

THE NOCEBO EFFECT: THE PLACEBO'S “EVIL TWIN”

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Treatments are designed to help people fight diseases or their symptoms, and they are supposed to make us feel better. However, some treatments can have unpleasant side effects. But did you know that we can sometimes feel side effects because we *expect* them to happen? Imagine that you have a cold and your parents give you a pill to help you get better. If they tell you that the pill could give you a headache, you might feel the headache coming on as soon as you take it—but if they had not told you, you might not have felt the headache at all. Such negative expectations are the driving force behind what is known as the *nocebo effect*. This article explains what the nocebo effect is, how it works, and how we can combat it.

THE NOCEBO EFFECT

Imagine that you have a cold and one of your parents gives you a pill to help you get rid of it. Your parent says that the last time they took this medicine, it helped them get better but it also gave them a bad headache. If you then keep thinking about how your head feels, you

might notice a headache... although you might *not* have noticed it if you were not paying such close attention!

SIDE EFFECT

An additional effect, typically negative, that we feel when taking a medication. For example, a medication reduces fever but also gives you a headache.

NOCEBO EFFECTS

From the Latin "I will be harmful"; these are harmful outcomes on wellbeing and health produced by negative expectations about a treatment.

PLACEBO

From the Latin "I will please"; a drug or treatment with no active ingredient, and thus no pharmacological effect, that can still support healing by promoting positive expectations.

This example shows that we sometimes experience something negative only because we expect to. Even if you take sugar pills containing no medication, if you are told it is a medication with **side effects**, you might develop some of them. This is called the **nocebo effect**. The word "nocebo" is Latin, and it translates to "I will be harmful" [1]. You may have already heard of its more famous counterpart, the **placebo** effect, which refers to positive effects people experience when they receive an inactive treatment, like a sugar pill, which they are told will help them. Nocebos are sometimes called the placebo's "evil twin" (for more information on the placebo effect, see this [Frontiers for Young Minds article](#)).

Nocebo effects can happen with real medications, too. It can make those medications work less well, can cause specific side effects, or can even worsen existing symptoms. For example, if you think that a cheap pill will be less effective at curing your headache than an expensive one, the nocebo effect makes sure this is the case! The nocebo effect is largely caused by negative expectations about a treatment, for example, "My parents said this pill will give me a headache, I can already feel it!" or "This pill looks cheap and will not help me much". In sum, nocebo effects are harmful outcomes on our wellbeing and health produced by our negative expectations about a treatment [1]. We believe that a fair part of all side effects reported by patients are actually based on nocebo effects.

THE POWER OF NEGATIVE EXPECTATIONS

How can a mere sugar pill generate very real side effects? Several things that can influence our negative expectations and fuel nocebo effects, even without our knowing that it is happening ([Figure 1](#)).

What Other People Tell Us

Our expectations are shaped by the information that is communicated to us and how it is communicated. Simply telling people about possible side effects increases the chances that they will develop those side effects. Since the actual side effects of medical treatments must not be kept secret from patients, the choice of words is important. In one experiment, patients getting an injection to numb the skin before a procedure felt more pain when the injection was described as feeling "like a bee sting" and "this is the worst part" than did patients who were told that the injection "will help you to feel comfortable during the procedure" [2].

What Happens Around Us

The strength of the nocebo effect is dependent on the type of treatment. For example, since getting an injection or surgery might seem more serious than using a cream or taking a pill, you might

Figure 1

There are many things that can influence the strength of nocebo effects, including what other people tell us, what happens in our environment, what past experiences we remember, and our personalities and reactions to certain situations (Figure created using Canva: <https://www.canva.com/>).

