Taking Notice of the Nocebo Effect on Drug Therapy

Grace Chan, B.Sc.(Pharm.) Candidate 2014
Anthony Le, B.Sc.(Pharm.) Candidate 2014
1Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

While the nocebo effect has been interpreted and classified in a number of different ways by researchers from all over the world, many agree that its existence is real and can significantly influence clinical outcomes. Both the nocebo and placebo effects share similar triggers, but their physiological mechanisms differ significantly. Given the compelling cases that have been published in literature, we believe that the nocebo effect impacts patient care and drug therapies in important ways that should not be ignored. Studies have shown how it can affect common healthcare practices such as generic substitution and ADR (adverse drug reaction) reporting, and can be influenced itself by important aspects of healthcare such as clinician-patient interactions and patient autonomy. Based on this information, we will be extending the concept of the nocebo effect to include a broader range of expectation triggers, and we assert that recognizing the nocebo effect can play a significant role in improving pharmacy practice.

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Compared to the placebo effect, the nocebo effect is seldom heard in pharmacy practice, generating 183 results on PubMed as opposed to 55,600,000 for the term “placebo”. The nocebo effect is traditionally defined as an unfavourable experience resulting from a therapeutically inert drug or procedure, though a recent article in the New York Times has broadened its definition to include any harm arising from negative patient expectations, regardless of whether the drug is real or placebo (1). Certain studies have used the term “nocebo-related effect” to describe similar expectation-induced exacerbations of symptoms, but which exclude the involvement of any inert drug (2). Some researchers believe that the nocebo effect is merely a negative aspect of the placebo effect and should therefore be classified as the same phenomenon (3). Others consider it distinct from the placebo effect, based on observed differences in neural activation and duration of effect (4, 5). Despite varying opinions on how to best classify and define the nocebo effect, we acknowledge that all theories have their merits and can be integrated to provide a more encompassing view of the phenomenon’s implications on different patients under different circumstances.

In exploring the neural profile of the nocebo effect, many studies have focused on the perception of pain and how it is influenced by verbal suggestions (2). These studies have utilized brain imaging to reveal that anticipated enhancements in pain that trigger nocebo-like effects can activate the anterior 21thernet21d cortex, insula, thalamus, and prefrontal cortex without any pre-conditioning events (2). In contrast, the placebo effect has been linked to dopamine release in the nucleus accumbens, and there is a general consensus that these effects are strengthened through learning (5, 6). Indeed, it has been shown that prior positive experiences with an analgesic can lead to more successful therapeutic outcomes from a placebo analgesic (4). One rationale for the difference in activation pathways between the nocebo and placebo effect is that the areas of the brain known to be involved in the nocebo effect: the thalamus, insula, and anterior cortex, can be considered as more “primal” centres of the human brain (6). They are innately involved in danger perception and fear responses and have evolved to protect mankind from immediate danger (7). Moreover, the nocebo effect has been associated with cholecystokinin release and activation of the HPA axis in fear mediation and pain transmission (2).

While high-quality controlled studies on the nocebo effect are limited due to ethical concerns of deliberately inflicting distress on study participants, many examples of the nocebo effect in healthcare can still be found in literature. One case report illustrating the “classical” definition of the nocebo effect describes a 26-year-old male who experienced severe hypotension after swallowing 29 inert capsules labeled as a new experimental drug to treat his depression (8). The patient, believing that he had fatally overdosed himself on antidepressants, required intravenous fluids to restore his blood pressure. He was immediately revived when one of the physicians involved in the study revealed the true nature of the capsules. This event demonstrates the powerful physical and psychological impact of the nocebo effect, and suggests the possibility that the phenomenon may also influence the reporting of...
adverse drug events. Because health care professionals rely on the testimony and presentation of their patients to discover and report novel or unusual adverse effects of drugs, nocebo-related adverse events can easily be interpreted as novel events and be reported along with adverse events being caused by the drug itself. Furthermore, reports of adverse drug reactions have been known to be influenced by negative expectations of the reporting professional themselves, as shown by a study investigating the reporting trends of AEFIs (adverse events following immunizations) conducted in France (9). This study found that health care professionals disproportionately reported AEFIs to non-live vaccines that reflected the symptoms of diseases the vaccines were designed to prevent.

