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Nocebo and Psychological Factors in Irritable Bowel Syndrome: A Scoping Review

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Review Article

Abstract

Background: There is considerable information about the interrelation of functional gastrointestinal disorders (FGIDs) and psychological disorders, called gut-brain interaction. Physiological and psychological variables have been linked with the etiology and severity of IBS. The nocebo effect (the opposite of placebo) is defined as increase in pain or other symptoms after use of an inactive or inert treatment/agent purported to increase pain or unpleasant symptoms. Some psychological mechanisms of nocebo include expectancies, conditioning, learning, memory, motivation, somatic focus, reward, anxiety, and meaning. Moreover, neurobiological factors are associated with the etiology of this phenomenon. The aim of present study is a discussion of the definition, existence, prevalence, etiology, and characteristics of the nocebo effect in irritable bowel syndrome (IBS).

Methods: This paper presents a scoping review of the existence, frequency, and importance of the nocebo effect in IBS patients. Data sources included PubMed, PsycINFO, Google Scholar, and Scopus which were searched from their inception dates to 2022.

Results: The review of the obtained articles showed that psychological factors such as depression, anxiety, psychological distress, and some personality traits such as neuroticism are related to the occurrence of nocebo responses in IBS patients.

Conclusion: The psychological factors associated with nocebo responses include expectancies, conditioning, learning, memory, patient's personality. Moreover, societal factors and the quality of the patient-physician interaction, and neurobiological factors influence the process of diagnosis, course, and treatment of IBS through nocebo responses. Compared to the extensive research data related to the placebo effect, there is

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little information and few articles on the role of nocebo, especially in FGIDs. This paper summarizes the scope and importance of the nocebo effect and IBS and its interrelations with psychological factors like personality, anxiety, depression, and psychological distress.
Keywords: Nocebo; Irritable bowel syndrome; Personality; Anxiety; Depression

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Introduction

Hippocrates said: "All disease begins in the gut."

Irritable bowel syndrome (IBS), a common functional gastrointestinal disorder (FGID), is characterized by recurrent abdominal pain, discomfort, and alterations in bowel habits that are not explained by structural or biochemical abnormalities that include the coexistence of bloating, flatulence, and abdominal distention (Yan et al., 2021). According to the symptom-based Rome IV diagnostic criteria, IBS can be subtyped into the four categories of constipation dominant (IBS-C), diarrhea dominant (IBS-D), mixed IBS (IBS-M), and unclassified (IBS-U) (Drossman & Tack, 2022). Following the introduction of the Rome IV criteria in 2016, the prevalence of IBS was reported to be 4-5% in the general population. Studies showed that 4.7% of adults in the United States, 4.6% in the United Kingdom, and 4.5% in Canada suffered from IBS (Palsson, Whitehead, Tornblom, Sperber, & Simren, 2020). According to a population-based, cross-sectional survey, 7.9% of Australian adults have a self-reported medical diagnosis of IBS (Stocks, Gonzalez-Chica, & Hay, 2019). According to the 18 epidemiological studies that were included in a systematic review, the prevalence of IBS in Iran varied from 1.1% to 25% (Jahangiri, Jazi, Keshteli, Sadeghpour, Amini, & Adibi, 2012). Although the etiology of IBS remains unclear, emerging evidence indicates that IBS is one of the disorders of gut-brain interaction (DGBI) (Ishiguchi, Itoh, & Ichinose, 2003; Carco, Young, Gearry, Talley, McNabb, & Roy, 2020), meaning it engages in homeostasis regulation via the gut-brain-microbiome axis (Pigrau et al., 2016; Person & Keefer, 2021). According to the biopsychosocial model of IBS, disturbance in intestinal motility and enhanced visceral sensitivity interact with other factors (Spiller et al., 2007; Flik, Bakker, Laan, van Rood, Smout, & de Wit, 2017). Moreover, psychological and social factors can influence digestive function, symptom perception, illness behavior, and outcome (Longstreth, Thompson, Chey, Houghton, Mearin, & Spiller, 2006). Research to date suggests that 44% of IBS patients have accompanying psychological disorders including depression and anxiety, and 37.6% of IBS patients have reported sleep problems, such as sleep fragmentation, poor sleep quality, and reduced sleep duration (Yan et al., 2021).

