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Psychological distress, perceived stress and nocebo effect (multifood adverse reaction) in irritable bowel syndrome patients

Hamid Nasiri-Dehsorkhi[1,2], Shahram Vaziri[1], Ahmad Esmaillzadeh[3], Peyman Adibi[2]

Abstract:

BACKGROUND: Psychological distress and perceived stress may complicate the clinical presentation, course, and treatment of patients with functional gastrointestinal disorders. The correlation between psychological distress, perceived stress, and the nocebo effect (multifood adverse reaction) in patients with irritable bowel syndrome (IBS) was the main aim of the present study.

MATERIALS AND METHODS: In this cross-sectional correlation study, data on 4,763 Iranian adults, 748 of whom by purposive sampling were patients with IBS (65.1% female), working in 50 different health centers affiliated to the Isfahan University of Medical Sciences across Isfahan province were examined. For assessing dietary intake, a 106-item self-administered Dish-based Semi-Quantitative Food Frequency Questionnaire that was specifically designed and validated for Iranian adults was used. General Heath Questionnaire 12 and Stressful Life event Questionnaire were used to assess psychological distress and perceived stress. By using a modified Persian version of the Rome III questionnaire, IBS was assessed. Based on researcher-made definition of nocebo effect (multiitem food intolerance), 164 people had the nocebo phenomenon in IBS group.

RESULTS: Age, sex, education, marital status, antidepressant use, and specifically chronic underlying disease (odds ratio [OR]: 3.54, 95% confidence interval [CI]: 1.73-7.23) of general characteristics had a significant correlation (P <.05) with presenting nocebo responses in IBS patients. Psychological distress (OR: 1.415; 95% CI: 0.992-2.020; P = 0.056) had a significant correlation with nocebo effect and did not find significant correlation with perceived stress (OR: 0.999; 95% CI: 0.990-1.008; P = 0.865). Data were analyzed by Chi-square test, analysis of variance, and OR.

CONCLUSION: The present study showed that psychological distress with chronic underlying disease and antidepressant use are important elements in presenting multifood adverse reactions that we named here as the nocebo effect in IBS patients. Reducing psychological distress and managing chronic underlying diseases appear to be an effective factor in reducing the nocebo phenomenon in IBS patients. For managing the nocebo responses in IBS patients, these findings may help clinicians to improve their interventions. Further studies are required to confirm these findings.

Keywords:

Irritable bowel syndrome, multifood adverse reaction, nocebo effect, perceived stress, psychological distress

[1]Department of Clinical Psychology, Roudehen Branch, Islamic Azad University, Roudehen, Iran, [2]Isfahan Gastroenterology and Hepatology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

Address for correspondence:
Dr. Shahram Vaziri, Department of Clinical Psychology, Roudehen Branch, Islamic Azad University, Roudehen, Iran.
E-mail: vaziri@riau.ac.ir

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Introduction

Irritable bowel syndrome (IBS) is an idiopathic, functional, and chronic relapsing disorder, which may be caused due to psychosocial factors, altered motility, and/or altered sensory function of the gastrointestinal (GI) tract,[1] that is not explained by structural or biochemical abnormalities.[2] Physiological and psychological variables have been linked

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with the etiology and severity of IBS.[1] Several neurobiological mechanisms have been proposed for IBS. As per the bio-psycho-social model of IBS, a disturbance in intestinal motility and enhanced visceral sensitivity interacts with other factors.[3,4] In addition, psychological and social factors can influence digestive function, symptom perception, illness behavior, and outcome.[5] An IBS diagnosis is based on symptoms including abdominal pain and disturbed bowel function often related to and aggravated by psychosocial factors and perceived stressful events.[6] Several personality traits and constructs, such as neuroticism and alexithymia, are closely associated with IBS.[7] A lot is known about the interrelation of functional gastrointestinal disorders (FGIDs) and mood disorders, the co-occurrence of FGIDs, and depression is estimated at 30%; hence, it is called gut-brain interaction.[8] Psychological distress and major life events are frequently present in IBS and are responsible, at least in part, for some outcomes.[9] Psychological distress is also referred to as stress or emotional distress. These terms are used interchangeably in the literature to refer to negative emotional states.[10] Based on the Rome IV criteria, IBS is associated with increased levels of psychological distress and somatization compared with functional diarrhea or functional constipation.[11] Because of the limited effect of pharmacotherapy, there has been increasing interest in psychological treatments for IBS.[4] Any pharmacological or nonpharmacological treatment has two components, one related to the specific effects of the treatment itself and the other, nonspecific, related to the perception that the therapy is being administered.[12] The nonspecific effects of treatment are called placebo effects when they are beneficial and nocebo effects when they are harmful.[13,14]

