Placebo, control groups and the challenge of inferring causality

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Target audience: 10-12th grade students (15-17 years old)
Domain: Biology, Health Sciences
Topic: Neurobiology, Human Physiology
Duration: Two 45 minute lessons
Equipment: None

Objectives: Students will

a. Understand the terms placebo treatment and placebo effect.
b. Understand the challenge of inferring causality in medical contexts.
c. Learn the importance of using control groups with placebo treatments in clinical trials.

1. Placebo and Placebo Effect (CASE 1)

CASE 1 - Jim is 3 years old. Jim stumbled and hurt his knee while playing, and started to cry complaining that his knee hurt. His father felt that this pain was real: his son was not faking or exaggerating, but he saw no bleeding or other signs of injury. He put a colored band-aid on the child's knee. Jim stopped crying, said that his wound did not hurt any more and continued to play as usual. What happened here?

The discussion should lead to the conclusion that in many cases there is a dramatic difference between "no treatment" and a "fake treatment," which we call placebo. Define the term **placebo treatment**, and note that placebo treatment may actually affect healing– this is called a **placebo effect**. The placebo effect is the effect of a placebo treatment **on our brain**. In the case above, the bandage serves as an analgesic (pain-reliever) but placebo treatments may even be used as therapies for serious diseases.

The exact mechanisms of placebo effects are still not understood, but they are thought to be related to complex interactions between the brain and other body systems, especially the **immune system**. Placebo treatments may also cause adverse effects, because people believe that medications have negative side effects. For example, healthy people who are given specific placebo pills and are told that they are given a new medicine often report nausea symptoms (more often than healthy people who do not take any pill).

Tip: Some students may suggest that religious practices (such as prayers said by a sick person's bed) may fit the definition of a placebo treatment, and therefore if someone gets well this is actually a placebo effect. This is a culturally charged issue that should be discussed with care.

2. Causality in Medical Contexts (CASE 2 and CASE 3)

CASE 2 - Maggie has been complaining for three days about a sore throat. Her parents gave her antibiotics, without taking her to see a doctor. After two days she reported that the pain was gone. What is your conclusion and why? Do you think that the antibiotics cured Maggie? Explain.

The discussion should lead to the conclusion that **we are unable to tell** if the change in Maggie's condition was caused by the treatment. We do not even know if she had a

bacterial infection, for which antibiotics are an appropriate treatment. A sore throat may be a symptom of several diseases, and its disappearance may be due to other factors. For example, Maggie may have been infected by a virus, and her immune system handled it without any medical treatment.

Event A (taking antibiotics) comes before event B (symptoms disappear). This order of events is a ***necessary*** condition for causality, for claiming that A caused B, but it is not a ***sufficient*** condition.

Our inability to infer causality in such cases applies also to negative effects. For example, if Maggie complains of nausea after she takes the antibiotics, it is difficult to know if the nausea is caused by the antibiotics, another symptom of her illness, or has a different cause altogether.

Next, ask the students if it is possible that a placebo effect played a role in Maggie's case just like it did in Jim's. The answer is that it is possible, **but we just do not know**. Maggie knew that she was being treated with a drug, and this knowledge may have helped her body to fight the disease.

CASE 2 - Maggie has been complaining *again* that she had a sore throat. This time her parents took her to the doctor who after extensive tests, found that she had a bacterial infection and prescribed antibiotics. After two days she reported that the pain was gone. Is there a placebo effect here?

The discussion should lead to the conclusion that **the placebo effect exists even when the patient takes a potent medicine that is the optimal treatment for his or her condition**. The antibiotic medication may have affected the bacteria, but at the same time the placebo effect could have affected Maggie's brain and therefore her whole body. We cannot quantify the relative importance of the placebo effect in this case.

Conclusion: knowing that a person was sick and that the person received a specific treatment and then became healthy is not enough to deduce that the treatment cured the patient. Other causes, including the placebo effect, may be responsible for the effect.

Tip: be aware that students may take the lesson learned from these cases one step too far and claim that it is impossible to test whether drugs are effective. That is why we now turn from single cases to discussing quantitative studies of populations.

3. Clinical Trials and Placebo Control Groups (CASE 4)

CASE 4 - An advertisement for herbal tea claims that drinking this tea cures a sore throat. We would like to test this claim scientifically. What should we do?

Ask the students to describe in their own words a study design that is meant to answer this question. Write on the board features of a scientific study mentioned by the students.

An optimal study design will have the following features:

* **Many participants -** Why? Because we want to generalize and there is variance between people. How many is enough?

* **Measurements before and after treatment** - one measurement is not enough, we want to know the difference). Measurements have to be at the same time points and conditions for all participants.
* **Control group** - the measurements from this group are used as reference – this is what happens if there is no treatment. We need a control group even if we compare two treatments or more. Results are presented as comparison – treatment vs. control (e.g., text, tables, graphs). The control group is necessary for comparing results of different studies, for example one study compares one treatment with a control group, and another study compares another treatment with a control group.
* **Placebo** - The people in the control group receive a placebo, rather than nothing. Why? Because of placebo effects. The control group may show a placebo effect, and the treatment group will show a sum of the placebo effect and the effect of the treatment (this point is very unintuitive to students!). Only if there is a difference between the two groups may we relate this to an effect of the tea itself. Note that not all clinical studies use placebo. For example, in certain cases ethical reasons prohibit the use of a placebo treatment, and therefore new treatments are tested in comparison to a benchmark treatment.
* **Randomized assignment** – we start from recruiting a group of participants and then randomly assign each one to either the treatment group or control group. This ensures that neither group has any unique characteristics that could bias the results.
* **Blinded study** – participants should not know if they were assigned to receive the real treatment or the placebo. Otherwise, the control group will not show placebo effect but the treatment group will. This may bias us to conclude that the tea is effective. Many such studies are **double-blind,** when the people (the researchers) who provide the treatment and measure the condition of the participants are also blind to which people are in a particular group. A double-blind design prevents the possibility that doctors and researchers treat patients differently.

Tip: In cases where students raise important experimental design features, review the rationale to make sure that the entire class understands why these features or procedures are carried out. Use partially correct or incorrect answers to highlight possible experimental biases and the features or procedures that are carried out to avoid bias and to enable conclusions about causality.. Alternatively, prepare in advance faulty experimental designs (e.g., no before after measurements, one participant, no control) to discuss these issues. You can also use examples of "non-scientific evidence" - for example the difference between scientific studies of methods (medical and behavioral) for reducing weight, and advertisements ("I used this diet and reduced 8 Kg of my weight in 14 days" – single case, no control group, perhaps placebo effect).

Conclusion: A treatment is considered effective if its results are significantly better than the results obtained from placebo treatment. A treatment may be related to an adverse effect if it is more common in reports of patients who received the medication than in reports from patients who received the placebo treatment.

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