Because of the limited effect of pharmacotherapy, there has been increasing interest in psychological treatments for IBS (Longstreth et al., 2006). Any pharmacological or non-pharmacological 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 (Colloca & Benedetti, 2005). The nonspecific effects of a treatment are called placebo effects when they are beneficial and nocebo effects when they are harmful (Benedetti, 1996; Aslaksen & Lyby, 2015). Placebo and nocebo response include all health changes observed after the administration of an inactive treatment (i.e., differences in symptoms after treatment compared to before treatment); thus, including natural history and regression to the mean (Enck & Klosterhalfen, 2021). The underpinnings of placebo and nocebo are psychological and neurobiological. Psychological mechanisms include expectations, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction, meaning (Chavarria et al., 2017), and neurobiological factors, such as cholecystokinergic hyperactivity (Benedetti & Shaibani, 2018). Expectations have a strong influence on health outcomes (Petrie & Rief, 2019). Expectation facilitates the perception of a specific sensation and of stimulus categories; thus, 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, patient's personality, societal factors, and the quality of the patient-physician interaction (Benedetti, Lanotte, Lopiano, & Colloca, 2007; Schedlowski, Enck, Rief, & Bingel, 2015). In addition, a high somatic focus (Adibi et al., 2012), and the presence of certain psychological states like depression or anxiety and personality traits such as pessimism (Schedlowski et al., 2015) or neuroticism have been associated with the occurrence of nocebo effects (Planes, Villier, & Mallaret, 2016). The consequences of the nocebo effect in clinical practice are always undesirable. It may make therapeutic interventions more painful, reduce response to treatment, worsen symptoms, or lead to adverse events, in turn causing therapeutic non-compliance, non-adherence, or discontinuation of treatment (Blasini, Corsi, Klinger, & Colloca, 2017).

Methods

Data sources: In order to provide the available evidence of the nocebo phenomenon and IBS and to guide further research, we started to review the scope (Arksey & O'Malley, 2005). Unlike traditional systematic reviews, the purpose of the present study was to provide a preliminary assessment of existing research or ongoing studies, and to identify potentially important research areas. We kept our search broad due to the lack of information on the extent of the nocebo phenomenon and FGIDs in the literature. We searched four databases (PubMed, PsycINFO, Google Scholar, and Scopus) for primary studies from their respective inception dates to June 2022.

Search terms: We started a preliminary search of these databases to identify papers and establish terms that may refer to nocebo, psychological factors, and IBS. This search showed that few publications use 'nocebo, psychological factors, and IBS' anywhere in the article; some databases had no or very few publications in which these terms were used. We found no established search strings for identifying nocebo, psychological factors, and IBS-related papers and no alternative MESH phrases. Several papers used alternative phrases such as "negative placebo effects", "nocebo side effect", "adverse effects of placebo" and "side effects of placebo", and FGID. Since the word "placebo" is commonly used in clinical trials, using it would make the subject of study weak and disproportionate. We tried to limit the search terms to "nocebo", "psychological factors" with IBS, and one specific alternative term - 'negative placebo effects'. The reference lists of the included articles were searched for relevant studies. The inclusion and exclusion criteria are presented in table 1.

Table 1. Study selection criteria

Inclusion criteria	Exclusion criteria
1- Empirical articles • The prevalence of nocebo effect and IBS • Demographic characteristics related to the nocebo effect and IBS • The neurophysiological basis of the nocebo effect and IBS • The psychological basis of the nocebo effect • Effect of nocebo on clinical presentation • Influence of healthcare provider-patient relationship on nocebo effect prevalence in patients • Effect of nocebo on adherence to therapy in IBS patients	1- Non-empirical articles, including audits, letters, opinions, and editorials 2- Empirical articles that only emphasize placebo 3- Nocebo articles related to conditions other than FGIDs 4 Studies not in English 5 Case histories

Selection criteria: Titles and abstracts of all studies were reviewed considering the inclusion and exclusion criteria. Full texts of all articles that either clearly met or possibly met the inclusion criteria were obtained. The obtained articles were reviewed. The differences in the articles were examined and the data were extracted. The quality of the selected articles was evaluated using the five-step process proposed by Woods et al. (2005) (Table 2).