The placebo phenomenon is psycho-neurophysiological response that appear after the administration of inert substances or treatments.[15] The nocebo effect is defined as increased pain or other symptoms after administration of an inactive treatment purported to increase pain or unpleasant symptoms,[16,17] or negative outcome following the application of an inert treatment that the recipient believes to be effective.[18-20] The underlying of placebo and nocebo effects are psycho-neurobiological. Psychological mechanisms include expectancies, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction, and meaning. Expectancies, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction, and meaning, for example, can be considered as psychological mechanisms.[21,22] Expectations have a strong influence on health outcomes.[23] Because expectation facilitates the perception of a specific sensation and stimulus categories, this effect helps clarify why side effects often occur as a cluster of multiple symptoms. Placebo and nocebo responses are mediated by expectations, associative and social observational learning processes, the patient's personality, societal factors, and the quality of the patient-physician interaction.[24,25] Negative expectations may increase anxiety and amplify somatosensory data and information, consequently intensifying the nocebo effect. Anxiety may be a core mechanism for nocebo effects.[26] Other mechanisms may be at work in the nocebo response, including patient-related factors, psychosocial context, and neurobiological factors, such as cholecystokinergic hyperactivity. However, negative expectations of patients are the most studied and understood mechanism in this regard.[27]

One of the possible effects of nocebo can be seen in food adverse reactions or food intolerance refers to a condition in which IBS patients develop an adverse outcome as a consequence of eating certain foods.[28] The psychological wellbeing of patients may be affected by the presence of food intolerance. Anxiety, depression, and somatic symptoms are more frequent in patients with food intolerance compared to controls.[29] It is important to recognize that food intolerances can be either GI or nongastrointestinal-related. For instance, many patients describe symptoms similar to IBS such as abdominal pain or discomfort, bloating, or altered bowel habits, after eating. Particularly, food intolerances may be associated with some symptoms like constipation or diarrhea. Other patients may develop a myriad of nongastrointestinal-related symptoms, such as brain fog, depression, joint pain, or skin rash. The nocebo response also plays a role in some patients with food intolerance. In other words, if an individual believes that certain foods will worsen his or her symptoms, there is a greater likelihood that food will indeed worsen those symptoms.[28] Some studies focusing on psychosocial correlates showed a possible association between food intolerance and younger age, female gender, higher education, and IBS.[29] In addition, a high somatic focus[30] and the presence of certain psychological states like depression or anxiety and personality traits such as pessimism[31] or neuroticism have been related to the occurrence of nocebo effects.[14] It seems that stress like increased state anxiety, perceived stress, experimentally induced fear, daily psychosocial stress moderate's placebo, and/or nocebo effects.[32] The consequences of the nocebo effect in clinical practice are always undesirable. It may make therapeutic interventions more painful, reduce responses to treatment, worsen symptoms, or lead to adverse events, in turn causing therapeutic noncompliance, nonadherence, or discontinuation of treatment.[33] Considering the importance of the nocebo effect in the process of diagnosis, course, and treatment of functional GI disorders, this study aims to describe the relationship between psychological distress, perceived

stress, and multi-item food intolerance is possibly a nocebo effect in employees with IBS working in centers affiliated to Isfahan University of Medical Sciences and Health Services were completed. It seems that reducing the nocebo effect has an important role in improving the treatment process of these patients.

