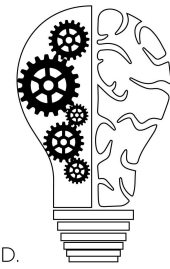


## Episode 034: Understanding Placebo

David Puder, M.D., Mikyla Cho, Mark Ard, M.D.

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There are no conflicts of interest for this episode.

### What is placebo?

The original meaning of the word placebo is, “I will please.” That statement comes from a time when doctors didn’t have our modern code of ethics, and they would prescribe whatever would make the person feel better. They probably had the best intentions, but they also would have known that whatever they were prescribing might not have been a real medication for the symptoms the patient was experiencing.

Doctors, even then, knew that suggestion was powerful, sometimes more powerful than the medicine they were prescribing.

Laypeople who hear the word “placebo” automatically think of sugar pills. They may think only that it’s something a doctor gives to placate and make people feel better when they aren’t getting the active medication. Placebos have long been used as a comparison arm for clinical trials. Usually it is in the form of an inert sugar pill or sham-procedure. Researchers can observe a psychobiological response known as the placebo effect.

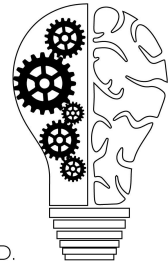
But when thinking about the word “placebo,” we must think of the entire effect of it, and it is perhaps better termed “the meaning effect.” As I discussed in last week’s episode of the podcast, the meaning we give something creates belief, and belief is a potent change mechanism, even when it comes to our physical health. It is especially potent when it comes to mental health.

The placebo effect encompasses the therapeutic alliance, expectations, natural healing of the body and mind, and the environment of therapy. It involves the power of suggestion, mood, and the beliefs behind even one positive or negative interaction with a doctor. It also, as we will see, involves studies involving heavy-hitting medication.

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When there is an increased ritual, there is an increased placebo effect. During a hospital stay, the surgery preparation, meetings with doctors, nurses and therapists can have an incredibly therapeutic effect on a patient. It is possible to see biological mechanisms triggered by psychosocial context and attribute it to a placebo effect.



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What is the power of suggestion, the meaning effect, placebo effect, and how do we use it or avoid it in our practices and when testing new medical treatments?

### **Why do we study placebo?**

We study placebos because we need to understand how meaning works, how belief works, and on the other side, if a medicine actually works.

As doctors, we need to be able to read studies critically, with an eye for placebo. We need to see what actually works and what the study was controlling the treatment group to. We also need to know if there parts of the treatment that are working only because of the placebo effect, and if so, how do we use that to heal people.

### **How does the placebo effect work?**

The efficacy of the placebo goes up because of the expectation and meaning we give to placebo.

In one study, half of the patients got the actual medication, half got the placebo. In the same study, in another group, 25% of the patients got the placebo, and 75% of them got the actual medication. In both of these studies, the participants were told the percentage chance they would get the real medication. In the study where only 25% of patients received the placebo, more people experienced positive changes from the treatment, whether they received the placebo or not. Most people **believed**, because of hearing the percentages, that they would probably get the medicine. That belief increased the placebo effect.

In groups with lower percentages receiving the actual medication, the response is lower, even with real medication.

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Researchers think placebo effect works because of **expectation and classical conditioning** mechanisms. Such understanding may be an oversimplification of a very complex phenomenon but it provides a useful framework.

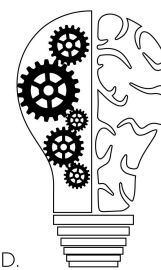
**Expectation** is how much the patient believes in the therapy. Higher expectation leads to hope and positive outlook, which results in better outcomes. Exactly how this works is still under investigation. There are multiple theories as to the underlying mechanism, but overall, we can say that there is a bidirectional interaction between expectations and emotions, and we respond better when expectations are high and our mood is good.

**Classical conditioning** contributes to the placebo effect by modulating conscious expectation and non-conscious learning. The white coat effect is a classic example of how our body responds to a conditioned stimulus. Also, when a patient feels better after taking a pill, it becomes a conditioned stimulus, and the body may respond positively even after taking a placebo medication because of its conditioned response.

**Expectation** can be shaped by many factors. Broadly, these factors can be grouped into patient effect, clinician effect and study design effect. **Patient effect** refers to patient characteristics such as beliefs, values, cultures, and the meanings associated with the illness and the treatment.