Results

Databases were searched from their inception to 2022. After the elimination of duplicates, we identified 176 potentially eligible studies (Figure 1). After applying the selection criteria to their abstracts, this number reduced to 14 articles. With 1 additional paper identified through the reference lists, 15 papers were included for full text reading. Subsequently, 7 studies were excluded as they did not include empirical evidence, frequency, or correlates, etc. of nocebo and IBS. This left 8 primary empirical studies which met the selection criteria (1 experimental study and 7 surveys). Finally, 8 studies provided data on the existence, incidence, psychosocial correlates, and underlying mechanisms of the nocebo effect and IBS, although there was substantial overlap between categories.

Definitions of nocebo: An original definition of nocebo effect is an adverse effect from an inert treatment. It seems that, the nocebo effect is complementary to the placebo effect, the beneficial health effect that occurs following an inert or inactive treatment (Lembo, 2020). In general, placebo has received more attention in researches than nocebo, although the nocebo effect has an arguably more important impact on medical and health care. The high rates of nocebo effects attached to medical treatments result in impaired quality of life for many patients and can cause significant issues in adherence and persistence with medical therapy that lead to increased medical costs. (Petrie & Rief, 2019). There is also evidence that the negative effects of a treatment reduce the effectiveness of future therapies (Kessner, Sprenger, Wrobel, Wiech, & Bingel, 2013). Few articles have attempted to define nocebo; however, some articles have defined it as 'I shall harm', which implies a kind of intentional action that can be challenging. Some other definitions emphasize the 'negative equivalent' of placebo, in their study equating to 'an increase in perceived pain due to negative expectations and/or previous learning'. It has also been defined as "adverse reactions experienced from taking a placebo" (Petrie & Rief, 2019). Liccardi et al. (2004) define it as "the onset of untoward reactions following the administration of an indifferent substance". However, the question remains whether a placebo is necessary to detect a nocebo effect or not.

Despite a growing number of relevant publications, the terminology associated with nocebo-related phenomena remains confusing. Nocebo effects may account for 38–100% of side effects reported in pharmacological trials, including serious adverse events (Nestoriuc, Pan, Kinitz, Weik, & Shedden-Mora, 2021).

Table 2. The five-step process of article quality evaluation

1) Are the aims and objectives of the research clearly stated?
2) Is the research design clearly specified and appropriate for the aims and objectives of the research?
3) Do the researchers provide a clear account of the process by which their findings were produced?
4) Do the researchers display enough data to support their interpretation and conclusions?
5) Is the method of analysis appropriate and adequately explicated?

Source: Woods et al. (2005)