Materials and Methods

Study design and setting

The data of the present correlational-cross sectional study are a secondary analysis of the Study on the Epidemiology of Psychological, Alimentary Health and Nutrition (SEPAHAN) database; a cross-sectional study that investigates the prevalence of FGIDs and their relationship with lifestyle factors and psychological disorders. The SEPAHAN study was done among Iranian general adults working in 50 different healthcare centers affiliated with Isfahan University of Medical Sciences across Isfahan province. In the SEPAHAN study, data were collected in two stages between April 2010 and May 2010. To collect information about anthropometric indices, demographic and lifestyle factors, including dietary intake and physical activity, self-administered questionnaires were distributed among 10,087 subjects in the first phase and 8,691 participants returned the completed questionnaires. In the second phase, data regarding psychological factors were collected for 6,239 people. Finally, 4,763 questionnaires were matched in the second stage with their equivalent questionnaires in the first stage. More detailed information about the SEPAHAN project has been published in other articles.[30]

Study participants and sampling

The participants of the present study include 748 people studied in the SEPAHAN project who had diagnosis of IBS. The sampling method was purposeful and people with IBS were selected as per the inclusion and exclusion criteria. The studied sample was divided into two groups based on having nocebo phenomenon (164) and not having it (584).

Data collection tools and techniques

Assessment of psychological distress

The Iranian-validated version of the General Health Questionnaire (GHQ) with 12 items was used to assess psychological distress.[34] GHQ-12 is a popular and brief and easy-to-complete questionnaire for the assessment of current mental health and psychological distress[35,36] that asks the respondents whether they have experienced a particular symptom of psychological distress or a change in their behavior recently. Each item includes a four-point scale (less than usual, no more than usual rather more than usual, or much more than usual). In present study, we used the bimodal (0-0-1-1) scoring method. The scores ranged from 0 to 12. Higher scores indicate a greater amount of psychological distress.[35] In the present study, a score of 4 or more was defined as having psychological distress. The convergent validity of GHQ-12 was examined in 748 Iranian young people. A significant inverse correlation was seen between the GHQ-12 and global quality of life scores (r = -0.56, $P < .0001$).[34]

Assessment of perceived stress

Self-perceived frequency and intensity of stressful life events were assessed by Stressful Life Event (SLE) questionnaire.[37] The questionnaire consists of 11 domains including home life events (financial problems, social relations, personal conflicts, job conflicts, educational concerns, job security, daily life, home life, loss and separation, sexual life, health concerns). All items measured on a 6-point Likert scale (0; never, 1; very mild, 2; mild, 3; moderate, 4; severe, 5; very severe) about life stressors at 6 months ago. Cronbach's score for SLE was ranging between 0.65 and 0.83 for each 11 domain and 0.92 for the total score. Details about stressful life event questionnaire such as validity and psychometry properties in Iranian population have been previously reported.[37]

Dietary assessment

A validated 106-item semiquantitative food frequency questionnaire (DS-FFQ) was used to assess usual dietary intake in the preceding year. Detailed information about the design and validity of this dish-based FFQ was reported elsewhere.[38,39] Doustmohammadian *et al*. indicated that DS-FFQ is a valid and reliable instrument for assess usual dietary intakes intraclass correlation coefficient (ICC for reliability ranged between 0.42 and 0.76 [P = 0.0001]).[39] In the present study, individuals who had reported consumption of different foods and dishes as "never or less than once a month" were defined as "nonconsumers" of that food. For each food item, we asked about the self-perceived GI symptoms following taking that food item. The symptom descriptions were classified by the investigators into the following: no problem, dislike, abdominal pain, abdominal bloating, diarrhea, acid regurgitation, or heartburn. In other words, after reporting the frequent of consumption of each food, participants were requested to report their feeling when consuming this food. They were able to choose the abovementioned symptoms. In this part, they were free to choose more than one option. To determine the number of people with "no consumption" of food items because of GI symptoms, we considered participants' responses to both parts of frequency consumption and the GI symptoms when eating that food. When a participant had reported "never or less than once a month" consumption of a given food item and at the same time he/she had reported one of the abovementioned GI symptoms when consuming that

food, this subject was counted as a "nonconsumer" of that food item due to a GI problem after eating that food.

