

# Placebos: A Brief Review for Family Physicians

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Placebos are as old as the practice of medicine and for thousands of years represented nearly the totality of medical therapeutics. Positive and negative placebo effects occur in about 35 percent and 10 percent of individuals, respectively. Without exception, all medical therapeutics may be assumed to have significant placebo components. Factors contributing to the success of placebos are many, but include the expectations of physician and patient, the doctor-patient relationship, and societal norms. Ethical issues regarding the use of placebos are not clear-cut but, in general, the use of placebos is contraindicated except as an adjunct to specific therapy, or as a research tool with informed consent.

In this era of the controlled, double-blind research study, the placebo has acquired a bad press. Placebos are seen as embarrassingly unscientific and as interfering with "real" medicine. Any treatment studied is discarded if, after appropriate statistical contortions, it is shown to be no better than placebo, ignoring the undeniable facts that placebos are uniformly effective in three or four out of ten patients, and that virtually all medical therapeutics depend in part on the placebo effect for success. None of the standard texts in pharmacology or medical therapy discuss placebos in any depth.

I do not propose to endorse the uncritical use of placebos in a family physician's practice. To do so would surely mean the systematic rejection of all that has happened in the last 200 years in scientific medical therapeutics. There is, however, a great deal to be learned from the placebo, both historically and from current research.

## Definitions

*Placebo*, first person singular, future indicative tense in Latin, means "I shall serve." The word's first medical use was probably in the 1787 *Quincy's Lexicon*, defined as "a commonplace method or medicine." The 1811 *Hooper's Medical Dictionary* definition added a new dimension: "an epithet given to any medication adopted more to please than benefit the patient."<sup>1</sup> The modern era is represented by *Dorland's Medical Dictionary* definition of the placebo as "an inactive substance or preparation, formerly given to please or gratify a patient, now also used in controlled studies to determine the efficacy of medicinal substance."<sup>2</sup> For the purposes of this review, I shall accept the definition proposed by Arthur Shapiro in 1964: "any procedure which is given deliberately to have an effect, or unknowingly has an effect on a patient, symptom, syndrome, or disease, but which is objectively without specific activity for the condition being treated."<sup>3</sup>

## History

Until about 100 years ago, the history of the placebo was the history of medicine since few, if any, treatments up to that time had any specific

therapeutic benefit. Further, the scientific method, used to establish validity of those few treatments which probably were rational, was not available.

Sir William Osler felt that the desire to take medicine was one which distinguished man from his fellow creatures.<sup>4</sup> Certainly we have evidence of physicians being an active part of society for many thousands of years. Perhaps the first portrait of a physician dates from 20,000 BC, and the hairy, horned creature represented must have had a profound psychological effect, regardless of the specific therapy he was administering.<sup>5</sup> The solemnly magical atmosphere pervading surgical procedures depicted on television is perhaps comparable.

The history of medical treatment is generally incredible. The Egyptians treated patients with lizard's blood, crocodile dung, swine's teeth, the hooves of asses, putrid meat, and fly specs. In the seventh century AD Paul of Aegina detailed uses of blood from a number of animal species to treat conditions as diverse as dropsy, poor visual acuity, and droopy breasts. The 17th century *London Pharmacopeia* recommended worms, dried viper, oil of frog sperm, human perspiration, spider's web, and *usnea*-moss scraped from the skull of a hanged criminal.<sup>1</sup>

I could go on — powdered mummy, mandrake root, bezoar stones, the royal touch, etc. The point of this is to illustrate the enormous power of the placebo, since physicians continued to be highly respected and honored members of society throughout all of these useless and even harmful treatments.

Historically, of course, astute observers have always perceived the shortcomings of medical practice and the usefulness of "the benevolent deception." In *The Republic* Plato commented, "A lie is useful only as a medicine to men. The use of such medicine should be confined to physi-

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cians."<sup>6</sup> Sir William Osler extolled the factor of faith as the physician's most important therapeutic tool.<sup>4</sup> However, my favorite is Oliver Wendell Holmes' acknowledgement of the hazards of medication in 1860: "If all the drugs now in use could be sunk to the bottom of the sea, it would be all the better for mankind and all the worse for the fishes."<sup>7</sup>

Scientific medicine probably began with Sydenham's discovery of the specific effectiveness of *cinchona* bark, containing quinine, for malaria. In spite of the intervening technological advances, however, the placebo is still very much with us — in fact an ever-present component of medical therapeutics.

