

A Brief Review of the Placebo Effect

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Abstract

The present manuscript addresses introductory information and a review of the literature regarding the placebo effect. Included is a discussion on the many definitions of the placebo effect; what it is and how it works. A detailed history follows that includes specific time periods where there was more placebo effect than scientific medicine, and an up to date argument about some placebos of today. The role of desire and expectation will also be explored, along with conditioning theory debates. Finally, this report discusses neuroanatomical evidence for the placebo effect.

Keywords: Placebo, Nocebo

The Placebo Effect

Throughout the many years of early and modern medicine, there is a phenomenon that seems to occur to a great extent, but has only recently begun to be understood. This experience can occur when a patient is given a substance or treatment to relieve specific symptoms. Unknowing to the patient, the substance is pharmacologically irrelevant and the treatment for the situation is inappropriate. The substance could be a sugar pill, saline injection, or any other kind of pseudo-treatment that should not alleviate any symptoms. Surprisingly, however, thirty to forty percent of the patients that are given the counterfeit substance or treatment seem to find relief [1, 2]. This finding can be attributed to a patient being extremely confident in the physician's decision or in the drug they have been given. The phenomenon is commonly known as the placebo effect [3].

Even though this trend is generally accepted as "the placebo effect," developing a generally accepted definition is more difficult. The scenario above was obviously only a very narrow description of the placebo effect. Medical settings are just one of the many environments or states where this can occur. Early definitions of the placebo effect only included medical substances and procedures. After further research and debate, the definition has broadened to include placebo surgery, placebo acupuncture, and placebo psychotherapy procedures [4].

One of the most encompassing, complete, and generally accepted definitions of the placebo effect is proposed by Shapiro and Harrington as "the nonspecific, psychological, or psychophysiological therapeutic effect produced by a placebo, or the effect of spontaneous improvement attributed to the placebo [5]." Another valuable definition that is suggested by Williams and Podd states "A placebo effect is a genuine psychological or physiological

effect, in a human or another animal, which is attributable to receiving a substance or undergoing a procedure, but is not due to the inherent powers of that substance or procedure" [4].

There are many claims that have been associated with the placebo effect. Some of these claims and theories have been founded on science and research, while many have not. To try and dispose of some nonscientific assumptions, Steve Stewart-Williams has compiled a list of characteristics of the placebo phenomenon that any good theory must include [3]. First, the theory must be able to explain the full range of the placebo effect, both the subjective and objective measures. Second, the theory needs to account for both the desirable and undesirable effects of the placebo. Placebos have been shown to simultaneously improve symptoms and also produce unwanted side effects. Third, a theory must account for why some placebos may have a stronger effect in different dosage forms. For example, a placebo morphine injection works better than a placebo morphine pill [6]. Fourth, the theory must clarify why stronger placebo effects are found with subjective reports, rather than objective measures. Finally, a good theory must explain why placebo effects are found in both healthy and ailing people [4]. By using these characteristics and combining the previous definitions, one can now gain a better picture of this enormously complex phenomenon.

The Nocebo Effect

Harrington's previous definition of the placebo effect includes improvement and therapeutic effects credited to the phenomenon, but what happens when a person expects to get worse? The placebo effect also works in the opposite direction. "A surgical patient expects to die on the operating table and does die - not from the surgery itself, but from the expectation and associated effect". This expectation is the direct opposite of the placebo effect, and is called the nocebo effect [7].

Hahn gives us an explanation of the nocebo phenomenon through the acquisition of expectation in seven situations [7]. “It begins with (1) the inner, mental world of the nocebo subjects, moves to (2) their world view, (3) their nosological categories and self scrutiny, (4) the process of diagnosis and prognosis, (5) the “labeling” of deviance, (6) sociogenic illness, or mass hysteria, and (7) the deliberate invocation of sickness or symptoms.”

History

The placebo effect has always been around in medicine, whether the people who treated others knew it or not. Only until relatively recently, the clerics, witches, and physicians who were supplying some of these substances and treatments believed they were effective. This idea undoubtedly played a major role in their effectiveness and usefulness. Researchers have found records of 4,785 drugs and 16,843 prescriptions that were used in ancient China, India, and the Middle East. These were used for the same reasons treatments are used today, to alleviate symptoms and cure diseases. Many of these were the cutting edge, new science of their time. Countless numbers of people were aided and in some cases cured by these substances. At one point, the authors of Galen’s pharmacopeia, which governed treatment for over fifteen hundred years, wrote “He cures most successfully in whom the people have the most confidence.” This statement reflects on the foundation of what we now know as the placebo effect. After careful investigation, all of these drugs and prescriptions mentioned above, with the exception of a few, were recognized to be placebos [5].