Assessment of nocebo effect

As per the researcher make a definition of nocebo, multichemical sensitivity or multi-item food intolerance is possibly a nocebo (based on responses to dietary assessment DS-FFQ) and can be considered as a definition of the nocebo effect. In this study, the nocebo effect is referred to the occurrence of any gastrointestinal symptoms following the consumption of food items. The FFQ questionnaire asked 106 food items how they felt about eating this food. One could state one or more of the following at the same time: no problem, dislike, abdominal pain, abdominal bloating, diarrhea, acid regurgitation, or heartburn. If the reason for not eating food person was one or more of the following: abdominal pain, abdominal bloating, diarrhea, acid regurgitation, or heartburn; That person was considered to have a positive nocebo phenomenon about that food. Also, he would get one point for that food, otherwise he would get 0 points. Scores for all food items were added together for one person, ranging from 0 to 106. Finally, the person who received a score of 8 or more (≥ 8) based on percentile rank was considered a person with the nocebo phenomenon.

Assessment of irritable bowel syndrome

For IBS screening, the revised Persian version of the Rome III questionnaire was used as part of the main questionnaire.[30] Participants were asked whether they had specific symptoms in the past three months. The IBS was defined as per the Rome III criteria as recurrent abdominal pain or discomfort in the past three months with two or more of the following: (1) improvement with defecation, (2) pain associated with changes in stool frequency, and (3) pain associated with changes in the shape (appearance) of the stool. Face and content validity of the revised questionnaire was found to be acceptable.[40]

Assessment of other variables

Information on age (years), gender (male/female), marital status (married, single), self-reported weight (kg), height (cm), smoking (none, former, and current smokers), home ownership, chronic underlying disease (diabetes, asthma, colitis, stroke, myocardial infarction, heart failure, and cancers), and antidepressant and supplements (vitamins, minerals, calcium, and iron) use was obtained from demographic and medical history questionnaires. By using the General Practice Physical Activity Questionnaire, participants were classified into two categories: physically active ($\geq$ 1 h/week) and physically inactive (< 1 h/week) Physical activity was assessed.[30,41] Although this level of activity might seem low, earlier publications have revealed that even 1 h per week of walking can reduce the risk of chronic conditions.[42] Body mass index was calculated by dividing weight in kilograms by height in meters squared. Educational attainments are categorized into three categories, that is, lower than diploma (12 years' formal education), diploma, and university graduation (including bachelor, master, and doctorate).[30]

Ethical considerations

Ethical approval was obtained through the Tehran Islamic Azad University of Medical Sciences Institutional Research Ethics Research Committee (IR.IAU.TMU.REC.1399.107), and approval date was 2020.06.07. All participants provided a written informed consent before participation in SEPAHAN project ethically approved by the Regional Bioethics Committee of Isfahan University of Medical Sciences.[30]

Statistical methods

First of all, from the whole sample (n = 4763) we selected IBS patients (n = 748) through the Rome III questionnaire, secondly classified participants based on FFQ-Dish Based score, and the researcher made a nocebo definition (without nocebo = 584, with nocebo = 164). General characteristics of study participants across demographic questionnaires were expressed as means ± standard deviations for continuous variables and percentages for categorical variables. To examine the differences, we used analysis of variance and independent samples t-test for continuous variables and a Chi-square test for categorical variables. We also used binary logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the nocebo phenomenon across anxiety, depression, and psychological distress. We fitted logistic regression in different models, including a crude model for just psychological distress and perceived stress with nocebo. In model 1, we adjusted age (continuous), sex (male/female), education (diploma or under-diploma/university graduate), and marital status (married/single/divorced). In model 2, we added antidepressant use (yes/no) and chronic underlying disease (yes/no); in model 3, we added the variable of general psychological state (based on GHQ). In the present study, a cut-off score of $\geq$ 8 was used to define the nocebo effect. In GHQ-12, a score of 4 or more was defined having psychological distress. All statistical analyses were done using the Statistical Package for Social Sciences (version 22; SPSS Inc.). P <.05 was considered statistically significant.

