activity Impairment questionnaire--irritable bowel syndrome version (WPAI:IBS). *Aliment Pharmacol Ther*. 2004;20(4):459-467.
36. Ross PL, Littenberg B, Fearn P, Scardino PT, Karakiewicz PI, Kattan MW. Paper standard gamble: a paper-based measure of standard gamble utility for current health. *Int J Technol Assess Health Care*. 2003;19:135-147.
37. Sainsbury A, Sanders DS, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with celiac disease: a meta-analysis. *Clin Gastroenterol Hepatol*. 2013;11(4):359-365.e351.
38. Fairbrass KM, Costantino SJ, Gracie DJ, Ford AC. Prevalence of irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease in remission: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2020;5:1053-1062.
39. Hookway C, Buckner S, Crosland P, Longson D. Irritable bowel syndrome in adults in primary care: summary of updated NICE guidance. *BMJ*. 2015;350:h701.
40. Vasant DH, Paine PA, Black CJ, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. *Gut*. 2021;70:1214-1240.
41. Black CJ, Craig O, Gracie DJ, Ford AC. Comparison of the Rome IV criteria with the Rome III criteria for the diagnosis of irritable bowel syndrome in secondary care. *Gut*. 2021;70:1110-1116.
42. Drossman DA, Tack J. Rome Foundation clinical diagnostic criteria for disorders of gut-brain interaction. *Gastroenterology*. 2021. doi:10.1053/j.gastro.2021.11.019
43. Black CJ, Ford AC. Assessing the impact of changes to the Rome IV criteria for clinical practice in irritable bowel syndrome. *Gastroenterology*. 2022. doi:10.1053/j.gastro.2022.01.021
44. Brazier J, Deverill M, Green C. A review of the use of health status measures in economic evaluation. *J Health Serv Res Policy*. 1999;4:174-184.
45. Lacy BE, Yu J, Crowell MD. Medication risk-taking behavior in functional dyspepsia patients. *Clin Transl Gastroenterol*. 2015;6:e69.
46. Chang JY, Locke GR 3rd, McNally MA, et al. Impact of functional gastrointestinal disorders on survival in the community. *Am J Gastroenterol*. 2010;105(4):822-832.
47. Staller K, Olén O, Söderling J, et al. Mortality risk in irritable bowel syndrome: results from a nationwide prospective cohort study. *Am J Gastroenterol*. 2020;115:746-755.

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