### Scope of Placebo Effects

The effects of a given placebo may broadly be divided into positive and negative.

We have known for a very long time that placebos can simulate the effects of other drugs. In a 1951 controlled study of pain relief in post-operative patients, Keats found that 26 percent were relieved by intravenous saline infusion vs 55 percent by intravenous procaine and 77 percent by intravenous morphine.<sup>8</sup> Lasagna found an overall 39 percent relieved of pain by intravenous saline compared with 85 percent by intravenous morphine.<sup>9</sup> These are *positive* placebo effects.

Henry Beecher reviewed 15 studies concerning over 1,000 patients in 1955. Illnesses studied were as diverse as chronic anxiety, headache, and post-operative wound pain. He found the overall positive effectiveness of administered placebo to be 35.2, plus or minus 2.2 percent.<sup>10</sup> The narrow range of the standard deviation indicates the extent to which placebos operate in a wide variety of conditions within very similar limits.

If one begins reading current literature looking at the response to placebo rather than the response to the experimental treatment, one readily observes that positive placebo effects are omnipresent. Studies dealing with internal mammary ligation, oral hypoglycemic therapy, insomnia, chronic anxiety, headache, and many others, all show about the same result: three or four

out of ten patients may be expected to respond positively to administered placebo.

Perhaps even more interesting are the *negative* placebo effects. In a study on placebo sedatives for insomnia, Wolf found a ten percent incidence of "toxic reactions." Some patients suffered weakness, palpitations, nausea, or rash, and one developed angio-neurotic edema — all after placebo administration.<sup>11</sup> A 1969 study on oral contraceptives found that those who received placebo experienced side effects at a high level: 30 percent decreased libido, 17 percent increased headaches, 14 percent increased menstrual pain, and 8 percent increased nervousness and irritability.<sup>12</sup> Similarly, a study on cold vaccines found the incidence of toxic reactions to be seven percent in both experimental and control groups.<sup>13</sup> The Lancet published a 1972 study in which 56 London medical students were given placebo sedatives and stimulants. Results showed that 30 percent of the students so treated promptly experienced motor impairment, headache, nervousness, tachycardia, anxiety, vomiting, and diarrhea.<sup>14</sup> (Certainly susceptibility to placebo effects is not dependent on educational level!) These are all negative placebo effects and may be assumed to occur in about ten percent of patients overall, although the variability is considerable.

Studies have further shown that placebos have a characteristic pharmacology. Lasagna found that orally-administered placebos have a specific onset of action and half life, and that patients so treated demonstrate tolerance and even dependence on the placebo. He concluded that placebo effects are not an all-or-none phenomenon and that time relationships are important for the placebo to be effective.<sup>15</sup>

The psychiatric literature has many case reports of patients "addicted" to placebos — requiring increasing doses, developing toxic side effects, and even experiencing withdrawal symptoms. A classic 1969 study of a neurotic woman who was followed for 12 years on a placebo documented a requirement increasing from 1 to 12 placebo capsules daily. At this point she experienced predicted toxic side reactions which abated when the dose was lowered. Withdrawal symptoms of

anxiety, tremulousness, headache, and nausea were noted when the placebo was stopped entirely.<sup>16</sup>

To summarize then, placebos are known to have both positive and negative effects, occurring in about 35 percent and 10 percent of patients, respectively. Further, their effects on a given patient may closely approximate the effects of active drugs, even to the extent of the person's demonstrating tolerance, dependence, and withdrawal symptoms.

### Factors Contributing to Placebo Effects

An essential component of placebo effectiveness is faith or, for the less theologically minded, the expectation of success. This was probably taken to its extreme by Mary Baker Eddy, founder of Christian Science, who said, "When the sick recover by the use of drugs, it is the law of general belief, culminating in individual faith, which heals."<sup>17</sup> The success of this cult may testify again to the effectiveness of faith, or the expectation of success, in placebo therapy.