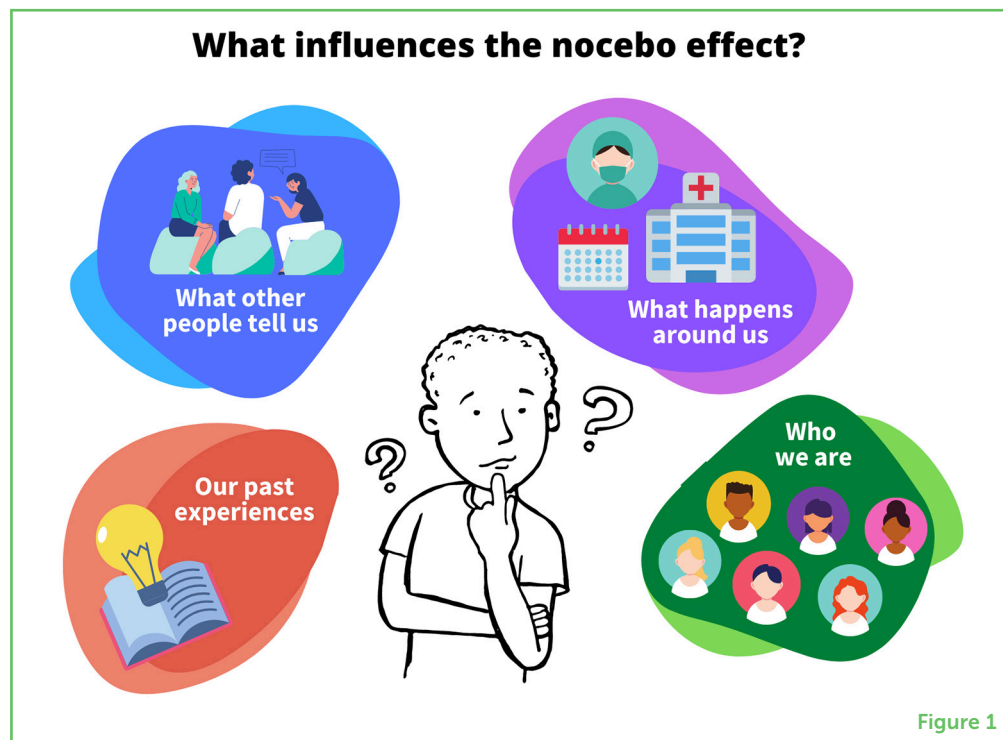


Figure 1

experience more side effects in the first two examples. The nocebo effect can also be influenced by how the doctor or doctor's office looks—many people are a bit scared by people in white lab coats or by the “hospital smell”.

Our Past Experiences

Learning and memory also play a big role in the nocebo effect. If you have to take a cough syrup that tastes so bad that you almost throw up, you might feel nausea even just looking at the bottle the next time. The brain makes bad experiences difficult to forget, and the unpleasant memory of the nasty taste might be stronger than the memory of the syrup actually helping you get better. Interestingly, learning from negative experiences happens even when you simply observe negative effects in other people! If you see a friend feeling bad when taking a medication, your brain automatically thinks that you will likely feel the same way if you take the same medication. Sometimes even reading reports on the internet or in newspapers can stimulate the nocebo effect. Is our mind not amazing, creating all these associations even though we did not make any negative experiences ourselves?

Who We Are

How we feel or what we think, including our moods or how nervous, worried, or stressed we are when taking medication, can influence the development of nocebo effects. Also, certain people just tend to have stronger nocebo effects than others. Research indicates that these differences are caused by our genes and also by the ways our brains are wired.

NEUROTRANSMITTERS

Chemicals that can act as “messengers”, communicating messages between nerve cells in your brain and between the brain and the rest of the body.

CHOLECYSTOKININ

Pronounced “col-eh-sist-oh-kineen” means “mover of the gall bladder”. It is a hormone which signals our body to get our digestion going. However, it also works as a neurotransmitter in our brain.

OPIOIDS

Pronounced “oh-pee-oyds”; a chemical in the brain that helps the body deal with pain. It is released when we hurt ourselves and helps us feel less pain.

Figure 2

Certain regions of the brain are important when we make negative associations between things, like a medication and an unwanted side effect, for example. Brain chemicals called neurotransmitters, including opioids, dopamine, and cholecystokinin, are involved in generating these negative associations. This tells us that the nocebo effect is not “just in our heads”, it has real effects on the body and the brain (Figure created using Canva: <https://www.canva.com/>).

There are many other factors that might contribute to the nocebo effect, and researchers are working hard to understand this effect and, importantly, how to combat it [1].

THE BRAIN SHAPES OUR THOUGHTS AND FEELINGS

How do we create these complex connections? The brain is a powerful organ and our thoughts and feelings affect how we perceive the world around us—to a greater extent than we can even imagine. Our memories and beliefs play an important role in how we experience something. If we think something bad will happen, for example because a doctor tells us so, that thing may likely happen because we are paying more attention to it.