Results

The general characteristics of study participants are presented in Table 1. Comparing individuals who participated in the analysis, we find some significant

differences in several variables of general characteristics. In comparison to IBS patients with nocebo phenomenon and without it, a significant difference ($P < .05$) in terms of age (35.72 ± 7.60 and 37.18 ± 7.10) was observed. On the other hand, this group had a significant difference ($P < .05$) in terms of having a university education with a rate of 63.9% in people without nocebo and 54.9% in people with the nocebo phenomenon. There was a significant difference ($P < .05$) in antidepressant use with 7% vs. 14.6% in the group of people with the nocebo phenomenon. Home ownership is another variable that had a significant ($P < .05$) positive association (OR: 0.56 [0.35-0.89]), which means that home ownership could decrease to approximately 50% chance of nocebo phenomenon in IBS patients. Last but not least, having a chronic underlying disease (diabetes, asthma, colitis, stroke, myocardial infarction, heart failure, and cancers) had a significant difference ($P < .05$) with a rate of 5.7% vs. 15.2% in these two groups. We observed a significant association between the nocebo effect and chronic underlying disease (OR: 3.54, 95% CI: 1.73-7.23), so that having chronic underlying disease could increase the chance of having the nocebo phenomenon in IBS patients up to three and a half times. We did not find any significant differences in other variables of general characteristics.

The psychological distress and perceived stress obtained from the GHQ-12 and LSE; their association with the nocebo phenomenon is presented in Table 2. The findings of the study showed that the IBS patients with nocebo phenomenon had a significant difference ($P = 0.05$) by having more elevated scores on psychological distress and the relative frequency difference of these two groups was 8.1. These findings suggested that the IBS patients with nocebo phenomenon had more psychological distress than non-nocebo patients. Results showed that IBS patients with and without nocebo phenomenon have no significant difference about perceived stress ($P > .05$). Crude and multivariable-adjusted ORs (95% CIs) of psychological distress and perceived stress with nocebo phenomenon are illustrated in Table 3. Psychological distress was associated with a greater chance of having nocebo phenomenon (OR: 1.415; 95% CI: 0.992-2.020; $P = 0.056$) in the crude model. It means that in the study group, people with psychological distress have a higher chance of having nocebo effect than nondistressed people, that is, the risk of nocebo is increased to 41.5% with a minimum of 0.992 and a maximum of 2.020. Adjustment for multiple potential confounders strengthens these associations ($P = .017$) and increases nearly 59.5% chance of the nocebo phenomenon (OR: 1.595; 95% CI: 1.087-2.167; $P = .017$) in model 1. Further adjustment

Table 1: General characteristics of study participants based on the nocebo status in the IBS patients

Variables	IBS patients	Nocebo		P[a]	Nocebo ORs and 95% CIs	P
	n=748	No (*n*=584)	Yes (*n*=164)			
Age, y (M±SD)	36.04±7.51	35.72±7.60	37.18±7.10	0.03	1.02 (0.99-1.05)	0.14
BMI, kg/m^2 (M±SD)	24.91±3.90	24.78±3.96	25.37±3.65	0.09	1.02 (0.96-1.08)	0.40
Sex[1] (Female, %)	65.1	65.1	65.2	0.96	0.95 (0.59-1.55)	0.86
Marital status						
Married, %	83.8	82.4	88.9	0.12	1.00	
Single %	14.7	15.9	10.5	0.12	0.91 (0.42-1.97)	0.82
Divorced %	1.5	1.7	0.6	0.12	0.45 (0.05-3.82)	0.46
Current smokers, %	15.1	15.8	12.8	0.35	1.64 (0.81-3.29)	0.16
Education[2] (university graduate), %	61.9	63.9	54.9	0.03	0.85 (0.54-1.35)	0.51
Family size[3] (≤4 members), %	73.9	74.3	72.6	0.65	0.76 (0.45-1.29)	0.31
Home ownership[4] (owner), %	67.2	68.3	63	0.24	0.56 (0.35-0.89)	0.01
Antidepressant use[5], %	8.7	7	14.6	0.002	1.52 (0.76-3.01)	0.22
Vitamin supplements[6], %	37.2	36.8	38.4	0.70	1.07 (0.67-1.70)	0.77
Smoking status[7] (current smoker) %	15.1	15.8	12.8	0.35	1.64 (0.81-3.29)	0.16
Physical activity[8] (≥1 h/week), %	12.4	12.3	12.8	0.87	1.01 (0.51-2.01)	0.95
Chronic underlying disease[9], %	7.8	5.7	15.2	<0.001	3.54 (1.73-7.23)	0.001

