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Addressing the Nocebo Effect: Limiting the Potential for Negative Clinical Outcomes

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Abstract

In contrast to the familiar placebo effect, increased positive outcomes triggered by positive expectations, the opposing and less favorable phenomenon known as the nocebo effect results in aversive outcomes stemming from negative expectations. While currently being a rather new and trending field of research, associated ethical conflicts have restricted the types of studies conducted and the available knowledge concerning the topic. The ethical dilemma and lack of complete understanding make it difficult for clinicians to develop changes that effectively reduce the likelihood of nocebo responses affecting clinical trials, patient treatment outcomes, side effect severity, and overall negative feelings surrounding medical settings. Regardless, some semi-successful modifications in patient-physician communication and interactions have been able to decrease the probability of nocebo responses occurring. Further research is needed to obtain more knowledge about the way the nocebo effect works, to better identify susceptible patients, and to develop more effective methods of controlling the nocebo effect.

Defining the Nocebo Effect

The placebo effect is a well-known phenomenon that has been proven to affect patients' clinical outcomes. This highly researched topic is defined as a positive result that occurs when a patient receives a fake or inactive treatment, meaning the improvement of their condition stems from their positive and hopeful expectations. The lesser-known opposing phenomenon also plays a role in clinical treatments: an adverse effect is brought on by the negative expectations and feelings of a patient, resulting in a decrease in the patient's quality of life and willingness to continue receiving medical treatment. This is known as the nocebo effect (Colloca & Miller 2011), which is derived from the Latin verb *nocere*, meaning 'to harm' (Planes, Villier and Mallaret 2016). The nocebo effect can result in unwanted symptoms ranging from nausea, gastrointestinal discomforts, allergic symptoms, fatigue, etc. (Bartels et. al.). While these symptoms are common for a wide range of conditions, when they unnecessarily occur due to the nocebo effect, they can cause a patient to be given unnecessary tests or treatments. This possible increase in costs and time wasted proves that a better understanding of nocebo effects will greatly help a wide variety of medical fields.

Therefore, the nocebo effect is highly undesirable since it can increase patient costs and delay appropriate treatment. However, while the medical field recognizes that a better understanding of nocebo effects would greatly help a wide variety of medical fields, the nocebo effect is poorly studied and hard to control due to the vast number of variables that contribute to it: the inability to control the patient's mindset, and the ethical dilemma that both research of the phenomenon and its potential "solutions" to eliminate this response bring about. This challenge has hindered both clinicians and researchers who try to understand the effect and how best to prevent it from occurring. However, in the past decade, our knowledge of the brain and medicine has increased and technology has advanced to the point where the causes of the nocebo effect are being better understood. This review illustrates the concept of the nocebo effect and its importance in the medical field, as well as explores the previous and current research being done and the challenges that come with it.

Modern Research Conducted to Increase Understanding of the Nocebo Effect

Due to the medical field's recent recognition of the nocebo effect and the field's realization that the nocebo effect is highly under-recognized in clinical settings, it has been a recent popular topic in clinical research, especially because researchers have realized that the nocebo effect is far more prevalent and plays a much larger role in outcomes than it once was thought to. With the recent advances in technology and research, studies about the nocebo effect are becoming more common due to the researchers discovering ways to ethically test it.

Two main types of research are being conducted to study the nocebo effect and attempt to limit its occurrence and impact on clinical outcomes. The first type of research is more traditional, with researchers attempting to understand more about how the nocebo effect works and trying to confirm how much of an effect it actually has on clinical treatments (Kong et. al. 2008). Once this first type of research established a general understanding of the phenomena, the second type of research came about: the development of methods to minimize the prominence of the nocebo effect in clinical settings. Although the basic conceptual study style began first, both types are still being used in modern nocebo research.

Type One: Experimental Research Aimed at Understanding the Nocebo Effect

An important task in early nocebo research was understanding for whom and where the nocebo effect is most prevalent. The nocebo effect is caused by a variety of factors that relate to the individual patient, their environments and experiences, and the interactions they have in the clinical setting. Anyone can experience negative expectations about treatments, but not all patients are as susceptible to the nocebo effect taking place (Manaï et. al. 2019).

Genetics also plays an important role, as researchers have found that variations in the genome result in certain genotypes being able to detect sensations and sensation variation better than others, which leads to higher levels of sensitivity, stronger reactions to medication, and more concern about the effects of treatments (Wendt et. al. 2014). Personality also affects susceptibility, as pessimists have been discovered to be more likely to be affected by the nocebo effect than optimists (Corsi and Colloca 2017). Other personality traits that predispose patients to the nocebo effect include type A personalities (Drici et. al. 1995), introversion (Bartels et. al. 2014), and predisposition to chronic worry (Barsky et. al. 2002). Some mental illnesses have also been found to positively correlate with the nocebo effect: depression (Barsky et. al. 2002), anxiety (Löwe B et. al. 2008), and other types of psychological distress can overemphasize a patient's focus on negative outcomes and symptoms (Manaï et. al. 2019).

