

"We know that four sugar pills a day beats two sugar pills a day . . . and that's an outrageous finding."

-- Ben Goldacre, Epidemiologist

"[Alternative Medicine Advocates] tend to argue that what they do is useful and good because it's 'harnessing the placebo effect' for therapeutic purpose . . . [but] a good placebo requires on some level at least some deception of the patient by either saying or implying that he is receiving an active treatment or medicine of some kind."


-- David Gorski, M.D., Ph.D., Surgical Oncologist at the Barbara Ann Karmanos Cancer Center.

The Placebo Effect

Supplementary Material for
CFB3333/KNW2333/PHY3333

Professors John Cotton, Randy Scalise, and Stephen Sekula

Medical Claims

A hand holds a white sign with handwritten text against a clear blue sky. The sign is tilted slightly to the right. The background shows a crowd of people and some buildings, suggesting a public demonstration or protest.

WHAT DO WE WANT?
EVIDENCE-BASED CHANGE
WHEN DO WE WANT IT?
AFTER PEER REVIEW

Placebo: (LATIN) I shall please

“From the Latin ‘I shall please’, placebo entered ecclesiastical English in the 13th century, but did not appear in medical parlance until the late 18th century. Hooper’s Medical Dictionary of 1811 defined the term as ‘any medicine adapted more to please than benefit the patient.’”

-- Martin Edward. “Placebo.” The Lancet. Volume 365, Issue 9464, 19–25 March 2005, Pages 1023.

- Simply put, a “placebo” is . . .
 - a medically inert substance given to a patient as if it were an effective medicine
 - e.g. water, saline, sugar, a ritual.
 - a diagnostic tool, not a medical intervention
 - Doctors can give a placebo to a patient and instruct them to call back in 24 hours – this gives the body a chance to simply do what it usually does: heal and/or fight infection.
 - If the patient calls back and is the same or worse, the doctor is dealing with a potentially real disease requiring real medical intervention.

Simply Put, a “Placebo” is...

- A medically inert substance
- It is given to a patient as if it were medicine.
- Examples
 - Water
 - Saline (salt water)
 - Sugar (or sugar water)
 - A device that does nothing
 - An elaborate ritual

Simply Put, a “Placebo” is...

- A diagnostic tool, not a medical intervention
 - Doctors can give a placebo to a patient.
 - American Medical Association Opinion, 8.083:

“Physicians may use placebos for diagnosis or treatment only if the patient is informed of and agrees to its use. ... A physician should enlist the patient’s cooperation by explaining that a better understanding of the medical condition could be achieved by evaluating the effects of different medications, including the placebo. The physician need neither identify the placebo nor seek specific consent before its administration. ...

A placebo must not be given merely to mollify a difficult patient, because doing so serves the convenience of the physician more than it promotes the patient’s welfare.”

Simply Put, a “Placebo” is...

- A diagnostic tool, not a medical intervention
 - Doctors can give a placebo to a patient.
 - The patient can remain under care/observation after receiving the placebo
 - this gives the body a chance to heal/fight infection on its own, which it normally does anyway.
 - If the patient fails to improve, the physician knows that the ailment requires a more serious (real) medical intervention

Hypotheses

- People will not respond to a non-medical intervention as if a medicine had been applied
- Placebo response can be predicted by factors measurable in the individual
- Placebo response is inherent and cannot be manipulated (that is, an individual's response is pre-determined by their specific biological factors, e.g. genes)

What is “The Placebo Effect”?

- This is when a patient responds to placebo as if they had been given real medicine
 - they feel better, or the disease actually clears up
 - this is a real effect, but its power comes from the BELIEF and EXPECTATION that the placebo is real medicine. Degree of belief determines outcome.
 - effects vary – typically 20-30% of people respond positively to placebo, but it can be higher or lower.
 - for instance, about 34% of patients in a placebo control group for treatment of irritable bowel syndrome reported positive effects. (Ford, 2010)

What factors influence belief?

