The Placebo Effect

Vasant Natarajan

We discuss the placebo effect and its role in masking the effects of a drug. That is why every allopathic drug on the market has to pass through a placebo-controlled trial. Homeopathy is based on an unscientific premise and, not surprisingly, no homeopathic drug has successfully undergone such a trial.

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1. Introduction

I remember as a young child that many times when my elder brother used to fall sick, he just had to be taken to a doctor and would miraculously get better even before he started taking the prescribed medication. My mother would often think that my brother had been faking it all along, but modern medicine now understands this phenomenon as the *placebo effect*. In other words, a patient has to just *believe* that he or she is being treated for their illness, a sugar pill (called a 'placebo') then works just as well as the real McCoy! Surprising, but not unexpected, is the fact that the effect can be enhanced by using large pills compared to small ones, or coloured pills compared to white ones – the mind controls the body in unknown ways. In order to account for this important effect, every allopathic drug that comes to the market has to go through a *placebo-controlled, double-blind trial*.

Before we discuss such trials in detail, let us first highlight an important feature of modern scientific enquiry. Our rational mind tells us that every effect we see in the world around us has a definite, identifiable, natural cause. The goal of science is to establish this 'cause and effect' relation. In order to do this, one has to satisfy *ceteris paribus*, a Latin phrase meaning 'with other things

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the same'. In other words, a scientist doing an experiment has to ensure that all of the independent variables other than the one under study are controlled, so that the effect of a single independent variable on the result can be isolated. This is relatively simple when doing an experiment with the non-living world (such as in physics or chemistry), but can become notoriously difficult when dealing with complex living organisms, particularly humans.

So what is a doctor trying a new drug on humans to do? (S)he cannot obviously create a number of identical patients, as one can do for example in physics by repeating the same experiment several times. Patients with the same complaint will differ in their age, gender, overall health, diet, habits, etc. The best way *to control* for these variables is to take as large a statistical sample as possible and hope that any uncontrolled variation will be 'averaged over' the large sample. In addition, one would pick a group whose members match as closely as possible for the above variables.

2. The Importance of Placebo Control and Double Blinding

To understand how drug trials are done, let us say that you are trying a new drug for malaria. You would pick about 100 male patients suffering from malaria who are all in the same age group, do not smoke, and have similar diet and exercise habits. You would then divide them randomly into two groups of 50 each. As mentioned before, the placebo effect is a strong effect that must be accounted for. This is done by administering one group (called the 'control group') an identical-looking sugar pill and the other group (called the 'experimental group') the actual drug under trial. More importantly, the trial has to be double blinded (see *Box* 1), in the sense that both the patients and the doctors have to be blind to the knowledge of who is getting the drug and

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Box 1. Double-Blind Trials

Double blinding is an important component of drug trials. Just as the patient getting a placebo can show visible signs of improvement without being administered the actual drug, a doctor can also be biased into seeing a difference between the effect of the actual drug and a placebo, *simply because they expect such a difference*. Thus, if a doctor knows that a patient is getting the actual drug and not the placebo, (s)he may subconsciously see an effect even if there is none. This is why it is important to double blind the trial; both the patients and the doctors should not be biased by the knowledge of who is getting the drug and who is getting the placebo. There is no other way to avoid subliminal biases in the interpretation of the results.

who is getting the placebo. At the end of the study, if there is a statistically-significant difference between the control and experimental groups, we can safely say that the drug has some effect. If there is no difference, then the drug is no better than a placebo. Of course, what is statistically significant is well defined mathematically, and the statistical significance will improve as you increase the sample size (see *Box* 2).

Box 2. Statistical Significance

Tests of statistical significance answer the question, "What is the likelihood that an observed result could have occurred purely by chance?" In a sample set, this is done by first selecting a level for the probability of error (α level), and then computing this parameter for the data. For example, if you assume that errors have a 'normal' or Gaussian distribution and the standard deviation of the set is σ, then the statistical significance of an $n\sigma$ deviation can be converted into a value of α by the use of the error function:

$$\alpha = 1 - \mathrm{erf}\left(n/\sqrt{2}\right) .$$

For a 3σ deviation, the value of α is 0.0027, which means that the probability of observing the result purely by chance is 0.27%. Since the value of σ decreases as one increases the sample size, the statistical significance will also increase with sample size.

But a statistically-significant result does not mean that the observation is *important*, which is the meaning of the word 'significant' in everyday usage. For example, suppose we give 1000 people an IQ test, divide them into males and females, and ask if there is a significant difference between male and female scores. We find that the mean score for males is 98 and the mean score for females is 100. We use some statistical test and find that the difference is significant at the 0.001 level. But the difference between 98 and 100 on an IQ test is a very small difference, small enough that it is not important. And the statistical significance will improve further if we use a sample set of 10000 people, but that will not make the result any more important.

The placebo effect is accounted for by using a control group along with the experimental group, and looking for a statistically-significant difference in the effect between the two groups.