Treatments—even just a sugar pill—have very real effects on the brain and body. For example, if a person believes that a treatment leads to pain, this treatment activates the parts of the brain that are usually active during pain. This happens even if the ingredients do not actually cause any pain. The chemicals in the brain, called **neurotransmitters**, change with negative expectations (Figure 2). The fear that arises when something painful is coming triggers the release of a substance called **cholecystokinin**. This substance makes pain signals stronger, which means that more pain is felt [3]. On the other hand, when we have negative expectations, two neurotransmitters responsible for pain relief are decreased in the brain: **opioids**, which are responsible for tuning down incoming pain signals, and **dopamine**, which creates good feelings when pain relief is expected [4]. These important findings

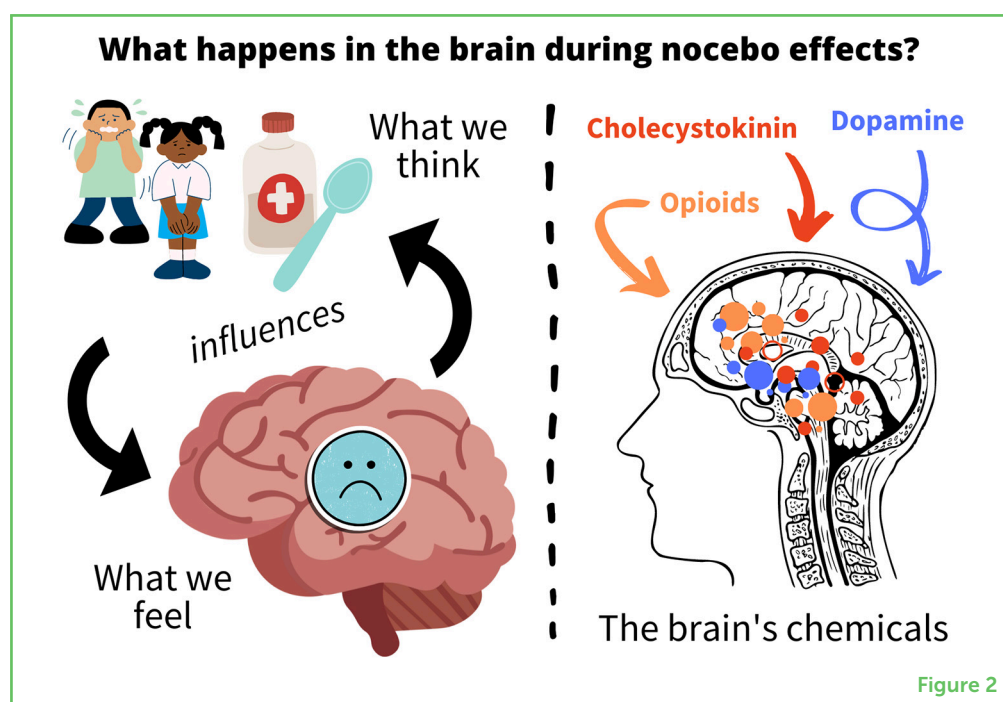


Figure 2

DOPAMINE

Pronounced “doh-pa-meem”; a chemical in the brain that is released when something related to reward happens, for example, when you get an ice cream because you did your homework.

Figure 3

There are several actions you can take to combat the nocebo effect. First, you can inform yourself by reading about it—and you are already doing that! Second, do not rely only on the opinion of a single person—ask other friends or family members about their experiences with a medicine. Try to combine information from several sources. Pay attention to *all* the information that your parents or doctor tell you—maybe it is not all that bad! Lastly, observe how your parents or doctor provide information, and how that makes you feel (Figure created using Canva: <https://www.canva.com/>).

show that the nocebo effect generates measurable changes in the way the brain works.

HOW TO COMBAT THE NOCEBO EFFECT

If you experience negative side effects, your first instinct might be to stop the treatment. This is one problem with nocebo effects—they can cause patients to stop taking their medications, even if the positive effects outweigh the side effects. So, what should we pay attention to, to combat the nocebo effect (Figure 3)?