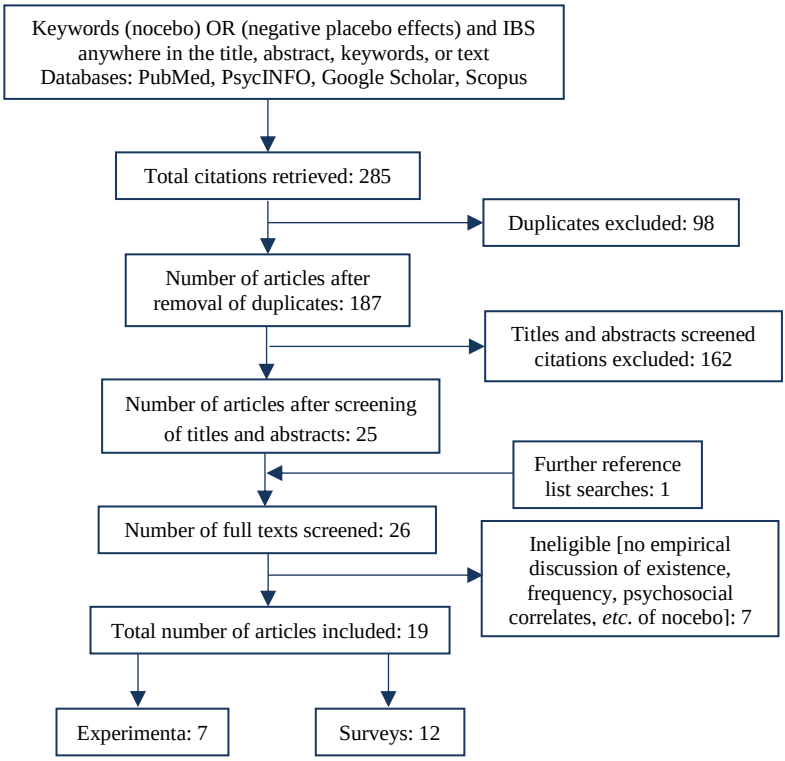

Figure 1. Summary of review process

Evidence for the existence and frequency of nocebo effect and psychological factors in IBS: Although there is no one widely accepted definition for nocebo, we identified significant empirical evidence from experimental and observational studies indicating that the nocebo effect/psychological factors in IBS is real, and potentially significant and important. For example, the study by Roderigo et al. (2017) supported the effects of acute psychological distress on placebo and nocebo responses in visceroception. Moreover, food intolerance in patients with non-gastrointestinal-related IBS can be an example of nocebo effect. For example, many patients describe symptoms akin to IBS, such as abdominal pain or discomfort, bloating, or altered bowel habits after eating. Notably, food intolerances can be associated with constipation as well as diarrhea. Patients may develop a myriad of non-gastrointestinal-related symptoms, such as brain fog, depression, joint pain, and skin rash. The nocebo response also plays a role in food intolerance in some patients (Chey, 2018). In another article of ours that is being published, the results showed a significant positive association between neuroticism score and nocebo effect among IBS patients. Lembo (2020) found that IBS patients with type A personality, who tend to have more neuroticism and pessimism, appear to have a higher nocebo response. In particular, anxiety, depression, and somatization are considered to be some of the psychological factors involved in the nocebo-related side effects in randomized clinical trials. A study indicated that individual factors like negative expectation and negative contextual factors can predispose individuals to psychological distress and the onset of the nocebo phenomenon (Amanzio, Howick, Bartoli, Cipriani, 2020).

Accurate and specific determination of the frequency and incidence of the nocebo effect, both in general and specifically in IBS, is difficult. Due to the lack of a clear definition for the nocebo phenomenon, we did not find a consistent methodology in studies related to the nocebo phenomenon. However, in various articles, the frequency of occurrence of nocebo effect, especially in IBS, has been reported. Regarding the frequency of the nocebo phenomenon, recent randomized controlled trials (RCTs) on adverse events in active treatment groups reported that approximately 70-80% of cases are probably not attributable to drug effects. Additionally, approximately 25% of patients randomized to placebo in clinical trials reported adverse events, and this prevalence increased significantly in studies when participants were asked about specific adverse events (Petrie & Rief, 2019).

Psychosocial correlates of nocebo: In the present study, the psychosocial correlates (both potential predictors/risk factors and sequelae) of nocebo in IBS patients were identified. These correlates included gender, prior experience or knowledge of harmful therapy, personality type, psychological variables (anxiety, depression, and distress), morbid conditions, and age. Many articles indicated that women were more likely to experience the nocebo effect. Strohle (2000) found that female patients with panic disorder had an increased nocebo response. The underlying causes of placebo and nocebo are psychological and neurobiological. Psychological underpinnings of placebo and nocebo effects include expectancies (positive or negative), conditioning (classical, instrumental, or observational), learning (with different approaches), memory, motivation, somatic focus, reward, anxiety, depression, and meaning (Chavarria et al., 2017). Negative expectations increase anxiety and intensify somatosensory information, thus intensifying the nocebo effect. Moreover, anxiety can be a key mechanism for the emergence of nocebo responses (McLemore et al., 2020). Other mechanisms may be involved in the induction of the nocebo response, including patient-related factors, psychosocial background, and neurobiological factors, such as cholecystokinergic hyperactivity. However, the most studied and understood mechanism is related to patients' negative expectations. Indeed, the task of the therapist in clinical practice is to maximize placebo effects while minimizing nocebo effects. However, in clinical trials, we want to minimize both placebo and nocebo effects (Benedetti & Shaibani, 2018).