In a study of IBS patients, Vase et al found that expected pain levels and desire for pain relief accounted for up to 81% in the variance in visceral pain intensity. There is also a greater dopamine release in patients who had **higher expectation**. ([De la Fuente-Fernández](#)). Conversely, **pessimists** were more likely to have negative side effects (when compared to optimists' responses) when told a placebo would make them feel bad. ([Geers](#))

How a patient interprets and generates meaning in a given treatment condition is widely variable and difficult to control for. A similarity in demographic characteristics would not account for all of them. Direct-to-consumer (DTC) advertising of antidepressants is an example of how a society can shape one's view and expectation of the illness and the treatment. The promotion of antidepressants inherently depends on the biological model of depression. By simplifying depression as serotonin deficiency, antidepressants were promoted as a simple solution to a complicated problem. These advertisements are designed to convey that "psychopharmaceuticals have an obvious, objective, and scientific relationship to the symptoms they are supposed to treat"(Greenslit, 2012). **The**



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**reality is more complex and difficult to understand than the advertising, but the narrative is believed and shapes decision making.**

An interaction with a clinician can shape the expectation of outcomes as well, especially if there is a strong alliance. Warmth, empathy, duration of interaction, and communication of positive expectation may significantly affect clinical outcome ([Kaptchuk](#)).

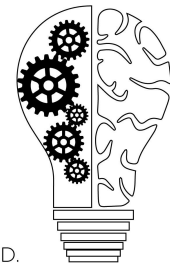
One article ([Verhulst et al., 2013](#)) deconstructed the correlation between the medical alliance and placebo. The placebo effect encompasses the beliefs, values, and expectations that patients have about a treatment. We can help shape a patient's belief and expectations by giving realistic illustrations of the treatment, which are more valuable than false hopes; this is the medical alliance that we as healthcare providers can utilize. Part of the medical alliance is the idea of concordance between the physician and patient. There is both narrative concordance, the shared understanding of the patient's condition, and the relational concordance, the shared relationship structured based on scripts, boundaries, and interactional rules. Ultimately, by utilizing the idea of concordance and a strong alliance with the patient we can influence how they view a treatment and better the outcomes via the placebo effect.

Study design can also change expectation. Having a higher chance of being assigned to the treatment group and having a choice (Rose 2012) increases the expectation. The degree to which placebo resembles the treatment is another important consideration, because unblinding can lead to decreased expectation. (Some studies utilize active placebo to make unblinding more difficult.) In pharmacological studies, active placebo usually contains some real medication that contains some of the expected side effects to imitate the expected treatment.

### **The mechanisms that control placebo effect:**

- **Opioid system**

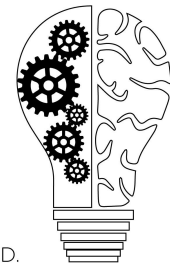
This system bolsters a lot of the evidence for pain relievers—you have more of a placebo effect on the patient if they know they're getting the medication than if it's snuck into an IV. The opioid system in the brain begins to work as a pain reliever before any actual medication sets in, if it's even administered.



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- **Dopamine system**

Dopamine signaling is involved in expectation and response. Our brains will respond as if something is happening if it believes it will happen. This pathway is also involved in habit formation and novelty seeking. The brain lights up in the same way to a placebo as it does to an active intervention. There is a fascinating link between dopamine deficiency and Parkinson's disease; **placebos can induce dopamine release**, leading to improvement in Parkinson's disease motor dysfunction.

In another study, people were told they were getting either a cheap medication or an expensive medication. Even though they both received placebos, the group who was told they were getting the more expensive medication experienced a greater placebo effect.

Even the color of medication can affect a person's response. Brand names can affect a person's response. A person who is told they are receiving an anti anxiety medication will calm down, even if it's a placebo.

- **Prefrontal cortex**

The third "system" is prefrontal cortex, which is involved in associations and meaning. This is also one of the main areas involved in improvement of depression ([Murray, 2013](#)).

## **What is the effect of placebos on the medical profession?**

### **Is placebo testing accurate?**

Some industries fail to examine things with an accurate and rigorous placebo. For example, in a recent study on Botox used for depression,  $\frac{3}{4}$  of the subjects knew if they had received the placebo or not ([Finzi & Rosenthal, 2014](#)). Some studies also neglected that placebos can actually change brain chemistry, and activate or deactivate different areas of the brain.

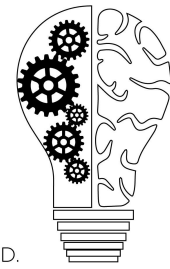
We often think that the patient who is administered a placebo, in taking the medication, thinks it is real and thus the whole placebo response is merely from taking the pill. But in those results we neglect the human factors that come into play when a person meets

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with a psychiatrist that is doing the patient interview, and how it could be the therapeutic alliance and feeling cared for that influences outcomes and spontaneous remission of symptoms.

For the medical field to determine that it's not only the placebo effect taking place, that the medicine or treatment actually works, many factors come into play.



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### **Discussing negative side effects with patients**

How do you talk about medication as a doctor without scaring the patients with a side effect list? Studies show that by listing side effects, people are more likely to experience the side effects.