The use of ineffective substances and treatments were not confined to the ancient cultures. More recently, the London Pharmacopoeias published in the seventeenth century included “such useless drugs as usnea (moss from the skull of victims of violent death), Vigo’s plaster (viper’s flesh, live frogs and worms), Gascoyne’s powder (bezoar, amber, pearls, crabs’ eyes, and black tops of crabs’ claws), and triangular Wormian bone from the juncture of the sagittal and lambdoid sutures of the skull of an executed criminal” [8]. These substances also had an extraordinary healing ability, not due to their pharmacological nature, but to the effect of the patients’ expectations.

Although the number of placebo treatments has been declining steadily in the period of scientific and modern medicine, they are still used fairly frequently. Up to the 1950’s, about forty percent of the patients that went to see a general practice physician received a placebo treatment [9]. After the 1950’s, the scientific and medical communities saw the increase of specific, non-placebo treatments. The reason for the increase of pharmacologically relevant substances and actual therapeutic treatment was the establishment of the double-blind experimentation procedure [5].

The double-blind procedure is defined by Leedy and Ormrod in Practical Research; “In a situation where two or more different methods are being compared, neither the participants in the study nor the people administering the methods (e.g., teachers, research assistants) know what the researcher’s hypothesis is or which method is expected to be more effective” [10].

Many of the placebo effects of today do not involve the medical or scientific communities, but rather the financial aspirations of businessmen. Religious and psychic healing, megavitamins, organic foods, stress reduction, jogging, holistic medicine, and alternative

medicine may be examples of popular placebos of today. There is very little scientific evidence demonstrating that these techniques or substances are effective, yet they rake in over \$13.9 billion every year in the United States [5, 11, 12].

Desire and Expectation

Shapiro and Morris suggest three categories of the placebo effect process: social influence, expectancy, and evaluation effects. Social influences include physician persuasion, patient suggestibility, and the desire to be a good patient. Expectancy influences include the anticipated results and the patient’s faith and hope for recovery. Evaluation effects include biases introduced to the patient by the therapeutic setting [2, 13]. Steve Stewart Williams believes “Placebo effects have traditionally been attributed to the recipient’s belief in the efficacy of the substance or procedure” [3]. Price and Fields advise, “Under conditions wherein patients have a strong need to be relieved of pain and/or they have expectations that pain relief will occur as a result of a treatment, and/or the treatment situation reproduces in some way a previously effective treatment, pain reduction may result from psychological factors” [1].

Desire and expectation undoubtedly play an enormous role in the placebo effect phenomenon. They are two subjects that arise in almost every article on the placebo effect. Price and Fields propose that these two factors mediate the placebo effect; a desire or need for relief, and an expectation that a given procedure or agent will work. Price and Fields also suggest that the power of the placebo effect is not infinite; it is relative to the situation. For example, a patient who is in extreme pain will not respond to the placebo as well as a patient who only has moderate to minor pain [1]. It seems that the effect of the placebo can only work up to a certain threshold, then the effectiveness declines.

Although expectation and desire influence the magnitude of the placebo response, motivation is another important factor to consider when dealing with this phenomenon. Jensen and Karoly have studied the effect of motivation on the placebo phenomenon [14]. In one of their studies that accounted for the differences in expectation and motivation, they found that motivation was a significant factor in placebo responses that included perceived sedation or stimulant effect but also obtained the same results from expectation [14]. Is the placebo effect just due to desire, expectation, and motivation? This is one of the many questions that placebo effect theorists aim to clarify.

Theories

There are two main and commonly cited theories associated with the placebo effect. These are the expectancy theory and the conditioning theory. Both theories try to explain many of the factors and problems that arise with the placebo effect.

Expectancy Theory

Expectancy theory is the most accepted and popular theories associated with the placebo effect today. This theory assumes that the hypothetical expectancy from an individual “sets the stage for the placebo effect”. The placebo then produces the expectancy. It is this principle that generates the placebo effect [3].

These hypothetical expectancies can occur in many ways. The first and most effective way is personal experience. For example, if a person has a headache and treats it with ibuprofen, their headache

is eliminated. If this person is treated for their next headache with what they think is ibuprofen, they will expect to have the headache relieved. The second way in which hypothetical expectancies can occur is verbal information, or suggestion. This can include a physician or family member telling a patient that they will get better with the certain treatment or drug. A third way where hypothetical expectancies can occur is by observational learning. This is where a patient might be convinced about the efficacy of a certain treatment by seeing another patient find relief from the same actions. These are just a few of the many ways where hypothetical expectancies are produced [3].