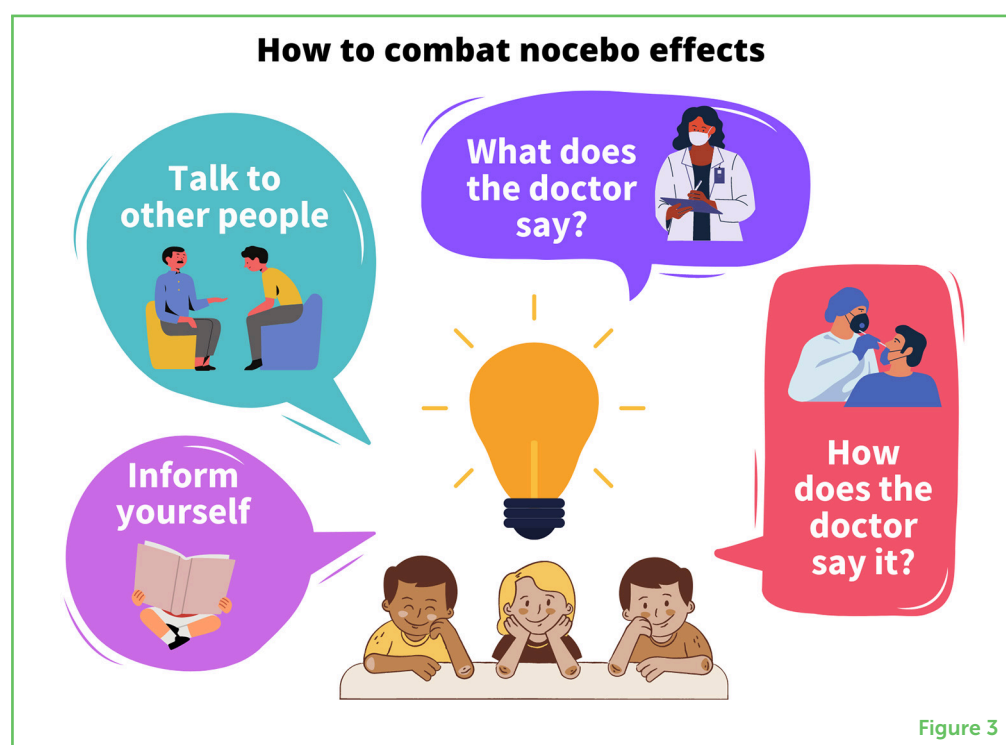


Figure 3

Inform Yourself!

You can read about the nocebo effect (like you are doing right now!) and also choose which people to listen to when you gather information. For example, credible sources, like your doctor or your parents, can generally be trusted, so the information they provide will be more accurate and helpful. Providing people with accurate information about side effects while simultaneously educating them about nocebo effects may help prevent unwanted negative reactions.

Talk to Other People!

Asking multiple people about their past experiences with a medication can help to balance out any misinformation or incorrect beliefs. One bad example does not mean that a medication will always result in a bad experience.

POSITIVE FRAMING

A technique used to think about certain events or situations in a more positive light; for example, using positive expressions that create hope without hiding the truth of side effects.

What Does the Doctor Say?

Choosing the right words can sometimes work magic [5]. Instead of saying “one out of 10 people experience dizziness with this medication”, doctors could choose to say “nine out of 10 people tolerate it well”. This is called **positive framing**. Positive framing is not about hiding side effects, but about promoting positive thoughts over negative ones. Journalists should be careful about their writing for the same reason—because what and how they write can influence the way people see certain treatments. For example, reading that many people felt sick after the COVID-19 vaccination might negatively influence how you feel when getting the shot.

How Does the Doctor Say it?

Nurses and doctors should be well-informed about the power of the nocebo effect. Most people are eager to listen to experts, so experts should pay attention to how they communicate because it may influence the effectiveness and tolerability of a treatment. Side effects can be dangerous if patients are not informed about them. For example, it would be a bad idea to ride your bike if a medication you are taking could make you dizzy. Describing side effects in a supportive yet honest way can help avoid nocebo effects, while bad communication habits like avoiding eye contact, speaking in a monotone voice, and not smiling can worsen them [1].

Does the nocebo effect mean that you should tell a friend, or your sister or brother, that any side effects are just in their imagination, or that they should not worry if they feel bad after taking a medication? Certainly not—not all side effects are caused by the nocebo effect, but even if a side effect *is* “only” caused by a person’s expectations, the suffering generated by these expectations is real. Now that you are aware of the nocebo effect, you can actively reduce it the next time you take a medication, by using all the information and tips in this article. You can also help others to understand the nocebo effect, so that they can benefit from the positive actions of a medication without suffering as much from its possible side effects!

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