[a]Obtained from ANOVA or Chi-square test, where appropriate Data are OR (95% CI). [1]Reference group: male. [2]Reference group: diploma or under diploma. [3]Reference group: >4 members. [4]Reference group: non ownership. [5]Reference group: nonuser. [6]Reference group: nonuser. [7]Reference group: nonsmoker. [8]Reference group: <1 h/week. [9]Reference group: no chronic underlying disease

Table 2: Psychological distress, perceived stress and their association with nocebo phenomenon

Variables	Nocebo		Δ[a]	Δ%[b]	P[c]	Nocebo %		Relative frequency difference
	No (*n*=584) M±SD	Yes (*n*=164) M±SD				No % (*n*=584)	Yes % (*n*=164)	
Psychological Distress	1.34±0.47	1.42±0.49	0.08	5.97	0.05	34.2	42.3	8.1*
Perceived stress	27.82±19.06	27.51±18.48	-0.31	1.11	0.59	62.24	64.86	0.73*

Data are mean±standard deviation (SD). [a]Δ. Difference of means. [b]Δ%. Difference percent of means. [c]Obtained from Independent Samples *t*-test. *P<0.0

Table 3: Multivariable-adjusted ORs (and 95% CIs) for psychological distress and perceived stress with nocebo phenomenon

Variables	OR (95% CIs for OR)	*P*[1]
Psychological Distress		
Crude model	1.415 (0.992-2.020)	0.056
Model 1[2]	1.595 (1.087-2.342)	0.017
Model 2[3]	1.464 (0.989-2.167)	0.057
Perceived stress		
Crude model	0.999 (0.990-1.008)	0.865
Model 1	0.998 (0.998-1.008)	0.634
Model 2	0.997 (0.987-1.008)	0.611

[1]Derived from a binary logistic regression; [2]Model 1: Adjusted for age, sex, educational level, and marital status. [3]Model 2: Further adjustment for antidepressant use and chronic underlying disease

for multiple potential confounders strengthens these associations (P = .057) and increase nearly 46.4% chance of nocebo phenomenon (OR: 1.464; 95% CI: 0.989-2.167; P =.057) in model 2.

The perceived stress was not associated with a chance of having the nocebo phenomenon (OR: 0.999; 95% CI: 0.990-1.008; P =0.865) in a crude model. It means that the present study did not show a significant relationship between perceived stress scores and the chance of having the nocebo effect (P >.05). Further adjustment for multiple potential confounders did not strengthen these associations in model 1 and model 2. In a crude and adjusted models have not seen a significant association between perceived stress and nocebo response.

Discussion

In this study, examining the association between psychological distress, perceived stress, and nocebo phenomenon (multi-item food intolerance is possibly a nocebo effect in IBS patients) among a large group of Iranian adults, we found that a higher score of psychological distress was associated with greater odds of multifood adverse reaction (nocebo phenomenon). The results of the present study are similar to previous studies in this regard. For example, Weimer *et al*. (2020) found that "within nocebo responders, physical symptoms correlated with greater state anxiety, negative mood, catastrophizing, and neuroticism."[43] Elsenbruch *et al*. found that pain expectation correlated with state anxiety.[32] The same study showed a statistically significant difference between groups and a high prevalence of moderate (42.9%) and severe (20.0%) anxiety in the IBS group compared with the non-IBS group (8.6%, 11.4%).[44] In another part of the same study, the article which is being published, the results showed that there was a significant positive association between neuroticism score and nocebo effect among IBS patients. It should be noted that anxiety is part of the subscales of the NEO Personality Inventory for measuring neuroticism. In contrast to these findings, Aslaksen *et al*.[16] could not show an effect of neuroticism on the nocebo responses. As opposed to the placebo response, neurophysiological correlates of the nocebo response seem to involve more pathways related to negative expectations and anxiety. Magnetic resonance imaging study of nocebo hyperalgesia highlighted the role of the emotional cognitive pain pathway. Nocebo hyperalgesia has also been shown to be related to hyperactivity of the hypothalamic pituitary-adrenal axis and cholecystokinin, a peptide hormone of the gastrointestinal system that is involved in anxiety states, also plays a role in the nocebo response.[24] Lembo (2020) showed that individuals with type A personalities, who tend to have more neuroticism and pessimism, appear to have a higher nocebo response in IBS patients.[45,46] However, another study revealed that the prevalence of anxiety disorders was higher in patients with IBS (45.67%) compared with the control group (30.71%); furthermore, the prevalence of the severe type of anxiety in patients with IBS was higher (53.45%), and anxiety disorders were diagnosed in 47% of patients with IBS.[44] Another study done in China in 2014 did not find a significant relationship between anxiety and depression with IBS, despite having higher scores for anxiety and depression in patients with IBS compared to the control group.[47]

