ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

Section Editor: William D. Chey, MD

Understanding the Placebo and Nocebo Effects in Patients With Irritable Bowel Syndrome

Anthony J. Lembo, MD
Associate Professor of Medicine
Division of Gastroenterology
Department of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

G&H What are the placebo and nocebo effects?

AL The placebo effect is an improvement in symptoms that a person may experience from an inert treatment that cannot be attributed to the treatment itself, as it has no physiological effects. In therapeutic trials, the inert treatment is most commonly a placebo pill, but may also be a sham surgery or procedure. The nocebo effect is the opposite—a worsening of symptoms that is not related to the treatment itself. For example, patients taking a medication (or a placebo) may experience adverse side effects, often associated with negative expectations or prior negative experiences, that are not related to the medication itself.

G&H What neurobiological and psychological factors are thought to contribute to the placebo effect?

AL We have come a long way in understanding the neurobiological mechanisms behind the placebo effect. Laboratory studies have demonstrated that a number of neural networks within the body are involved in the placebo effect. These include the opioid, endocannabinoid, cholecystokinin, and dopamine systems. Recent functional imaging studies have shown changes in the brain related to the placebo effect. Areas of the brain that appear to be involved in the placebo response include the anterior cingulate cortex, thalamus, posterior insula, and areas in the somatosensory cortex. Together, these findings suggest that the placebo effect has true neurobiological mechanisms, but what triggers these mechanisms is not perfectly understood.

A number of psychological factors are known to contribute to the placebo effect. One of the leading theories is expectation, which is a broad term that includes conditioning effects and learned behaviors. Essentially, how a treatment is presented to a patient affects the placebo response. If the expectation is high that a drug or treatment will be effective, a patient is more likely to experience a placebo effect. Clinician-patient interaction is another important element. My colleagues and I conducted a 6-week trial several years ago on this topic in which we evaluated factors such as empathy, physical contact (eg, limited physical examination), thoughtful listening (including short pauses in order to think about the information that the patient was presenting), and

asking more open-ended questions as opposed to going through a checklist of items. Incorporating these elements added approximately 30 minutes to the patient visit, yet the difference in symptoms was very significant; we found that patients with irritable bowel syndrome (IBS) who had an augmented interaction with their clinician had better outcomes compared to patients who had a limited clinician-patient relationship.

G&H Are certain people more likely than others to experience the placebo or nocebo effect?

AL Studies have found that certain personality characteristics may be associated with a higher placebo response. For example, individuals with more altruism and extroversion may be more likely to have a placebo response. An individual's previous experience as it relates to the context of the placebo may play a role in placebo response. Additionally, an individual's genetic makeup may contribute to the placebo response. For example, the catechol-O-methyltransferase (COMT) gene, which regulates the metabolism of a number of neurotransmitters, including dopamine, appears to predict placebo response, at least in some individuals in the appropriate context.

The nocebo effect is likely to be more reliant on expectation; that is, the way a treatment is presented may influence nocebo effects. For example, if a patient is told that a drug is likely to have side effects, he or she is more likely to report side effects. In addition, individuals with type A personality, who tend to have more neuroticism and pessimism, appear to have a higher nocebo response.

G&H What are the challenges of using placebo in clinical trials for treatments for IBS?

AL In IBS clinical trials, the average placebo response is approximately 40%. This high placebo response poses a challenge to the development of effective treatments, both because the treatment has to perform significantly better than the placebo and because a lot more patients are required to show a statistically significant difference over placebo, which makes conducting these trials more expensive.

G&H What factors contribute to a high placebo response rate?

AL A number of factors contribute to the high placebo response rate in IBS trials. For example, since IBS symptoms fluctuate and patients tend to enter a clinical trial when their symptoms are more severe, the tendency is for symptoms to improve. In addition, the lack of an objective marker to assess improvement and the relatively imprecise questionnaire to assess symptoms contribute to the high placebo response rate. Other factors such as the number of visits or interactions with the study team, the patient expectation of the treatment efficacy, and the higher the odds that the patient will receive the study treatment instead of placebo all may contribute to the placebo response.

G&H How should clinical trials be designed to minimize this placebo response?

AL A number of strategies have been used in clinical trials to reduce the placebo response. Some strategies have included using a single-blind placebo run-in phase prior to randomization to exclude placebo responders; reducing the number of office visits; standardizing the relationship between the patient and the study staff; reducing patient expectation of the effectiveness of the treatment; and excluding patients with high anxiety, somatization, or depression scores. Implementing these strategies in a real-world clinical trial can be difficult, if not impossible. It is also important to note that these strategies will likely reduce the placebo response in both the placebo and the treatment arms and, therefore, the response between treatment and placebo will likely not be different. An important assumption in clinical trials is that the placebo effect is the same in both arms of the trial. This has yet to be proven.

G&H What strategies are available to reduce the nocebo effect?

AL I try to reduce potential nocebo effects in my practice by managing patients' expectations. In other words, I emphasize the infrequent chance that they will experience a side effect as well as emphasize the number of patients receiving placebo in clinical trials who also experienced that side effect. For example, instead of stating that 10% of patients in clinical trials reported headaches, I would say that only 2% of patients in clinical trials reported having more headaches than patients who receive placebo. Of course, the serious side effects that truly occur need to be discussed with patients, and there is no way of getting around that in clinical practice. Therefore, the more a clinician de-emphasizes the side effects that may not be related to the drug, the better off patients may be.

G&H What is open-label placebo?

AL Open-label placebo is when patients know they are getting the placebo treatment, and that it is an inert substance being presented as a potential treatment for their

symptoms due to available data from placebo-controlled trials. The outcome is a subjective measure, such as trying to reduce IBS symptoms. Studies have found that presenting patients with a placebo treatment as a potentially beneficial treatment has a psychological effect on the brain, and that the positive effects occur for a longer period, even after stopping the treatment.

G&H How can the placebo effect be leveraged to improve treatment in patients with IBS?

AL Patients can experience a placebo effect just by going to see a clinician or participating in a trial. For some, filling out questionnaires is therapeutic. These nonspecific effects of placebo are called the Hawthorne effect. Studies have shown that augmented clinician-patient interaction is influential beyond the Hawthorne effect, and that empathy and decreased expectations of adverse events can have a positive effect on the brain.

G&H What are the priorities of research?

AL Understanding the mechanism behind the placebo effect is important. We know that certain neurotransmitters and areas of the brain may be involved, and further understanding how they work is critical for being able to control or optimize the placebo effect, in clinical trials as well as in clinical practice. Another priority is to find a way to harness the placebo effect, such as with open-label placebo, in clinical practice.

Disclosures

Dr Lembo has no relevant conflicts of interest to disclose.

Suggested Reading

Ballou S, Beath A, Kaptchuk T, et al. Factors associated with response to placebo in patients with irritable bowel syndrome and constipation. *Clin Gastroenterol Hepatol*. 2018;16(11):1738-1744.e1.

Dorn SD, Kaptchuk TJ, Park JB, et al. A meta-analysis of the placebo response in complementary and alternative medicine trials of irritable bowel syndrome. *Neurogastroenterol Motil*. 2007;19(8):630-637.

Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One*. 2010;5(12):e15591.

Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomized controlled trial in patients with irritable bowel syndrome. *BMJ*. 2008;336(7651):999-1003.

Patel SM, Stason WB, Legedza A, et al. The placebo effect in irritable bowel syndrome trials? A meta-analysis. *Neurogastroenterol Motil*. 2005;17(3):332-340.