Expectation, the Placebo Effect and the Response to Treatment

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ABSTRACT

What we believe we will experience from a treatment – our expectation – has a substantial impact on what we actually experience. Expectation has been established as a key process behind the placebo effect. Studies in both laboratory and clinical settings consistently show that when people ingest a pharmacologically inert substance (placebo) but believe that it is an active substance, they experience both the subjective sensations and physiologic effects expected from that active substance. Expectation has an important place in the response to "real" treatment as well. This paper provides an overview of the data which point to the role of expectation in both the placebo effect and the response to treatment. These data suggest that clinicians might enhance the benefit of all treatments by promoting patients' positive expectations.

KEYWORDS: expectation, placebo effect, response to treatment

In 1962 the Kyoshu Journal of Medical Science included a report that is as baffling today as it was when it first appeared.[1] Ikemi and Nakagawa had studied 13 boys who were hypersensitive to the leaves of the Japanese lacquer or wax trees. These leaves produce effects similar to those of poison ivy. The researchers touched the students on one arm with leaves from a harmless tree but told them that these were poisonous leaves; they then touched the students on the other arm with poisonous leaves but told them that the leaves were harmless. All 13 arms touched with the harmless leaves showed a skin reaction but only two touched with the poisonous leaves did so. In this study the harmless leaves not only induced a dramatic skin reaction but that reaction was greater than the one produced by the poisonous leaves. According to this study, the mere thought that one is being touched with a poisonous leaf can bring on a skin eruption.

That the expectation alone of a skin eruption can lead to one smacks more of science fiction than of science. The results of this study are difficult – no, impossible – to reconcile with what we know about how leaves cause contact dermatitis. Although the study was methodologically sound, the investigators were experienced scholars and researchers in psychosomatic medicine, and the journal was a respected one, we are tempted to dismiss this report as either fraudulent or a fluke. Even those convinced that the mind and brain are linked to the body find it difficult to come up with a pathway by which a thought could produce skin inflammation. In fact, this contact dermatitis study has not been replicated so it's hard to know just how solid its remarkable findings may be.

Nevertheless this study does not stand alone. A library worth of reports attests to the fact that what we believe we will experience from a treatment – our expectation – has an enormous impact on what we actually experience. Countless studies, many of which stand up to replication and rigorous scrutiny, show that the power of expectation is as dramatic-and perplexing as it was in the poison leaf study. Not uncommonly, as was the case in the poison leaf study, expectation alone can both duplicate and annul a treatment's specific effects.

For example, Benedetti et al looked at the influence of expectation in 6 patients with severe Parkinson's disease who had been implanted with stimulating electrodes.[2] When the electrodes were turned on, these patients underwent a dramatic improvement in their ability to move. When the electrodes were turned off, they once again froze up. But after several weeks of stimulator treatment, simply the thought that the stimulator was on or off had almost as much impact on movement as the stimulation itself. When the patients were told that the stimulator had been turned off, their motor velocity decreased even though, in fact, the stimulator had remained on. When patients with asthma inhaled an innocuous substance that they were told was an allergen, their airways constricted; when they inhaled an innocuous substance that they were told was a bronchodilator, they began to breathe more easily.[3]

The Power of Expectation

Expectation has been established as a key process behind the placebo effect. Studies in both laboratory and clinical settings show time and again that when people ingest a pharmacologically inert substance (placebo) but believe that it is an active substance, they experience both the subjective sensations and physiologic effects expected from that active substance.

Although studies conducted over the past several decades have established the fact that expectation alone can produce the effects of medicinal and recreational drugs that span the entire pharmacopoeia, controlled laboratory investigations have focused on the ability of expectation to mimic the

effects of caffeine, alcohol and analgesics. These substances lend themselves particularly well to controlled studies of expectation; they are widely used, their effects are well known and they can be given safely to healthy subjects.

Schneider et al's study of caffeine expectation is noteworthy for its rigorous methodology.[4] The investigators took great care to both promote the expectation that caffeine would be ingested and to maintain double-blind conditions. Two groups of 15 subjects each were given decaffeinated coffee. One group was told that the coffee was decaffeinated, the other that the coffee was regular (caffeinated). Both groups watched as the experimenter added scoops of coffee to the coffee machine and brewed the coffee. Before drinking the coffee, all participants read a one-page flyer about the effects of caffeine on the cardiovascular system, cognitive efficiency and alertness.

Participants who were told that they would consume caffeinated coffee reported greater alertness than those who were told (accurately) that the coffee was decaffeinated. The caffeine expectation group also showed an increase in diastolic blood pressure and an improvement in reaction time not seen in the control group.

A key feature of expectation – induced placebo responses – is that they are shaped by what a person believes they will experience from a substance and not by the pharmacologic properties of that substance. In many instances what a person believes about a drug's effects is close to its actual effects. But when belief diverges from reality, it is the belief more than the pharmacologic reality that determines the nature of the response.

