



The Placebo Effect: the Good, the Bad, and the Ugly

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ABSTRACT

The placebo effect is defined as any improvement of symptoms or signs following a physically inert intervention. Its effects are especially profound in relieving subjective symptoms such as pain, fatigue, and depression. Present to a variable extent in all therapeutic encounters, this effect is intensified by hands-on contact with close verbal communication between caregiver and recipient. Thus, it may be used to benefit patients but provides a ready avenue for unscrupulous “healers” of all types. Conventional medical practitioners often intervene in some way and, without knowing what caused the improvement, may claim credit for the apparent benefit. Physicians must be skeptical about apparent “responses” to treatments, using the information described herein to better understand what we are—or are not—accomplishing to provide the best possible outcomes for our patients. Less well studied, the “nocebo effect” defines negative responses to placebo interventions. This latter effect may be quite profound and likely is causative in many maladies believed to have psychic origins.

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According to the standard dictionary, a placebo is defined as “an inert medication used for its psychological effect, or for purposes of comparison in an experiment,” the latter usually referring to the performance of a controlled study to determine the efficacy of a new treatment. In this situation, the placebo is identical in form to the active agent and is usually provided to equal numbers of recipients in order to ascertain whether the “active” treatment is superior to the placebos. To avoid biasing the results, these studies are usually “double-blinded,” meaning that both those administering the treatments and those receiving them are unaware of who is receiving the active agent.

The *placebo effect* can be defined as any improvement or change in subjective discomfort or illness resulting from an intervention possessing no physical effect. This broadened definition includes unconventional methods of treatment,

such as that provided by faith healers and, for the most part, practitioners of various forms of alternative medicine. The placebo effect also plays an important role for almost all conventional medical caregivers.

Few people—even within the medical profession—fully understand the power of the placebo effect. It has been aptly characterized as “something to control in clinical research, something to cultivate in clinical practice, and something present in all healing encounters.”¹ Although not well understood, the mechanism of the placebo effect relates to the power of the brain to affect bodily sensations and functions. It is especially effective in relieving pain, anxiety, fatigue, insomnia, and depression but can go further to enhance the effectiveness of medical treatments with acknowledged physical benefits. With this expanded definition we can review some of the experience with this phenomenon, and lessons learned, over the past half-century.

Based on previous studies, placebos improve or relieve symptoms in a widely divergent percentage of individuals suffering from many ailments. But the cause for such variable responses depends on the type of illness treated, the context of its administration, and how long the subjects are observed.² For instance, when used to evaluate new drugs, researchers generally focus solely on the difference between

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the active drug and the placebo, and the placebo effect itself is rarely analyzed or compared with an absence of treatment. Compared in this latter way, one study reported little difference between a placebo and no treatment³; however, this information was tempered by the inclusion of numerous physical diseases and did not evaluate the nature of the interaction between caregiver and patient. Pain, however, did show a significant placebo response when compared with no treatment.

Generally, subjective symptoms unrelated to underlying organic diseases, such as pain or fatigue, are the most likely to respond to a placebo. A beneficial response occurs most often when the treatment is provided by a caregiver who explains that s/he expects improvement. It also is most likely to occur in individuals who are highly receptive to suggestion.⁴ Additionally, the responses are more profound when a given medication is thought to be more expensive than a cheaper one,⁵ an effect likely transferable to all types of treatment.

Perhaps the most potent placebo effects result from physical interventions such as acupuncture. Marked improvement may follow either traditional acupuncture or a sham, which employs superficial needling at non-acupuncture points. For example, in a trial of over 1100 patients with chronic low back pain who received 10 30-minute sessions over 5 weeks,⁶ the improvement rate after 6 months was 48% for traditional acupuncture, showing no significant superiority over the sham procedure. By contrast, only 27% of patients receiving customary care (physiotherapy plus as-needed pain medication) improved, clearly confirming the striking placebo power of acupuncture. Similar results occur⁷ with migraine and tension-type headaches, irritable bowel syndrome, chronic low back pain, and others.