For example, in 2017, a study was led by A. Tinnermann, aiming to understand how the nocebo effect plays a role in treatment outcomes involving pharmaceuticals. At the time, it was well known that many patients who are prescribed drugs tend to stop taking them over time, but the reasons for this cessation were unknown. Tinnermann's group explored how drug information, which has no direct impact on treatment results, impacted the patient's outcome from taking it. Tinnermann et al. used brain imaging to measure the neural activity in various parts of the brain and spinal cord during a skin heat-pain treatment in which the skin was treated with one of two inert creams following a pain stimulation, visibly labeled as either inexpensive or expensive. The areas of the brain that were observed for increased activity are directly involved in nocebo hyperalgesia, which is increased pain sensitivity based on expectation. By studying the changes in brain activity in these specific areas, Tinnermann et al. (2017) concluded that the monetary value of the treatment influences adverse treatment outcomes. The expensive label led to higher nocebo hyperalgesia than did the medication with the inexpensive label. The importance of this study is that it confirms that the nocebo effect, or the negative thoughts and feelings a patient has about a treatment, is in fact important and plays a role in the likelihood of a positive outcome.

Unfortunately, this study joins only a handful of others that have been able to explain the nocebo effect. For obvious ethical reasons, unnecessary harm cannot be induced on clinical trial patients or research participants. These ethical standards, along with the many factors that contribute to the likelihood of the nocebo effect occurring, greatly limit the ways the nocebo effect can be tested. Therefore, with this ethical debate and the lack of a solid understanding of these factors, solutions for nocebo responses are being determined and implemented more slowly than desired. However, for the most part, clinicians and other medical professionals have opted to believe the research results regarding the importance and prevalence of the nocebo effect from the small pool of studies that have been conducted. The experimental research is great for base knowledge about the nocebo effect and allows for a better understanding of the concept as a whole; however the second type of research is more important. This is because the second type of research aims to take what we know about nocebo

responses in the medical field and works directly to control and limit them. The high rate of acceptance among researchers and medical professionals of the limited research has allowed for a quicker shift to the second type of research.

Type Two: Clinical Research Aimed at Controlling the Nocebo Effect

The second type of research on the nocebo effect includes studies that aim to control this effect. In other words, these studies are attempting to find the best pre-procedural methods to avoid the adverse effects caused by the nocebo effect, such as decreased treatment success and worsening of symptoms. As more research is done regarding the nocebo effect, researchers continually conclude that increased side effects could be a result of patients' mental expectations. The nocebo effect involuntarily causes the patient to experience physical symptoms based on verbal suggestions (Aslaksen P. & Lyby P. 2015). Since the symptoms result from the patient's negative expectations about the particular treatment, researchers are more focused on studying the patient's psychological differences rather than physiological. Researchers aim to increase the likelihood of positive outcomes, by limiting the likelihood of negative expectations arising in the first place. Therefore, by implementing tactics/methods to help stop a patient from having negative expectancies of treatment, doctors can better create a productive exchange of information between patients and themselves.

The nocebo effect has also been found to be influenced by the information that is disclosed to patients about possible outcomes and side effects that come with each treatment, as well as how this information is presented to them. This finding brings up an issue that remains difficult for researchers and clinicians, which is how to remain ethical while also limiting the nocebo effects. With early solution suggestions involving limiting the amount of information shared with patients regarding the possible adverse side effects and outcomes involved with the treatment, the ethics of not informing patients enough was brought into the equation.

The Ethical Dilemma

Facing such an ethical dilemma, researchers have been working on developing specific methods for deciding what information is necessary to disclose to patients in order for the patients to be able to make informed consent. In other words, researchers are searching for forms of open communication between doctors and patients regarding any risks attributed to the patients' treatments. It is vital that healthcare professionals are able to find the right balance of how much to share with patients to allow for informed consent while at the same time limit the likelihood of the nocebo effect. Nocebo responses are linked to negative thoughts, so oversharing risks and side effects to patients can actually be harmful (Colloca & Miller 2011). This ethical median is the major challenge for researchers trying to limit the nocebo effect in clinical settings.