We argue that the nocebo effect can also influence real drug therapy, outside of its traditional definition regarding side effects arising from a placebo treatment. Indeed, it has been shown that verbal suggestions of pain can induce hyperalgesia, an increase in pain sensitivity from an already painful stimulation, as well as alldynia, the induction of pain from a painless stimulation (5). This observation demonstrates physiologically significant nocebo-like effects that can have applications in a patient care setting. As well, hyperalgesia can be seen in this case as an analogy for heightened side effects experienced from a real drug, and alldynia as an analogy for side effects occurring from the use of an inert drug. Further, it is known from studies on analgesics that anxiety about a drug can activate cholecystokinin, which facilitates pain transmission, dampening the drug’s effectiveness (2). This concept may apply to other drugs not used to treat pain, but whose side effects include pain or discomfort that may be intensified with the nocebo effect.

One clinical study investigated the role of the nocebo effect in postoperative patients requiring opioid painkillers. The study found that verbal suggestions by the clinician and the quality of the clinician-patient interaction had a psychological influence on the amount of opioids required by the patient after surgery (10). In a phenomenon termed “anxiebo” by the study’s researchers, patients who did not receive words of encouragement during the procedure required on average more opioids than those who did (10). Though subjective in its classification of what constitutes good clinician-patient interaction, the study described the potential use of guidelines that would help clinicians identify and interact with patients more prone to the anxiebo effect (10). This raises the question of whether or not pharmacists should be intentionally shaping the expectations of patients to optimize the outcomes of their drug therapies. But it also creates the ethical dilemma of uninformed consent if pharmacists choose to downplay the side effect profiles of medications in order to allay patients’ fears of taking them. In a medical culture founded on respect for patient autonomy, where patients normally make decisions based on full disclosure of all risks and side effects associated with a treatment, filtering information that may potentially trigger the nocebo effect can be problematic.

Patient autonomy is critical to most Western medical practices and has been known to influence the success of drug therapies. Meynen and Swaab have investigated the role of the nocebo effect in the treatment of non-compliant psychiatric patients (11). Though they conceded that it is difficult to extrapolate placebo and nocebo effects from study observations to multifaceted clinical settings, it was generally observed that coercive administrations of psychiatric medications resulted in less favourable outcomes than administrations in settings where patients could voluntarily take their medications (11). This suggests that patient autonomy may play a role in minimizing the nocebo effect, since it allows patients the chance to identify the benefits of a particular treatment before receiving it. If universal, this finding can be applied to community pharmacy settings where patients may benefit from a more supportive and encouraging environment that optimizes success of their drug therapy. Particularly in chronic illnesses such as cancer and hypertension, where maladaptive thinking can affect the rate of disease progression in certain patient demographics (12), it is important to empower patients with not only the knowledge of how their medications work, but also the choice of whether or not to take them after assessing the evidence against their own values.

Regardless of how we choose to classify the nocebo effect, there are examples of therapeutic outcomes that can sometimes be affected by fatalistic thinking, a mentality shaped not only by the patient’s personal beliefs and experiences, but also the manner in which information is presented by a pharmacist. Particularly in psychiatric disorders and other conditions where an optimistic mindset can play a great role in recovery, how a pharmacist communicates with the patient may determine whether and to what extent side effects could occur. Furthermore, the nocebo effect may be especially potent during stressful or demanding situations experienced by patients, such as in waiting for surgery or being newly diagnosed with a chronic or critical illness. These patients may be particularly sensitive to the effects of negative connotations conveyed by health care professionals and their caregivers, whether inadvertently or not. Thus, a patient’s first encounter with the pharmacist to learn about their medication(s) for the first time is critical in determining the ultimate success of their treatment.
Researchers have suggested establishing guidelines that would allow clinicians to identify the patients who seem more susceptible to the nocebo effect. While this may not be possible without generating discriminatory stereotypes of patients based on their apparent character or behavioural traits, the potential therapeutic benefits of identifying patients at risk of this phenomenon may allow for many advances in the field of personalized medicine. Furthermore, the likelihood of a nocebo reaction occurring is influenced by a myriad of complex, interrelated factors, such as past experiences, situational factors, cultural values, and personal belief systems. These factors, if to be discerned, require experience and sensitivity on the part of the pharmacist, as well as the understanding of the mind’s involvement in physical health. These considerations all point towards the importance of utilizing a more holistic approach in patient-focused care, one that recognizes individualized factors of both the mind and body.

References