- Cultural associations
 - color, context, history, etc
- Elaborateness and/or ritual
 - more complex ritual implies a more desirable outcome
- Quite generally speaking: conditioning
 - belief, however it is primed (physical, verbal), affects outcome
 - let's look at examples

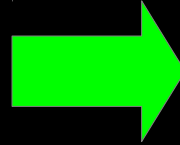
Conditioning a Placebo Response

(testing the hypothesis that placebo response is an inherent trait of the individual)

Pain and Placebo

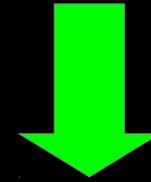
- Studies have shown it's possible to condition a group of people to expect a positive or negative response
- Researchers like Pavlov (1927) and Herrnstein (1962) observed animals could be conditioned to expect medical results from non-medical interventions.
- What about Humans?
 - *Voudouris, N. et al. "Conditioned Placebo Responses." Journal of Personality and Social Psychology, Vol. 48, No. 1, 47-53. 1985.*
 - *Voudouris, N. et al. "Conditioned response models of placebo phenomena: further support." Pain 38 (1989) 109-116.*
 - *Voudouris, N. et al. "The role of conditioning and verbal expectancy in the placebo response." Pain 43 (1990) 121-128.*
 - *Montgomery, G and Kirsch, I. "Classical Conditioning and the placebo effect." Pain 72 (1997) 107-113.*

Take 4 groups, each containing 8 randomly assigned people. Tell them the experimenters are testing a powerful new analgesic cream over 3 sessions by assessing its ability to reduce pain. Cream is placebo (inert). Pain is induced.



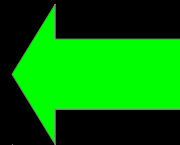
Session 1: Control

Test response to induced pain first without, then with, the application of the cream.



Session 2: Condition

Condition two of the groups to expect pain relief and two to expect pain exacerbation from the cream by manipulating the induced pain when the cream is applied.