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Because it is true that a patient's knowledge of all the ill effects of a treatment can increase the frequency with which the nocebo effect will take place, some researchers are exploring how to inform the patient on only what is necessary for them to know. By verbally easing the patients into the medical treatment, doctors can provide patients with all the critical information they need to know about the treatment that will be given to them. For example, patients with pre-existing conditions that could negatively affect the medical treatment will be told about the side effects that relate to that specific pre-existing condition. On the other hand, patients without any pre-existing conditions will only be given the information they need therefore not causing any excessive and unnecessary stress before taking the medication. Fear of medical pain is known to affect a patient's emotional response patterns, hence causing anxiety or increased fear (Aslaksen P. & Lyby P. 2015). Reducing the reasons why a patient may feel fearful of medical treatments should cause an overall decline in nocebo responses. Limiting every patient's likelihood of having a nocebo response is important for not only the patient's health, but also the physician's plan of action for the treatment: a reduction of fear inducing factors presented to the patient leaves less room for the patient's worry, and it places the focus on the optimal treatment plan outcomes.

Such a reduction of information, however, brings up the idea of deception. Deception is more than just telling the patients false information, as it was once thought to be (Hey 1998). Current understandings of deception include recognition that the withholding of necessary information can create false beliefs about a treatment. Such withholding of information is, technically, not banned in clinical research. However, the withholding often leads to poor results and a patient's ambiguous feelings about the practices. This is why although withholding information isn't illegal, it is not advised. Some studies have concluded that many patients do not mind being misled, while other studies observe patients feel anger and annoyance due to the deception (Webster 2018).

Some may argue that an unethical element of conducting research on the nocebo reducing methods in clinical practices is the withholding of possible side-effects caused by specific medical treatments. Therefore there have also been studies that are working not to change the specific information that is shared with the patient, but rather how the information is shared with the patients, to find a more effective way to get the necessary information across without creating unnecessary negative expectations. Overall, many different factors contribute to the difficulty of controlling and limiting the nocebo effect and this ethical dilemma is only one of them.

Modifying Classic Clinic-Patient Interaction Protocols

One example of how clinicians are changing their procedures to limit the nocebo effect is through the use of "framing" (Chamsi-Pasha et. al. 2017). Message framing is a method of delivering and disclosing information that focuses on the benefits rather than possible negative side effects. While all the necessary information is shared with the patient in order to allow for informed consent, the focus of the information is placed on positive outcomes. For example, a clinician prescribing a new drug to a patient would share the needed information about side effects and results but create a positive

frame by sharing information that focuses on good outcomes. One example of this is the mentioning to patients of the percentage of successful treatments or the number of users who didn't experience an uncommon side effect that was deemed necessary to mention. Another way of shifting the delivery of information arises with suggestion. Considering how the use of suggestion in clinical practice affects the amount of distress patients have and the number of exaggerated or uncommon symptoms, doctors' use of suggestion can make a big difference in the probability of nocebo responses. Suggestion is powerful and can easily change the way a patient thinks about something, both negatively and positively. Suggestion can come in many forms, including verbal and nonverbal as well as intentional and unintentional. All of these are factors that contribute to how a patient feels about any given treatment. Having physicians focus on suggestions that reinforces positive expectations can lower the worry and anxiety of their patients.

Conclusion

The nocebo effect was once often overlooked by doctors when making decisions on medical care and treatment for patients, but it has recently become a major topic of clinical research and in the last decade it has reformed the way medical interactions occur. This change was brought about by the realization of the large role the nocebo effect has in treatment outcomes and by the increased awareness of its negative associated effects. Research on the nocebo effect has proved challenging, though, as it has many different contributing factors, including both biological and personality characteristics, patient background, societal influences, and clinical communication and experiences. Along with the difficulty that comes with defining such a complex idea, researching and clinically combating the nocebo effect has introduced ethical concerns that have limited the opportunity of obtaining knowledge and implementing major changes to control nocebo responses.

Despite these roadblocks, a handful of studies had successfully provided results, giving medical professionals useful knowledge regarding the most common attributes and experiences that make patients susceptible to nocebo responses. From this information, clinics have been able to modify their protocols and implement different methods in order to reduce the likelihood of a nocebo effect negatively affecting treatment outcomes or increasing side effect severity. The most prominent change that physicians have made is that they now are more meticulous in deciding what is the most important information to share with their patients by choosing whether to discuss all the knowledge and outcomes a treatment has or limiting it to what is only necessary and medically relevant. This reduces the frequency of nocebo effect occurrence and lowers the chances of it inducing negative outcomes.

These tactics have been shown to help avoid negativity affiliated with medical settings, improve treatment success rates, lower the chances of unwanted adverse effects, and aid in patient-physician interaction and communication. Hopefully, as technology continues to progress and new research methods are introduced that nocebo-related research can advance in order to continue creating the best outlook for patients.

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