These findings establish 2 important points: the sham and “real” acupuncture procedures show little difference, qualifying both as effective placebos, and the efficacy of both acupuncture procedures far exceeded those of ordinary medical management. These and many other similar trials strongly suggest that acupuncture, a procedure that involves an elaborate treatment ritual with close caregiver–patient interaction, provides the basis for a maximum placebo effect.⁸ Thus, physical manipulations, as exemplified by acupuncture and probably chiropractic treatment, demonstrate more profound beneficial effects than do orally administered placebos.

Another study⁹ involving patients suffering from irritable bowel disorder reinforces the importance of personal interaction in the placebo effect. Patients were divided into 3

groups, the first 2 receiving sham acupuncture twice a week for 3 weeks. In the first group, there was a 45-minute conversation with the practitioner at the initial visit about the patient’s condition and positive expectations of successful relief; in the second group, initial communication was businesslike and limited to 5 minutes. A third group received no treatment. At 3 weeks after the “treatment,” 62% of patients in the first group reported adequate symptom relief, compared with 44% in the second group, and 28% in the third group. Thus, when enhanced by supportive communication, the placebo effect is most dramatic.

Recognizing that the placebo effect is closely bound to interpersonal contact, Kleinman et al¹⁰ advocate an informal process of medical psychotherapy as a basic component of care, focusing on the experience of chronically ill patients: “It is of the utmost importance that physicians achieve the highest possible placebo effect rates. To do this, doctors must

establish relationships that resonate empathy and genuine concern for the well-being of their patients.”

Predictably, sham surgeries also have demonstrated dramatic placebo effects. For instance, in the 1950s, a common belief held that individuals suffering from angina pectoris could benefit from the surgical ligation of internal mammary arteries, presumably enhancing myocardial blood supply. Because of the tenuous nature of this hypothesis, researchers divided 18 volunteer individuals into 2 groups. Half received the ligation procedure, and the others received only superficial incisions on chest without ligation.¹¹ The participants were unaware of which treatment s/he received. Surprisingly for the time, both groups experienced equal improvement in their symptoms. Of the total 18 subjects, 15 experienced total symptom relief after the procedures, persisting for periods up to 1 year. Shortly after that study, this treatment was abandoned, but this experience lent strong support to the concept that the placebo effect from surgical manipulation was indeed powerful.

The interaction between mind and body is so potent that it can affect the course and outcome of certain organic diseases. Mental depression is a well-known cause of poor outcomes in patients who have suffered myocardial infarctions, and treatment with antidepressant drugs has been found to improve not only quality of life, but also probably reduces recurrent infarctions and even mortality, although the data are currently too limited to enable a firm conclusion.¹² Because depression often responds profoundly to placebos,¹³ this raises the intriguing possibility that, under certain circumstances, the placebo effect could even be lifesaving.

CLINICAL SIGNIFICANCE

- The placebo effect is often unappreciated, being involved in treatments that extend beyond pharmaceuticals.
- Beneficial placebo effects can be strongly enhanced by the type of interaction between caregiver and recipient.
- Conversely, negative expectations play a role in drug side effects and psychosomatic disorders.
- The caregiver must understand these effects in order to obtain maximum benefits for patients, while at the same time, avoiding false conclusions.

The placebo effect may be beneficial in such organic conditions as Parkinson disease,¹⁴ asthma,¹⁵ and duodenal ulcer and inflammatory gastrointestinal conditions.¹⁶ Although placebos have no effect on progression of cancer, they have been found to reduce associated symptoms of pain, loss of appetite, anxiety, and depression.¹⁷ Interestingly, when compared with sildenafil (Viagra; Pfizer, New York, NY), the placebo produced a 21% success rate in promoting successful sexual intercourse.¹⁸

What is perhaps most amazing is the placebo's effect on physical sports performance! Clark et al¹⁹ studied the endurance of 43 cyclists in timed trials. Those given placebos and told they had received performance-enhancing carbohydrates performed 3.8% better than those given the same drink but told it was a placebo. Similar observations have been made in muscle endurance and power in other athletes.²⁰

Because placebo effects are influenced by the interplay between recipient and caregiver, some physicians likely obtain optimum results by having a *placebo personality*—a positive and upbeat attitude toward an expected successful outcome. Additionally, of all patients seen in most general clinics, I would estimate that a substantial proportion has self-limiting conditions that will improve or resolve without treatment. Thus, any actions taken by a caregiver will often be followed by a favorable outcome and, according to the so-called post hoc fallacy, both the patient and caregiver may be seduced into believing the treatment caused the subsequent improvement. Thus, all practitioners, legitimate or otherwise, will achieve apparent “results” through a combination of natural outcome, placebo effect, and post hoc reasoning. This can easily account for the claimed successes of practitioners of various forms of alternative medicine.