In summary, *ceteris paribus* is taken care of by taking a large sample of patients so that inevitable differences between patients will be nullified when looking for an average effect. The placebo effect is accounted for by using a control group along with the experimental group, and looking for a statistically-significant difference in the effect between the two groups. And finally, the study is double blinded so that there is no subconscious bias in the interpretation of the results.

3. Homeopathy and the Absence of Drug Trials

This section is devoted to the practice of homeopathy and is intended to highlight the fact that no homeopathic drug has successfully undergone a placebo-controlled double-blind trial.

The founder of homeopathy, Christian Friedrich Samuel Hahnemann (1775–1843), believed that all illnesses develop from only three sources: syphilis, venereal warts, and what he called 'the itch'. The motto of homeopathy is *Similia similibus curantur*, which means 'Like cures like.' It claims that doses of substances that produce certain symptoms will relieve those symptoms; however, since these substances are generally toxic to humans in large quantities, the 'doses' are extremely attenuated solutions or mixtures, *to the point that not a single molecule of the original substance remains.* In fact, the more dilute the solution is, the stronger its effect! Quantitatively, the dilution is at least 1 part in 10^{30}, which is less than the Avogadro number of 6×10^{23} (see *Box* 3). Since Avogadro's number gives the number of molecules in one mole of a substance, the probability that a single molecule of the original substance remains is zero (well, not exactly zero but zero for all practical purposes since the actual probability is about 10^{-7}). In other words, the homeopathic drug is nothing but pure water. The theory, formulated before modern allopathy took hold, is that the 'vibrations' or 'effect' of the diluted-out

Box 3. Avogadro Number

The Avogadro number, N_A, is based on Avogadro's hypothesis that the volume of a gas, at a given pressure and temperature, is proportional to the number of atoms or molecules *regardless of the nature of the gas*. It is numerically equal to $6.022\,141\,79(30) \times 10^{23}$, with the number in brackets giving the uncertainty in the last digit. It is now used to define the *amount of any substance*, along with the SI unit of 1 mole. Thus, one mole of a substance contains Avogadro number of basic entities. It is easy to see that N_A connects the microscopic world of single atoms and molecules to the macroscopic world of grams of a substance. One example of this is the relation between the microscopic Boltzmann constant k_B and the macroscopic gas constant R:

$$R = k_B N_A.$$

substance are still present and work on the patient.

The only concern of homeopaths is to treat the symptoms of disease and not the underlying causes, which they obviously do not recognize. In the US, where it is required by law to indicate the active ingredients on the label of every drug sold in the market, homeopathic drugs will tell you the scientific name of the active ingredient and how many powers of 10 it is diluted. But in India, the laws are not so strict and certainly not implemented well. That is why many standard pills prescribed by homeopaths (often put in an unlabeled bottle) will contain steroids, unbeknownst to the patient. Now it is well known (in allopathy) that steroids will provide symptomatic relief to a wide variety of ailments, but they can also have serious side effects. Allopathic doctors will prescribe steroids only as a last resort, and even then many patients refuse to take them because of the side effects. Not so with homeopaths, the patients do not know the drug contains steroids and happily take them. The harmful side effects only show up later.

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So the next time someone gives you anecdotal evidence (and any evidence can be anecdotal at best) that homeopathic treatment worked for them, remember that it could be just the placebo effect or steroids at work. The

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James Randi Educational Foundation (http://www.randi.org) has offered a $1 million prize [1] to any one who can prove the efficacy of a homeopathic drug, *under carefully controlled conditions* – basically a placebo-controlled double-blind trial. A recent televised attempt to win this prize by the BBC (on its science programme 'Horizon') ended in total failure – visit the website http://www.bbc.co.uk/science/horizon/2002/homeopathy.shtml for details.

As educated people, I know most of us would read the label and information (much of which is available on the internet through a simple Google search) on any allopathic drug that a doctor prescribes before taking it. More importantly, we would look for any known side effects documented in the drug trials. I urge you to use the same caution before taking any homeopathic pill, whatever be the pedigree of the person prescribing it.

4. Conclusions

In this article, we have seen the importance of not being biased by the placebo effect when studying the efficacy of a drug in allopathy. That is why every allopathic drug that comes to the market has to undergo a placebo-controlled double-blind trial. Any unwanted side effects observed during trials are listed in the information sheet that comes with the drug. On the other hand, homeopathy is based on the unscientific premise of 'vibrations' of a substance remaining in the water used for dilution, even though the dilution is to the point where not even a single molecule of the original substance is likely to remain. It is no surprise that not a single homeopathic drug has successfully undergone a placebo-controlled trial. No amount of anecdotal evidence of homeopathic drugs working in one-off cases can reduce the importance of showing the efficacy of a drug in a scientifically-controlled trial. Remember this the next time you pop a homeopathic pill.

Suggested Reading

[1] **M D Stephen Barrett, *Homeopathy*: *The Ultimate Fake*, http://www.quackwatch.org/01QuackeryRelatedTopics/homeo.html.**

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