A physician graduates from medical school confident that his education, which society *via* medical school has given him, equips him to cure. Experimentally, the faith or confidence of a physician bears a direct relationship to the effectiveness of a given treatment. In other words, the physician is probably the most important placebo of all.

Many investigators have shown that the efficacy of both placebo and active drug is increased when the physician has faith in the effectiveness of the drug he is administering. Similarly, the effectiveness of active drug as well as placebo may be decreased when the physician considers either one useless. In most studies, this effect of the physician's expectation alters outcome of therapy about 25 to 30 percent in either direction.<sup>3</sup>

New medications have long been known to work better than old, presumably because of the faith of physicians in modern technology. This prompted Sir William Osler to comment, "We should use new remedies quickly, while they are still

efficacious."<sup>18</sup>

Many believe that the doctor-patient relationship is the key to successful placebo therapy. An angry, rejecting, or preoccupied physician is thought more likely to elicit a negative placebo response whereas a friendly, reassuring, and relaxed physician is considered more likely to elicit a positive response to therapy.<sup>19</sup> Although intrinsically reasonable, these opinions have proven extraordinarily difficult to support with experimental data.

All agree that the patients' attitudes and expectations are critical to a placebo's success. The factors of suggestibility, personality, anxiety, sex, and age have all been experimentally studied, and the results are conflicting.<sup>3</sup> There seems little doubt that the patient's expectation of cure, reinforced by the physician's medical degree, his warmth and confidence, the ritual of the office visit, the writing of the prescription, the bottle in which the drug is dispensed, positive comments from the pharmacist, and so on — all may contribute to some degree. However, these factors have proven difficult to isolate experimentally and hard data are lacking.

Several investigators have studied placebo "reactors," and "non-reactors." In a random population about a third of patients may be classified as placebo reactors. Placebo reactors are likely to react more positively and with more side effects to active drugs than will non-reactors. Reactors are also more likely to experience both positive and negative placebo effects to an inactive substance. For example, the effectiveness of morphine sulfate may be 90 percent in placebo reactors and only 75 percent in non-reactors.<sup>19</sup> Although numerous studies have been published, attempts to reliably characterize reactors, or to predict whether a given individual will be a reactor or non-reactor, have failed.<sup>3,9</sup> Placebo reactors have obvious implications for research. If an experimental group contains an unusual number of reactors, results could be obscured positively or negatively, ie, the effectiveness of a useful drug might be obscured, as might the uselessness of a placebo.

Other patient factors have also been identified. Drug companies have long known that the color of medicine

correlates with effectiveness, as does size of the tablet, odor, and taste, presumably by appealing to societal norms about what specific colors mean, what a big vs a small pill is likely to do, or how unpleasant vs pleasant smelling or tasting medications are likely to help or harm. In the medical student study cited earlier pink tablets were more likely to cause stimulant side effects and blue ones depressant side effects.<sup>14</sup> The reasons why red stimulants work better than blue ones, or why large multi-colored capsules work better than small white pills, are entirely unclear. They simply do, and it is probably safe to assume that many other factors contribute at which now we can only guess.

### Placebos in Psychotherapy

There is little doubt that the credentials of the psychotherapist, the patient's faith in the truth of psychotherapy, and the expectation of cure on the part of both therapist and patient all have some effect on the success of psychotherapy. Psychiatrists have long acknowledged and exploited these effects, not only in analytic therapy, but also in Gestalt, client centered, and other therapies.