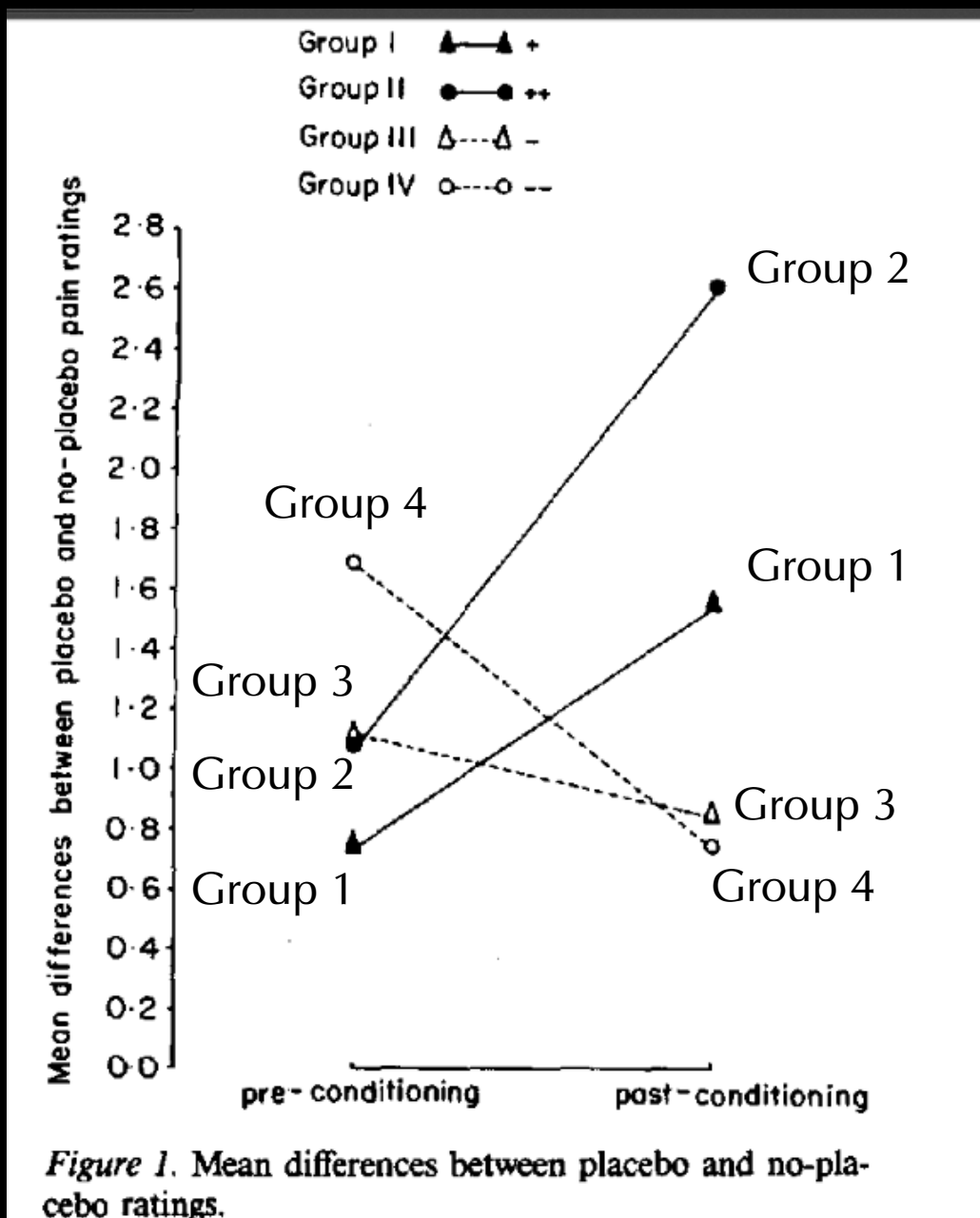
Session 3: Assessment

Assess the conditioned placebo response by again testing all four groups as in Session 1. Compare the results of the pre-conditioned response and the post-conditioned response.