Although the mechanism for the placebo's influence on the brain-body connection had previously been obscure, the discovery of endorphins produced by the brain has provided one possible answer to this enigma, at least with regard to the role of the placebo in combating pain. Endorphins are chemically similar to opiates and therefore, likely provide pain relief. The placebo effect likely stimulates the brain's production of endorphins, for one study demonstrated that naloxone, an agent that blocks the physical effects of opiates, also was capable of nullifying relief of pain that was attributable to the placebo effect.²¹ Similar analgesic effects also may be blocked by the peptide cholecystokinin,²² probably through an analogous mechanism.

Because most standard medical caregivers are aware of the placebo effect, it is not surprising that this principle would be applied in clinical practice. Placebos may be administered in a “subtle” form, wherein a barely effective medication (such as a mild tranquilizer) is given together with strong reassurance that said nostrum will be effective. Highly attenuated preparations are said to be “homeopathic” in nature, which is simply another means to achieve the placebo effect. An agent without any physical effect

whatever may be delivered with the same fanfare. Actual surveys of conventional practitioners confirm the widespread use of placebos: in a study by Nitzan and Lichtenberg,²³ 60% of physicians and nurses used placebos, usually as often as once a month or more, and in most cases the patients were told they were receiving “real” medication. Of this latter group, 94% reported they found placebos generally effective. Another survey among academic physicians in the US²⁴ disclosed that 45% had used placebos in clinical practice, most commonly to reduce anxiety and as supplemental treatment for physical problems. As many as 96% of these physicians believed placebos can have therapeutic effects, and 40% reported placebos could even benefit patients' physical problems. These studies were consistent with earlier surveys showing the same overall findings. Very few practitioners in any of these surveys considered placebo-giving as immoral or worthy of prohibition.

HOW DO THE DIFFERING FORMS OF PLACEBO COMPARE?

One recent study analyzed the relative power of differing methods of administering placebos,²⁵ and the outcome amplified the observations presented above. This review evaluated the various means of managing sufferers of migraine headaches. The investigators, in a meta-analysis, sought to compare the relative power of differing placebo methods in their ability to reduce the number of migraine headaches: 1) An orally given placebo identical to an active medication, 2) Sham acupuncture, consisting of superficial needling at nonacupuncture points, 3) Sham injections of inert agents, 4) Sham surgeries, consisting of small incisions in various locations of the body without any organ or tissue manipulation, and 5) Miscellaneous sham procedures such as exposure to electromagnetic devices.

If the headache frequency was reduced by at least 50%, subjects were judged to be “treatment responders.” The percentages of responders in each group receiving a placebo were as follows: Sham surgery showed a 58% response rate; sham acupuncture, a 38% rate; and placebo pills, a 22% rate. The remaining miscellaneous procedures showed response rates not significantly different from those of the placebo pills. Thus, the placebo effects were clearly greater in conjunction with those procedures employing hands-on contact with subjects. Inexplicably, however, they found no significant difference between oral placebos and sham injections, but this finding was at variance with previous studies that did find that injections possessed more potency.

THE REVERSE PLACEBO EFFECT, THE “NOCEBO EFFECT”

As presented above, the brain can be a powerful cause of relief—or even cure—of some illnesses. But the flip side of this coin, a symptom or illness resulting from expectation or fears of a bad effect, can be even more powerful. This has been labeled the “*nocebo*” effect,²⁶ or the “placebo's evil

twin.” This response refers to harmful, unpleasant, or undesirable effects after receiving an inert treatment. Although not as well studied as the placebos’ beneficial results, these negative reactions are likely due to subjects’ pessimistic beliefs that range widely in nature, often taking the form of headaches, gastrointestinal distress, and many others. If the administration is accompanied by warnings of specific potential reactions, those effects are more apt to actually materialize. This fact alone may account for why almost all drug trials demonstrate significant rates of undesirable “side effects” in the control (placebo) group. This provides ample reason for why proper research must include these latter comparisons.