In his book *Placebo Therapy*, Jefferson Fish stated that the psychotherapeutic transaction can be seen as taking place between two believers — the healer and the one to be healed. He went on to compare psychotherapy with faith healing, asserting that it is faith in both cases which is the active vehicle for cure. The argument of the importance of the placebo in psychotherapy was further developed in his discussion of group therapy. The ideas that screaming or shouting releases pent-up hostility, that looking into another person's eyes increases one's capacity for intimacy, or that falling backward and being supported by the group establishes trust (all currently popular techniques in various group therapies), are all unproven assumptions which may owe their therapeutic efficacy to the expectation of success and faith on the part of participants and leader.<sup>20</sup>

In an extensive 1958 review of the psychiatric literature, Foulds found that psychotherapy was 85 percent effective in those studies which were uncontrolled but only 19 percent effective in those studies where psychotherapy was compared with placebo. In many of the papers reviewed, no significant differences could be observed between formal psychotherapy and placebo psychotherapy.<sup>21</sup> Certainly these data suggest that psychotherapies owe part or, in some cases, all of their effectiveness to a placebo, or non-specific, effect. At least the obvious parallels between psychotherapy and other clearly placebo treatments should temper our enthusiasm toward literature taking the specific efficacy of a particular psychotherapy as proven fact.

### Ethics and Placebos

The question of ethics and the placebo is a difficult one, and its solution is not to be found in medical literature.

Leslie acknowledged that the administration of a placebo constitutes a deception, but drew a fine distinction between deceit and deception. He defended deception for the welfare of the patient as ethical medical practice, and further outlined five specific indications for placebo administration: (1) in research with informed consent; (2) in weaning patients off narcotics and sedatives; (3) in terminally-ill patients, interpolating placebo with active pain relief to lessen constipation and respiratory depression; (4) as a substitute for a conglomerate of useless drugs the patient may be taking, to aid in problem identification; and (5) as a temporary concession to the patient who cannot wait for a thorough diagnostic evaluation before demanding treatment. He went on to detail specific orders for the administration of placebos, including suggestions as to the size and color of tablets, taste and odor of liquid medication, and specific things a physician might say to the patient to increase the placebo effects.<sup>22</sup>

Sissela Bok took quite the opposite position, deploring the use of placebos in general and pointing to the danger of a domino effect: ie, if a physician begins to use them he is likely to use them more and more, eventually leading to abuse. She recommended their use only after careful diagnosis, when no other agents are known to be effective, without prescribing any active drug, without the physician telling lies, and under no circumstances to those who have requested not to receive them. The discussion was expanded to include inappropriate antibiotics, diagnostic tests, irrelevant surgery, and other procedures which may be undertaken simply "to do something."<sup>23</sup>

In the lay journal *Psychology Today*, Fred Evans took yet another view, recommending the regular use of placebos because of their safety, effectiveness, and the fact that they do not preclude the use of "real" medicine if the patient requires it.<sup>24</sup>

## Discussion

Any agent effective 35 percent of the time or causing side effects in one out of ten is a powerful tool. The fact that such agents are frequently placebos discomfords the more scientifically minded among us. The placebo still has a poor reputation: Hofling has shown that 75 percent of doctors interviewed asserted that they used fewer placebos than their colleagues.<sup>19</sup> Let us briefly examine the issues for family physicians and propose a few guidelines.

First we must recognize that placebo effects are everywhere — even in our favorite "specific" treatments. The dried viper, spider's web, and crocodile dung of old have been replaced by antibiotics for colds, B-12 injections for fatigue, or thyroid pills for non-specific weakness. The only difference is that today's placebos are more dangerous. The fact that these treatments work in about a third of individuals does not remove the physician of culpability for practicing bad medicine. The physician should always have in mind the question, "How much of the success of this therapy is specific (usually established in carefully controlled research), and how much is nonspecific, or placebo?" Only a criti-

cal, ongoing, scientific evaluation of therapy distinguishes us as physicians from the friendly chiropractor, naturopath, or megavitamin freak down the block. On this point I see no room for compromise. Placebos are certainly contraindicated when appropriate specific treatment is available, when they are used for diagnostic purposes (they will not work), when a patient asks not to receive them, or when they are merely a convenience for the physician.

Should family physicians ever exploit the placebo effect? I believe the answer is an emphatic "YES." Any specific treatment or drug may be made more effective by encouraging positive expectation. The use of placebo effects as an adjunct to specific therapy is something we all do every day, frequently without giving it a thought. The important thing to my mind is that we learn to (1) expect placebo effects, and (2) recognize them as they occur. Strictly placebo therapy runs the high risk of destroying the doctor-patient relationship should the ruse be discovered; the use of placebo effects as adjuncts to specific therapy does not.