Results

cream less effective

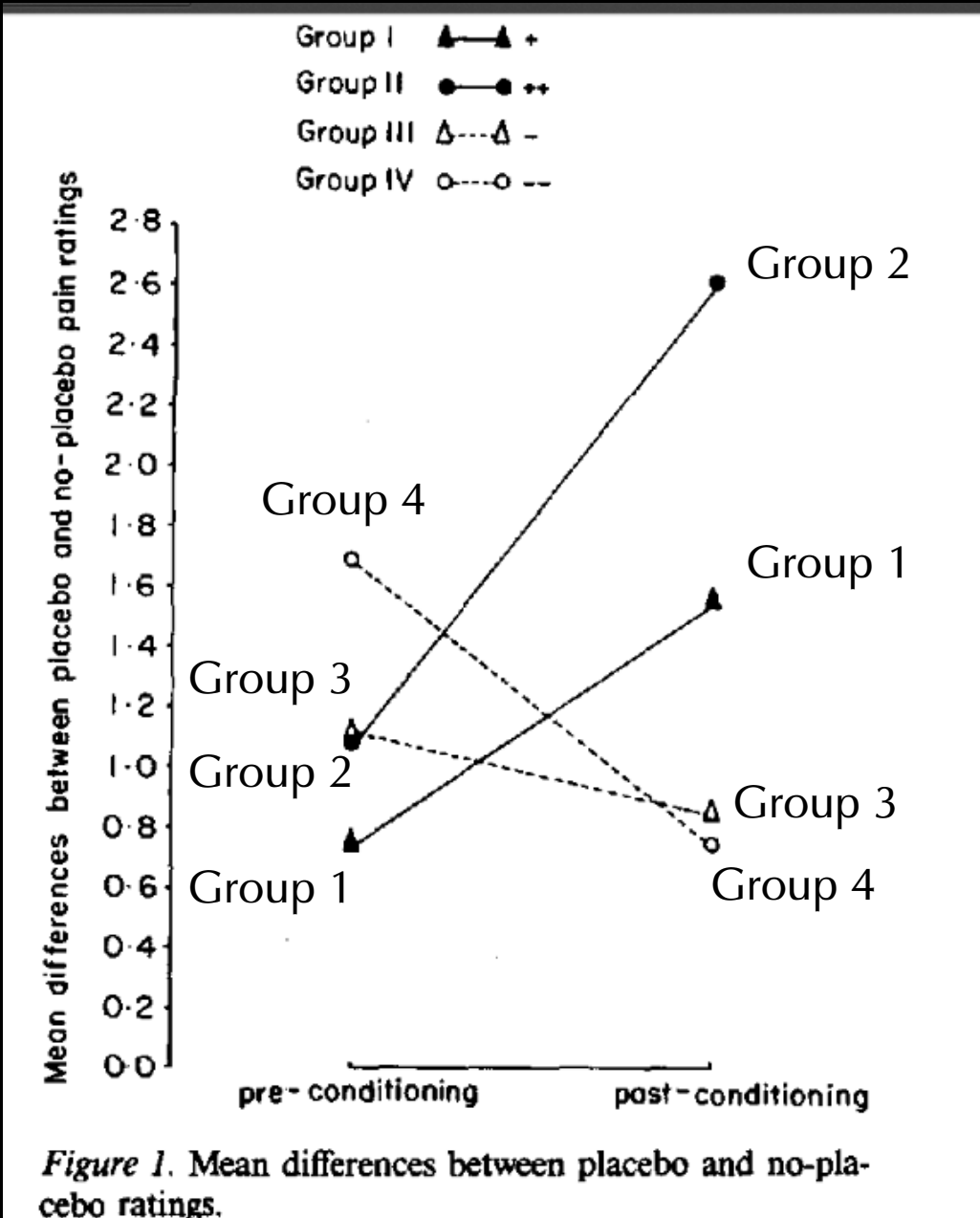
cream more effective



- Group 1:
 - Session 1: received a medium level of pain stimulus, first without the fake analgesic cream and then with. They rated the effectiveness of the cream on a pain scale, and tended to report only a small difference with and without.
 - Session 2: induced pain given without the cream, then was lessened after application of the cream, unbeknownst to the test subjects. This was to make them believe the cream had a physical effect. (“Physical Priming”)
 - Session 3: induced pain returned to Session 1 level, unbeknownst to the test subjects. They rate it with and without the cream.
 - Post-conditioning results: They reported a significant improvement in response to pain (less pain with cream applied) after physical conditioning.

Results

cream less effective ↑
↑
cream more effective



- Group 2: received a higher level of pain stimulus in Session 1 and 3 compared to Group 1. In session 2, the pain was intentionally reduced when cream was applied. They also showed a reported significant effect of the cream, consistent with their conditioning.
- Groups 3 and 4 similarly were conditioned at medium and high pain levels. However, in session 2 they were given MORE induced pain after the cream was applied, physically conditioning the idea that the cream wasn't effective. Both reported the cream worked WORSE once conditioned to expect it not to help, even though they were given Session 1 pain levels in Session 3.

Conditioning and Verbal Expectancy

- Which is to blame: conditioning or verbal expectancy?
 - physical conditioning: I prime you physically to believe the placebo is powerful
 - verbal expectancy: I tell you the placebo is powerful
- Findings
 - Voudouris et al. found that physical conditioning enhances verbal expectancy
 - Montgomery and Kirsch, two research psychologists, found that one could undo the physical conditioning with verbal expectancy.
 - Both seem to play a role.

Placebo and “Degree of Belief”

The more culturally significant the placebo, the more positively the patients responds.

This is true even for a real physical ailment, like duodenal ulcer, where objective quantitative measurement is possible.

You can scope a patient and measure the size of their ulcer. This can be monitored over the progression of the ulcer.



Placebo and “Degree of Belief”

The more culturally significant the placebo, the more positively the patients responds.

What happens when you use placebo in the treatment of ulcer?

- Craen et al. (“Placebo effect in the treatment of duodenal ulcer”, Br. J. Clin. Pharmacol. 1999, 48(6), 853-860) found that patients who got 4 placebo interventions each day over 4 weeks recovered at a rate of 44.2%, while those getting 2 a day recovered at a rate of 36.2%.
(a 22% increase in recovery rate)



Placebo and “Degree of Belief”

- Meissner and colleagues (Meissner, 2013) reviewed trial literature on 79 placebo-controlled migraine pain prophylaxis studies.
 - Findings: sham acupuncture and sham surgery was more effective than oral placebo (a pill) at relieving migraine or other pains, though none of these is a real medical intervention.