For example, people who believe (incorrectly) that alcohol increases sexual arousal, report an increase in sexual arousal when they drink either real or placebo alcohol. Likewise the extent to which people believe that alcohol will induce intoxication or result in problems with coordination determines the degree to which they, in fact, experience these effects.[5]

Expectation and the Response to "Real" Treatment

Although the role of expectation in treatment response has been most thoroughly investigated in experimental studies of placebo treatment, it is abundantly clear that expectation has a sizeable impact on the response to "real " treatments. Not uncommonly expectation has a greater impact on clinical outcome than a drug's pharmacologic activity. In one of the few studies that have examined the specific influence of expectation on the results of a clinical trial, a large number of depressed patients were treated with either placebo, St. John's wort or the antidepressant, sertraline.[6] Patients improved to the same extent with all three treatments. But when patients were asked to guess the treatment to which they had been assigned, those who thought they had been assigned to placebo showed little clinical improvement irrespective of what they had actually received; those who guessed that they had been given St. John's wort showed uniformly large improvement irrespective of what they actually received (including placebo) and those who guessed that they had received sertraline showed large improvements whether they actually got sertraline or placebo. The researchers concluded that, "Patient beliefs regarding treatment may have a stronger association with clinical outcome than the actual medication received." Consistent with these findings, depressed patients who expected an experimental antidepressant to be very effective were far more likely to respond to the treatment (90% responded) than those who anticipated that the same antidepressant would be only somewhat effective (33% responded).[7]

The importance of the placebo response, and in particular expectation, to the outcome of "real" treatment is dramatically illustrated in studies of open versus hidden treatment.[8] In hidden treatment patients are not aware of when they receive treatment. The treatment is delivered intravenously by a preprogrammed infusion machine. Open treatment is provided in the usual manner; a doctor comes to the bedside, administers the infusion, and tells the patient what to expect from the medication (eg, "This is a potent painkiller; your pain should subside in a few minutes."). Invariably open treatment produces substantially greater effects than hidden treatment. For example, in comparisons of open and hidden morphine infusion in patients with postoperative pain, the open morphine infusion provided significantly greater pain relief than the same amount of morphine administered without the patient's knowledge. In some studies of analgesics, patients given open treatment got substantial pain relief, whereas those treated covertly got no pain relief whatsoever.

Likewise in a study of postoperative patients treated for anxiety, those who received open infusions of diazepam experienced significant relief, whereas those who got hidden diazepam infusions had no reduction in anxiety.[8]

The difference in outcome between open and covert treatment is a measure of the placebo effect, or more precisely, the impact of the perception that one is receiving beneficial treatment on the response to that treatment. The facts that a treatment's effectiveness is notably greater when the patient knows that the treatment is being administered and that in some instances the treatment's effectiveness depends entirely on that knowledge can usefully inform the manner in which treatments are applied. Clearly patients benefit most from medication when it is given along with information and a ritual that promote the expectation of relief. Whether a deliberately enhanced treatment ritual – such as the wearing of a white coat and stethoscope or prolonged, elaborate cleansing of an area to be injected – further enhance medication benefit remain to be seen.

Patients come to treatment with a surfeit of expectations about what sort of treatment they need, what treatment will be of most benefit, and how they will respond to a specific treatment. But it's what their physician conveys to them about treatment that has the greatest impact on their expectations and, accordingly, on the component of their response – and it can be a considerable one – attributable to the placebo

effect. The doctor's words shape a patient's expectations, and more often than not their response to treatment, across the entire range of medical and psychiatric conditions. Take, for example, a patient with a backache. In one scenario the doctor hands the patient a prescription and says, "Try this, it may work." Alternatively the doctor could offer the same prescription and say, "This is a powerful painkiller. It's going to help you." Or consider the depressed patient who is likely to benefit from an antidepressant. As she presents the prescription, the doctor might say, "This is worth a try." An equally truthful statement but one that creates very different expectations would be, "Try this; it should help you to start feeling much better in a few weeks."

Although the idea that patients benefit when clinicians are optimistic may seem self-evident and collecting evidence in support of it unnecessary, this notion has, in fact, been subjected to and supported by empirical study. For example, in what has become a classic investigation, KB Thomas, a general practitioner in Southampton, England randomly assigned 200 patients with symptoms of minor illness – most had cold symptoms or muscle pains – to receive either a "positive consultation" with or without treatment or a "negative consultation" with or without treatment.[9] In the positive consultation, the patient was given a diagnosis and told that he would be better in a few days. If no prescription was given the patient was told that none was required; if a prescription was given the patient was told that the treatment would certainly make him feel better.

In the negative consultation the doctor said: "I cannot be certain what is the matter with you." If the doctor gave no prescription, he added: "And therefore I will give you no treatment." If he gave the patient a prescription, he said: "I am not sure that the treatment I am going to give you will have an effect." The negative consultation concluded with the doctor telling the patient to return if he or she were not feeling better in a few days. The treatment in both consultations was a prescription for thiamine hydrochloride tablets used as a placebo.

Two weeks after the consultation, a card was sent to each patient asking if he or she had gotten better; 64% of the patients who received a positive consultation reported that they were better, compared to only 39% of those who received a negative consultation.

A dozen or so other studies have compared the outcome of treatment when a doctor is deliberately enthusiastic and optimistic about the treatment or deliberately neutral or negative. Many of the studies involve patients treated for anxiety or pain in the context of dental treatment. The studies vary in methodologic quality and not all of them find that the clinician's attitude about the treatment influences outcome. But the majority of the studies show that when the treating physician conveys optimism about the treatment, patients perceive the treatment to be more helpful.

The studies of expectation are not entirely consistent; because of differences in methodology, they do not lend themselves to systematic comparison or collation; and publication bias (the tendency to publish the results of positive rather than negative studies) may be at play. Nevertheless, on the basis of a review of the existing published studies, the United Kingdom's Health Technology Assessment Programme, which advises the National Health Service, concluded in 1999 that the evidence to date justifies strategies to "enhance patients' beliefs in the benefits of effective medical treatments." They recommended that healthcare professionals should receive training in how to communicate positive expectations effectively.[10]

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