The importance of placebos as a research tool cannot be over-emphasized. Their usefulness in establishing positive and negative data regarding other more "specific" therapies is entirely unique and should be protected. The unethical use of placebos in research, as in withholding effective therapy or in deceiving a patient into thinking that he is receiving specific therapy (as we have seen, further obscuring results!), has only to be condemned; but their careful use with properly informed consent remains an essential tool in the development of new scientific knowledge.

Lastly, some dilemmas remain. Consumerism brushes a fundamental nerve in medicine, touching the image of physicians generally, the doctor-patient relationship, and certainly the way in which therapy is managed. The consumer movement and the demand for fully informed consent will, no doubt, alter the extent to which placebo suggestions might be effective. Additionally, full disclosure of possible side effects of a given treatment might increase the proportion of negative placebo effects. The impact of consumerism on research is already

being felt and may radically alter the guidelines within which clinical trials must operate. Physicians as a group are likely to exert little control over the outcome of these issues, but our individual awareness and participation should be an essential part of the debate.

## References

1. Shapiro AK: The placebo effect in the history of medical treatment: Implications for psychiatry. *Am J Psychiatry* 116:298-304, 1959
2. Dorland's Illustrated Medical Dictionary, ed 25. Philadelphia, WB Saunders, 1974
3. Shapiro AK: Factors contributing to the placebo effect. *Am J Psychother* 18:73-88, 1964
4. Osler W: *Medicine in the nineteenth century*. In *Aequanimitas*, ed 3. Philadelphia, Blakistons, 1932
5. Haggard HW: *The Doctor in History*. New Haven, Yale University Press, 1934
6. Plato: *The Republic*. New York, Oxford, 1964
7. Holmes OW: *Medical Essays*. 1842-1882. Boston, Houghton-Mifflin, 1895
8. Keats AS, D'Alessandro GL, Beecher HK: A controlled study of pain relief by intravenous procaine. *JAMA* 147:1761-1763, 1951
9. Lasagna L, Mosteller F, von Felsinger JM, et al: A study of the placebo response. *Am J Med* 16: 770-779, 1954
10. Beecher HK: The powerful placebo. *JAMA* 159: 1602-1606, 1955
11. Wolf S, Pinsky RH: Effects of placebo administration and occurrence of toxic reactions. *JAMA* 155: 339-341, 1954
12. Aznor-Ramos R, Giner-Velasquez J, Lara-Ricalde R, et al: Incidence of side effects with contraceptive placebo. *Am J Obstet Gynecol* 105: 1144-1149, 1969
13. Diehl HS, Baker AB, Cowan DW: Cold vaccines: Further evaluation. *JAMA* 115: 593-594, 1940
14. Blackwell B, Bloomfield SS, Buncher CR: Demonstration to medical students of placebo responses and non-drug factors. *Lancet* 1: 1279-1282, 1972
15. Lasagna L, Laties VG, Dohan JL: Further studies on the pharmacology of placebo administration. *J Clin Invest* 37: 533-537, 1958
16. Vinar O: Dependence on a placebo: A case report. *Br J Psychiatry* 115: 1189-1190, 1969
17. Eddy MB: *Science and Health*. New York, Harper & Row, 1875
18. Osler W, cited in Byerly H: Explaining and exploiting placebo effects. *Perspect Biol Med* 19: 423-436, 1976
19. Hofling CK: The place of placebo in medical practice. *GP* 11(6): 103-107, 1955
20. Fish J: *Placebo Therapy*. San Francisco, Jossey-Bass, 1973
21. Foulds GA: Clinical research in psychiatry. *J Ment Sci* 104: 259-265, 1958
22. Leslie A: Ethics and practice of placebo therapy. *Am J Med* 16: 854-862, 1954
23. Bok S: The ethics of giving placebo. *Sci Am* 231(5): 17-23, 1974
24. Evans F: The power of the sugar pill. *Psychol Today* 7(11): 54-59, 1974