The expectancy theory can explain some of the problems that are brought up when discussing the placebo effect. The theory can explain why “placebo injections are more effective than placebo pills and that placebo morphine is more effective than placebo aspirin” [1, 15]. The theory can also explain why there can be “positive and negative effects of the placebo, placebo effects in healthy people and localized placebo effects” [3, 16]. “Expectancy theory also offers an explanation for the greater efficacy of active placebos: The side effects by active placebos enhance people’s expectancies and consequently enhance the placebo effect” [3].

Conditioning Theory

The conditioning theory is a little different from the expectancy theory. This theory is based on Pavlov’s classical conditioning. Classical conditioning is “a learning procedure developed by Pavlov in which a neutral stimulus and an unconditioned stimulus are paired until the neutral stimulus evokes the same response as the unconditioned stimulus” [17].

For example, an active ingredient or treatment is paired with a various stimulus. These stimuli could include syringes, pills, the physician, procedures, or the entire setting. As a result, the stimulus has the capacity to obtain a response that is similar to the active ingredient or treatment [3, 4].

The conditioning theory can also account for what is known as extinction. Extinction is “the weakening of a conditioned response when a conditioned stimulus is presented by itself” [18]. When the syringes or the pills are continuously being presented with no therapeutic benefit, their effectiveness will continue to decline. In 1989, a researcher by the name of Fedele showed that extinction does occur in regard to the placebo effect. Fedele repeatedly gave patients a placebo instead of an analgesic for pain. The more the placebo was administered, the less effective it became for pain. This study illustrated the patient’s loss of the analgesic effects of the placebo with repeated administration [19].

Combining Theories

Many competing hypotheses in the field of psychology can be combined to formulate another enhanced theory that can explain an idea better. The nature versus nurture argument is a prime example. These were two opposing theories for decades. Today, they have been combined to give us a better picture of human development. The placebo effect theories might also work in this way. Williams and Podd believe that the expectancy theory and the conditioning theory of the placebo effect are both appealing, but they are often used against one another. They should be used to supplement each other rather than corrupt each other. Both of these theories can be, for the most part, interchangeable [4].

Take, for instance, the finding that placebo injections are more effective than placebo pills and capsules. This finding can be interpreted within the classical conditioning framework. As noted, a stronger US leads to a stronger CR. Injections would typically contain stronger doses than do pills or capsules, so it would be predicted that placebo effects based on conditioning with injections would be larger. However, the same finding can be construed in terms of expectancies. An expectancy theorist might argue that people expect injections to have stronger effects than pills or capsules, and it is this expectation that gives rise to the larger placebo effect [4].

Laska and Sunshine also agree that “expectation for relief may cause a placebo response without prior exposure to a therapeutic agent, though such exposure certainly will increase expectation” [20, 1]. Many authors agree that the placebo effect could be better understood by looking at the combination of the expectancy and conditioning theories, rather than having the two compete.

Neuroanatomical Evidence

Since the placebo effect is a relatively new subject of debate, little research has been conducted on its functional neuroanatomy. One study was done by Mayberg et al. and addresses some neuroanatomical evidence. The Functional Neuroanatomy of the Placebo Effect was completed in May of 2002.

The participants were hospital inpatients that had been diagnosed with unipolar depression. A simultaneous study was also being conducted on the effect of fluoxetine (prozac) on brain glucose metabolism. The participants were placed in a positron emission tomography (PET) scanner to assess the baseline brain glucose of each subject. The reason for the PET scan was to determine the changes in brain glucose metabolism for the fluoxetine and the placebo groups.

The placebo response “was associated with regional metabolic increases involving the prefrontal, anterior cingulate, premotor, parietal, posterior insula, and posterior cingulate” and “metabolic decreases involving the subgenual cingulate, para-hippocampus, and the thalamus” [21]. The fluoxetine response was very similar to the placebo response over the six-week study. The only significant difference between the two was that the fluoxetine also affected other areas of the brain such as the brainstem, striatum, and hippocampus [21]. As a result, the study has given us a very good foundation to precipitate more research on the functional neuroanatomy of the placebo effect.

Conclusion

The current report has discussed many areas associated with the placebo effect. While there is still much debate over even the definition of the placebo effect, it is an area that needs much more research and discussion. A history of the placebo effect revealed some classic placebos and some present-day placebos. Expectancy and conditioning theories were presented that attempted to explain some issues of the phenomenon. As with many other theories, these two might best be understood by combining them to supplement each other. The role of desire and expectation were also discussed. Finally, there was some neuroanatomical evidence to support the presence of the placebo effect. One implication the placebo effect might have is decreased medical costs. A morphine tablet could cost over \$2 a pill, while a placebo would only cost about 5 cents.

According to the placebo effect, if the efficacy is the same, why not use the placebo? The placebo effect is an issue that needs to be researched and studied more, particularly in the neuroimaging areas [22].

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