Anxiety, depression, and psychological distress: In an RCT on pain perception, Staats, Staats, and Hekmat (2001) found significant correlations between anxiety and mood, and nocebo responses. Weimer, Enck, Dodd, and Colloca (2020) found that the nocebo response had a significant correlation with physical symptoms, state anxiety, negative mood, catastrophizing, and neuroticism. Researchers found a significant correlation between personality type A, which has a higher level of neuroticism and pessimism, and the presentation of nocebo responses (Lembo, 2020). In another study, the prevalence of anxiety was 45.67% in patients with IBS and 30.71% in the control group, which indicates a higher level of anxiety in IBS patients. Furthermore, as previously mentioned, the Prevalence of nocebo responses is higher in IBS patients (Mohammed, Moustafa, Nour-Eldein, & Saudi, 2021). According to a clinic-based study, the prevalence of depression and anxiety in IBS patients is 1.37%, and 31.4%, respectively. According to the results of this study, IBS-M is associated with a higher level of depression and anxiety, and the prevalence of depression and anxiety was the highest in IBS-C (Hu et al., 2021). Amanzio et al. (2020) found that people with anxiety, depression, and somatization are more likely to illustrate nocebo effects and responses. Anxiety, depression, and somatization are some of the psychological factors reported to

be involved in nocebo-related side effects in RCTs. Furthermore, the severity of psychopathology, such as the severity of anxiety and depression symptoms, significantly influenced the attribution of their bodily sensations to the drugs (Amanzio et al., 2020). It is interesting to note that most IBS patients with concomitant anxiety and depression present with gastrointestinal symptoms before the onset of psychiatric symptoms (Zhang et al., 2022). Patients with depression may be at risk due to obvious cognitive errors and frequent catastrophic thoughts, and hence, they are more likely to have negative expectations and show nocebo responses (Roderigo et al., 2017). There is, significant comorbidity (50-90%) among patients with functional GI conditions (disorders of brain-gut interaction) and psychiatric disorders (Montero & Jones, 2020). The disease burden of IBS is significant, IBS imposes a substantial economic burden in direct medical costs and in indirect social costs such as absenteeism from work and school, and lost productivity, along with the less-measurable costs of a decreased QOL (Hulisz, 2004). In fact, patients with chronic digestive disorders manifest higher rates of psychological distress, have lower QOL than the general population (Hauser, Janke, Klump, & Hinz, 2011), and some 38% even experience active suicidal ideation related to GI symptoms (Miller, Jones, & Whorwell, 2007). Research supports effective psychological treatments for varying GI disorders, with numerous RCTs demonstrating a marked reduction in GI symptoms, as well as an overall improvement in QOL and emotional well-being (Palsson & Whitehead, 2013). Understanding psycho-gastroenterology, including identifying appropriate patients for this service, can help increase patients' utilization of psychological treatments with the goal of reducing GI symptoms, improving overall emotional health, and ultimately decreasing the high health care costs of this population (Montero & Jones, 2020). According to the report of the American Gastroenterology Association (AGA), a detailed study showed that psychological distress aggravates digestive symptoms such as diarrhea and abdominal discomfort (Umrani, Jamshed, & Rizwan, 2021). The increase in abdominal pains both in terms of frequency and intensity of symptoms in patients with IBS based on the Rome criteria was associated with the presence of psychological distress symptoms (Shiha et al., 2021).

Personality traits: A review of personality studies shows that the personality traits of neuroticism, conscientiousness, and alexithymia are related to the occurrence of IBS (Muscatello, Bruno, Mento, Pandolfo, & Zoccali, 2016). Furthermore, studies have shown that nocebo responses have a significant relationship with personality type A and pessimism (Quilty, Sellbom, Tackett, & Bagby, 2009). It seems that some personality traits reduce individual risk and resilience and impact treatment responses in some psychological and psychosomatic disorders, such as major depressive disorder and bipolar mood disorder, which is associated with neuroticism/extroversion traits (Kelley et al., 2009). In addition, extraversion is associated with the occurrence of placebo responses in the context of empathy in patients with IBS (Beissner, Beissner, Brunner, Fink, Meissner, Kaptchuk, & Napadow, 2015). Moreover, Corsi and Colloca (2017) found that the personality trait of openness to experience plays no role in the placebo response; in addition, they found that personality trait alone did not have an effect on the nocebo response.