Placebo and “Degree of Belief”

- Blackwell et al (“Demonstration to Medical Students of Placebo Responses and Non-Drug Factors”, *The Lancet* 1:1279-1282, 1972):
 - inert pills, colored red and blue, will be classified by US participants (who are told one is a stimulant and one is a depressant) more often as red = stimulant and blue = depressant.
 - a similar study in Denmark in 1996 repeated the cultural effect



*de Craen, AJ et al. “Effect of color of drugs: systematic review of perceived effect of drugs and of their effectiveness.” *BMJ (Clinical Research edition)*. 1996. 21-28;313(7072):1624-6.*

de Craen et al. Drug Color Review

- Perceived actions of drugs:
 - red, yellow, orange associated with stimulant effect (but no stimulant given)
 - blue and green associated with tranquilizing effect (no tranquilizer given)
- Color and its effects on drug effectiveness
 - color could degrade the effect of real drugs

Experimental Design

- Given the complexity of the placebo effect, we can see that one needs great care in designing a trial of a medical claim
 - At least one placebo control group must be in place
 - Placebo and Medicine must match: smell, color, size, texture, taste, ritual, verbal description, etc. No cues as to which is the placebo.
 - Double-blind, ideally: the researchers should be fire-walled from knowing what treatment (none, placebo, medicine) each patient gets and the patient should not know which they are receiving.
 - Randomization: patients should be randomly assigned to groups, and the only care here is to make sure the randomization doesn't skew a group in some way (age, medical history, etc.)

Brainstorm

- Let's think about how to design placebo for different claims
 - a pill
 - a physical intervention (e.g. acupuncture, chiropractic, surgery)
 - a ritual, like a faith healing event
- Does science-based medicine have anything to learn from alternative medicine?
 - we'll investigate the efficacy of the actual treatments in a couple of cases and test them against placebo
 - the only clear lesson so far is that patient-doctor relationship and attentiveness of the doctor to the patient can have an effect on outcome, independent of the treatment (ritual, personal interaction, etc.)



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Homeopathy for Breast Cancer?

March 28, 2010 No Comments

Homeopathy for Breast Cancer? Promising study from MD Anderson Cancer Center shows two remedies have pronounced cytotoxic effects

A recent study performed at the prestigious MD Anderson Cancer Center in Houston may help open the eyes of homeopathy's habitual nay-sayers. Ultra-dilute homeopathic preparations of two remedies, *Carcinosin* and *Phytolacca*, both showed cytotoxic effects (cell death — desirable) on breast cancer cells — effects similar to Taxol, a regular chemotherapeutic agent used to treat breast

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An example from the web (one of so, so many): "... I also believe that the clinical methods of homeopathy...are excellent at harnessing the powers of the placebo effect, altogether desirable." (Alan Inglis, M.D.)

Comment: “Harnessing the Placebo Effect”

- Alternative Medicine systems will often make the claim that they are “harnessing the placebo effect.”
- This is a rebranding of their original claims about standing apart from medicine; it allows them to claim they are ahead of medicine, as if medicine is not affected by the placebo effect, too.
- Scientifically, what would it mean to “harness the placebo effect?”

Comment: “Harnessing the Placebo Effect”

- Alternative Medicine systems will often make the claim that they are “harnessing the placebo effect.”
- Scientifically, what would it mean to “harness the placebo effect?”
 - research to identify the physiological/biological origin of the placebo effect
 - there is a little progress on this – pain relief appears correlated with the release of natural opioids by the body
 - development of drug (or other intervention) to activate the response
- **Alternative medical systems have spent no money on the actual science of the placebo effect. They just keep selling their products and make their vacuous claim.**

More Placebo Resources

- *Meissner, K. and Linde, K. "Placebo and Pain". "Chapter 23: What are the best placebo interventions for the treatment of pain?". Academic Press. 2013.*
- *A. C. Ford and P. Moayyedi. "Meta-analysis: factors affecting placebo response rate in the irritable bowel syndrome." Alimentary Pharmacology and Therapeutics. Vol 32. 2:144-158. 2010.*