Suffering from a high burden of depression and anxiety is prevented by IBS patients. As per a clinic-based study, the prevalence of depression and anxiety in IBS patients is 37.1% and 31.4%, respectively.[48] The results indicated that IBS-M was more likely to be associated with a higher level of depression and anxiety and the prevalence of depression and anxiety in IBS-C was highest.[48] Amanzio *et al*.[49] showed that individuals with pathologies such as anxiety and depression, and those with a tendency toward somatization, were more likely to develop nocebo effects and responses. Specifically, anxiety, depression, and somatization are considered some of the psychological components rolled in nocebo-related side effects in randomized clinical trials. Moreover, the level of psychopathology, such as the severity of positive symptoms and signs of anxiety and depression, widely affected their perceptions and attribution of bodily sensations to medications.[49] It is interesting to note that most IBS patients with comorbid anxiety and depression manifest gastrointestinal symptoms before presenting with psychiatric symptoms.[50] Patients with depression might particularly be at risk due to frequent catastrophic thinking and, hence, are more prone to developing negative expectations and presenting nocebo responses.[51] It should be kept in mind that anxiety, depression, somatization, and malfunctional behavior are the part of the psychological distress assessment. Psychological distress was investigated in this study showed that there is a significant relationship between

nocebo responses and psychological distress in IBS patients. The pathogenesis of IBS is multifactorial and some factors may be more dominant. Several clinicians find psychological distress as a dominant factor in IBS.[47] Psychological distress is also referred to as stress or emotional distress. These terms are used interchangeably in the literature to refer to negative emotional states.[10] The study by Roderigo *et al*. supports the effects of acute psychological distress on placebo and nocebo responses in visceroception.[52] American Gastroenterology Association reported similar findings in a recent technical review. It showed that psychological distress is known to aggravate gastrointestinal symptoms leading to severe diarrhea, abdominal discomfort, etc. Moreover, psychological and psychiatric comorbidity is generally found among IBS patients.[1] Individuals with Rome IV IBS have significantly greater levels of anxiety, depression, and somatization compared with Rome IV functional constipation or functional diarrhea, and increasing abdominal pain frequency correlates positively with psychological distress and somatization.[11] Several clinicians find psychological distress as a dominant factor in IBS pathogenesis, as seen in previous research.[47] Some studies indicated that individual factors like negative expectations and negative contextual factors can predispose individuals to psychological distress and the onset of the nocebo phenomena.[49] Interestingly, some studies could not find correlation between autonomic arousal and nocebo hyperalgesia. Likewise, in another study found no correlations between placebo effects and stress markers. Clearly, stress and nocebo responses involve many cognitive, emotional, and psycho-neurobiological factors that remain to be fully understood.[32] The limitations of the present study include nocebo phenomenon is one of the important and new topics in clinical studies and has more limited articles compared to other clinical topics. Detailed definitions and specific evaluations are scarce in the research literature related to nocebo and the nature of the nocebo phenomenon could possibly influence the study in patients.

Conclusion

The present study showed that psychological distress with chronic underlying disease and antidepressant use are important elements in presenting multifood adverse reaction that we named here as a nocebo effect in IBS patients but we did not find any relationship between perceived stress and nocebo effect in this study. The results of the present study indicate that the management of psychological distress and chronic underlying disease in IBS patients can affect the nocebo responses and facilitate clinical intervention in these patients. Further studies are required to confirm these findings.

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Conflicts of interest

There are no conflicts of interest.

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