Several common maladies seem to emanate solely from the same mechanism, often called psychosomatic disorders. They usually feature various aches and pains or other subjective symptoms not explainable by objective medical testing. I believe such symptoms are really felt; that is, they are not “all in the head,” as is sometimes alleged. By contrast, pure fakery of symptoms (ie, malingering) falls outside of this realm. Sometimes these disorders are given various names such as somatoform disorder, psychogenic arthritis, fibromyalgia, and chronic widespread pain disorder. More focused areas of pain also can result from emotional factors, and these include, among others, tension-type headaches, back pain, and chest pain. All are commonly associated with emotional tension and depression, which often is associated with an unexplained sense of fear. These conditions are quite prevalent and can be severely disabling, persistent, and often resistant to treatment. They are commonly accompanied with “panic attacks,” which are marked by extreme fear, diaphoresis, breathlessness, light-headed sensations, numbness and tingling of the extremities, bodily pains (often in the chest), general weakness, and even fainting. Extreme fear also often triggers hyperventilation—which produces chemical imbalances in the blood that account for many of the symptoms, including numbness and tingling of the extremities, weakness, and disturbed consciousness with fainting. This part of the disorder is easily confirmed by reproducing the primary symptoms in an office setting by instructing the patient to perform purposeful rapid breathing for at least 2 or 3 minutes. Once recognized, prevention and control are usually successful through explanation of symptom causation, combined, if necessary, with either intentional breath holding or rebreathing in a simple paper bag. These maneuvers not only relieve these symptoms, but help to allay the underlying anxiety that initially triggered the attack. This combination of anxiety and real physical consequences of hyperventilation is quite common, but the physical sensations of the latter are often overlooked components of “panic attacks,”²⁷ and the combined disorder is quite common in general medical clinics,²⁸ estimated as high as 5%-10%, a percentage that accords well with my personal experience.

Another fascinating disorder with a purely mental origin is called “sociogenic illness” or, less commonly, “mass hysteria” or “conversion disorder.”^{29,30} This condition

usually occurs in several individuals within a group but has no identifiable physical cause. It demonstrates how suggestion can produce apparently physical ailments, which can be quite variable, including blindness, nausea, headache, paralysis, inability to speak, and many others. Reports vary widely, and may include outbreaks of spasms, tics, and “seizures,” being especially common in young girls. Most of these outbreaks appear to result from stress to one individual that rapidly spreads by unconscious mimicry. For instance, in 2007 a mysterious illness swept through a boarding school in Mexico,³¹ causing 600 girls to suffer nausea, general discomfort, and buckling knees that left many unable to walk. Batteries of tests revealed no physical explanation. Many other similar outbreaks militate strongly in favor of purely psychogenic origins, and further underline the complexity among the brain–body interactions.

CONCLUSIONS

When apparent improvement follows a given intervention, the results are often attributed to a preceding act. Confusion about causation may result from not only the placebo effect, but also from the post hoc error that results from failure to recognize that many illnesses will improve or resolve with time alone. Faith healers and those providing “miracle” alternative treatments take advantage of these same principles, often to great financial gain. Even conventional medical practitioners often intervene in some way—by pill or procedure—and, without knowing what caused the improvement, may claim credit for the apparent response. Because we all want good results when encountering such situations, a moral dilemma is created by the question of whether it is proper to inform a patient that s/he may have benefitted from a placebo effect, which may jeopardize the apparent improvement or relief. There is no answer to this ethical dilemma. Although most of our treatments are supported by scientific rationale, we often have no way of separating physical from placebo effects. Physicians must maintain a healthy degree of skepticism and humility about apparent “responses” to treatments, using the principles described above in order to better understand what we are—or are not—accomplishing to provide the best possible outcomes for our patients.

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