I usually discuss the side effects with patients if they occur in more than 1% of patients or if the side effect is life threatening. Also, if the patient feels like they need to stop the medication, I tell them to call or email me. Even knowing they can reach out if they are experiencing problems gives patients a sense of peace, and could decrease negative placebo effects of the medicine, and increase positive effects of it.

In medical education at large, there seems to be a loss of the science of connection and a focus on medicine rather than being able to emotionally connect to people, and mental health is part of the human experience.

### **Therapy and the placebo effect**

Placebo and psychiatry have an interesting and complicated relationship—both are concerned with the mind-body connection. Using placebo in psychiatric research is, therefore, more challenging. It is more difficult to tease out the true effect of a treatment since mental illnesses have significant psychosocial components.

Higher therapeutic alliance, higher empathy, and higher interpersonal skills all have better outcomes. Beyond the model of therapy, each therapist's kind of connection to their patients deeply affects a patient's response.

The value of the therapeutic alliance can be as powerful as medication, and also bolster the effectiveness as the medication itself.

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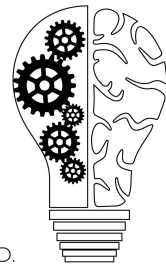
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In their paper Wampold, Frost, and Yulich ([2016](#)) reviewed the history of how placebo was used in randomized control trials for testing the efficacy of psychotherapies. They found that when poorly designed placebo therapies were used as controls, the psychotherapy treatment group had superior results. It is difficult to have a truly controlled placebo. For example, it can be obvious whether a therapy is a placebo or a true psychotherapy and the providers administering the treatments would also know which was the true treatment. People have advocated that different psychotherapies are beneficial because of their common factors such as the therapeutic alliance, discussing expectations, and instilling hope. These and other factors common to the variety of psychotherapies can also be found in the placebo effect, which facilitates the argument that placebo psychotherapies are not inert. Therefore when we look at studies that compare psychotherapies to a placebo therapy, we must be aware that the comparisons may not be completely accurate.

In therapy practice there are no effective placebos to be given to compare, so effect size with therapy is very different than effect size with medication vs placebo. A broader and more nuanced understanding of the placebo effect is important in two ways. First, it allows a clinician to critically evaluate studies that compare the treatment with placebo. Placebo should be evaluated within the framework of mental illnesses. Secondly, understanding placebo allows a clinician to maximize the clinical outcome by focusing on factors such as alliance. Placebo teaches us about the complexity of the mind body connection, and calls for a more integrated approach in treating mental illnesses.

The effect size in double blind studies, however, does not tell the whole story of the effectiveness of the psychiatric relationship, because it does not take into account the part of the placebo response that actually came from a psychiatrist's relationship with the patient.

Even since the beginning of psychopharmacology, in the 1940's, placebo effect has increased. In part, I believe that's because we've reduced mental illness to a few symptoms and then say those can be helped or fixed by a pill. For example, there is commonly believed language around depression that says it's a serotonin deficiency. So, patients take medicines to boost their serotonin (SSRI medication). That is not the only thing going on in depression, and it's not necessarily true. So SSRI medications have a large placebo effect.



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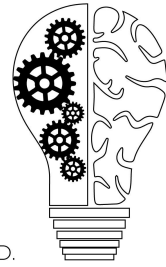
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Further, different psychiatrists will have different effectiveness with patients ([McKay, 2006](#)). The authors analyzed data from the Treatment of Depression Collaborative Research Program (TDCRP) that compared imipramine hydrochloride with clinical management vs. placebo with clinical management and found that 7% to 9% of outcome variabilities depended on the psychiatrist providing the treatment. When using BDI, the results were statistically significant ( $p < 0.05$ ) and when using the HAM-D the results were marginally significant ( $p = 0.053$ ). Therefore the authors concluded that the psychiatrist effect was at least equal to or greater than the treatment effects. The effectiveness of a psychiatrist is also critical in proving optimal treatment.



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### **Non-therapeutic medical fields and doctor-patient relationships**

Even the awareness that the placebo effect exists should make medical workers understand that we need to consider people's outside lives, not just the psychopharmacological effects of the medication. If little things have a placebo effect, and that is directly related to meaning and belief, what are the patients experiencing outside of the medical office that is influencing them?

### **Conclusion**

Our brains were made to create meaning out of things, and this meaning can change the very nature of the brain. When we understand placebo we become better guides to our patients, steering them away from things that don't do anything, and towards things like having a connected relationship with a caring person, which can be the treatment itself. We also look not only at how powerful a medication was compared to the placebo, but also if the patients thought they were taking the real medication or not. We also learn that belief is powerful and can understand how people get swayed into cults and taking things which have been proven to only be harmful.