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## Introduction

Placebo and nocebo effects are important in clinical research. Knowledge of those terms is essential for researchers as it can explain the benefit or harm patient experience during the course of a clinical trial while receiving a control substance that should not have any effect.

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## Placebo Effect

Typically, patients enrolling in double blind controlled clinical trials will be randomized to receive study drug or a substance with no medical effect (e.g. normal saline, vitamin). Some patients will experience placebo effect; which is a benefit to the health status of the patient due to the patient belief that the substance (placebo) is effective [1].

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## Nocebo Effect

On the other side, nocebo is defined as a substance without medical effects but believed by the patient to worsen their health status [2].

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## History of the Phenomenon

It was believed by some that the benefits of many therapies are due to the placebo effect. The placebo effect was first described by Elisha Perkins who stated that many diseases can be treated by touching the body with metal sticks. It was believed that those metal sticks may had a magnetic effect that helped with healing. But another medical doctor, John Haygarth painted wooden sticks to look like the metal sticks used by Perkins and found that they cause the same positive effects. That was the first experiment to describe the placebo effect [3].

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## Theories

There are several proposed theories to explain the placebo effect including the expectation model, reflex/Pavlovian conditioning, the opioid model, positive and negative thinking, self deception, self-fulfilling prophecy, optimism and pessimism personality traits, interpersonal expectation effect and more.

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Neurobiologic explanations have been proposed as well including:

- Reward-punishment system activation (dopaminergic pathways),
- Interpersonal effects (patient-doctor relationship),
- Sensitization mechanisms (placebo analgesia and nocebo hyperalgesia mediated by cholecystokinin and nitrous oxide),
- Trustworthiness or untrustworthiness activation (the higher the amygdala activity, the more untrustworthiness; oxytocin increases trust and placebo response by binding to its receptors in amigdala) and,
- Genetic predisposition to placebo or nocebo response [4, 5].

#### High Yield Points

- Placebo effect is a benefit experienced by patients when using a substance with no medical effects.
- Nocebo effect is a harm experienced by patients when using a substance with no medica effects.

### Questions

1. You are the principal investigator for a double blind controlled clinical trial and one of your patients told you he feels a lot of improvement in his condition after enrolling in the study.
  - A. This is a placebo effect
  - B. This is a nocebo effect
  - C. This is an effect of the study drug
  - D. Hard to determine

Answer: D
2. A patient enrolled in a double-blind controlled trial for treating chronic low back pain. The patient reported significant improvement. At the end of the study and un-blinding the group assignment, you found out that patient was in the control arm and received normal saline. This can be explained by:
  - A. Placebo effect
  - B. Natural improvement of the disease condition
  - C. Nocebo effect
  - D. A and/or B

Answer: D
3. A 60 year old patient enrolled in the same trial (treatment for chronic low back pain) mentioned at the end of the study that his back pain became a lot worse after participating in the study. This can be explained by:
  - A. Placebo effect
  - B. Worsening of his disease condition
  - C. Nocebo effect
  - D. B and/or C

Answer: D

### References

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