Biological and psychological mechanisms related to nocebo: Some studies have presented potential causes of nocebo. In a pain research, Benedetti, Amanzio, Vighetti, and Asteggiano (2006) found that nocebo hyperalgesia is verbally related to hypothalamus-pituitary adrenal axis hyperactivity. Moreover, other studies have suggested the role of dopamine (Scott, Stohler, Egnatuk, Wang, Koeppe, & Zubieta,

2008). Indeed, in some circumstances, a physiological effect (e.g., increased cortisol) may result from negative expectancy, even where nocebo is not ultimately evident in the results reported (Johansen, Brox, & Flaten, 2003). In addition, some studies emphasize the role of the hippocampus; nocebo hyperalgesia may be induced through a cognitive pain pathway (central pain system) and the hippocampus may play an important role in this process (Kong et al., 2008). Given other study evidence, the identification of cognitive pathways is not surprising. However, biological evidence can further support these findings. Moreover, cholecystokinin hyperactivity has also received much attention in this regard (Benedetti & Shaibani, 2018). The more specific psychological mechanisms involved in nocebo are the processes of learning and conditioning (i.e., the association of meaning and expectation through prior experience) (Klosterhalfen et al., 2009).

Discussion

According to the results of the present study, it is difficult to define the nocebo phenomenon; nevertheless, its identification is very important in clinical interventions as an important part of the effects of treatments can be negatively affected. The present study has provided good information while identifying the nocebo effect in IBS and the role of psychological factors in the creation, strengthening, and persistence of the nocebo effect. Researches have shown that the nocebo phenomenon is more common in women and its prevalence in clinical settings is 3-27%. Moreover, the results showed that some personality traits such as neuroticism, extroversion, conscientiousness, and type A personality are related to the occurrence of the nocebo phenomenon. However, psychological disorders are common in IBS, and can increase the occurrence of the nocebo phenomenon in these patients. As previously mentioned, the psychological and social correlates of the nocebo effect included type A personality (competitive, a sense of urgency, and tendency to hostility), pessimistic nature, and psychological disorders such as panic or depressive disorders. Biological and psychological mechanisms are the underlying causes of the nocebo effect with a major emphasis on prior experience or expectancy. Contrary to the results of other studies, van Laarhoven et al. (2011) did not find a relationship between neuroticism and the placebo and nocebo effects. Furthermore, Beedie, Foad, and Coleman (2008) observed a positive correlation between placebo trials and neuroticism. The existence of contradictory data in the studies related to placebo and nocebo motivates us to strengthen and increase the scope of our research in this regard. However, there is a controversial relationship between extraversion and the nocebo and placebo phenomena. Beedie et al. (2008) showed that more placebo effect is seen in people with extroverted characteristics. Amanzio et al. (2020) found that people with symptoms of depression and anxiety as well as somatization are more ready to provide nocebo responses and the level of psychopathology may be related to the occurrence of nocebo responses.

Strengths and limitations of the review: The present study provides a clearer picture of the nocebo phenomenon in clinical studies, and research related to functional gastrointestinal disorders and psychosomatic disorders in general. Furthermore, the lack of a precise definition or the variety of definitions for the nocebo phenomenon was a barrier to finding related articles. In addition, due to the specialization of the field of functional gastrointestinal disorders and its relationship with psychopathology and the nocebo phenomenon, there were very few related articles. However, this article provides an opportunity to further investigate this very

important and practical field.

Implications for practitioners: Although in some articles, the prevalence of nocebo responses was 3-27%, this rate can be higher in some disorders. A high level of nocebo reactions is observed in patients with functional gastrointestinal disorders, especially IBS. Therefore, experts' familiarity with the nocebo phenomenon and factors related to it can be effective in providing appropriate therapeutic interventions. It is important for practitioners such as physicians and clinical psychologists to identify those individuals most at risk of nocebo responses; not all risk factors will be as obvious as gender. This study identified neuroticism, anxiety, depression, psychological distress and panic disorder, and type A personality as nocebo predictors.

Conclusion

Research evidence shows that nocebo effects are both real and underlie an important part of the diagnosis and treatment process. However, they can cause disease complications, result in the patient's dissatisfaction with the treatment process, and also cause problems such as non-adherence to treatment or the occurrence of unusual reactions in the patient, and drug non-compliance. The results of studies on nocebo can assist therapists in the early identification of at-risk patients according to the identified risk factors for the occurrence of nocebo effects, such as personality traits, and clinical symptoms such as anxiety, depression, and pessimism, and the provision of appropriate interventions. These studies can reduce the cost of treatment and the burden of the disease while providing more satisfaction to the patient and the therapist.

Conflict of Interests

Authors have no conflict of interests.

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