Current Review

A guide to the pharmacology of placebos

CHARLES W. GOWDEY, D PHIL

The placebo effect is capable of relieving pain in a substantial proportion of patients; affective disorders also respond to the administration of inert medication. Changes in objective measures, such as blood pressure and blood glucose levels, demonstrate the action of placebos. The underlying mechanisms are not yet known, but because the nature and strength of the placebo response are governed by the patient's perceptions, both positive and negative results may be obtained. The complexity of human perception has made it extremely difficult to characterize the people who react. In clinical situations the placebo may be underused as a therapeutic agent, while in clinical trials the effect may be inadequately evaluated; the power and nature of the placebo effect truly warrant greater recognition.

L'effet d'un placebo est capable de soulager la douleur chez une proportion substantielle de patients; les troubles affectifs réagissent également à l'administration de médicaments inertes. Des changements dans des mesures objectives, telles que la tension artérielle et la glycémie, démontrent l'action du placebo. Les mécanismes sous-jacents demeurent inconnus, mais comme la nature et l'intensité de la réponse placebo dépendent de la perception du malade, des résultats positifs aussi bien que négatifs peuvent être obtenus. La complexité de la perception humaine fait qu'il est extrêmement difficile de caractériser les personnes qui réagissent. En clinique le placebo peut être sous-utilisé comme agent thérapeutique, alors que dans les essais cliniques son effet peut être insuffisamment évalué; la puissance et la nature de l'effet placebo méritent vraiment d'être mieux reconnus.

The placebo effect is a neglected and misunderstood aspect of patient care; a recent survey revealed that a majority of house officers and nurses were unaware of the relief obtainable from placebos.[1] The very word makes some physicians uncomfortable, and patients resent the implication that their suffering may respond to an inert medication.

Still, placebos have been known to relieve anxiety,[2] depression,[3] premenstrual tension[4] and chronic headache,[5] to prevent migraine attacks[6] and to induce and maintain sleep in patients with insomnia.[7] Coughs,[8] the common cold,[9,10] hay fever[11] and asthma have responded to placebo treatment; even intravenous administration of a saline solution has benefited some patients with status asthmaticus unresponsive to epinephrine.[12]

Investigators have made use of the placebo as a blank against which to judge the activity of potent drugs. The introduction of ever more esoteric chemicals as therapeutic agents, however, has made necessary examination of the effect of the placebo itself. Consequently, the power and ubiquitous nature of the placebo effect have been extensively documented. As this article will show, under the right conditions the therapeutic environment and even the character of the physician can make the placebo a powerful therapeutic agent.

Effectiveness of placebos

A practitioner would naturally find it more satisfying to ascribe some favourable response in a patient to the wise choice of a pharmacologic agent, but up to three quarters of patients with affective disorders improve with the administration of a placebo alone.[13] The most widely prescribed drugs are those used to treat anxiety and minor pains, yet these are conditions that often either remit spontaneously or else respond to reassurance and placebos or to extremely low doses of active drugs. Enuresis was prevented in a number of delinquent boys by giving placebos.[14] The behavioural deterioration of schizophrenic patients on neuroleptic drug holidays was slowed by the same means.[15] After injections of placebos some subjects have reported euphoria[16] and fatigued subjects have hallucinated.[17] In a study of morphine addicts injections of a saline solution were substituted for the drug without withdrawal symptoms appearing until these injections ceased.[18]

Pain

Patients with pain seem to be particularly responsive to placebo treatment.[13] Placebos have benefited pa-

From the department of pharmacology and toxicology, Health Sciences Centre, University of Western Ontario, London, Ont.

Reprint requests to: Dr. Charles W. Gowdey, Professor, Department of pharmacology and toxicology, Health Sciences Centre, University of Western Ontario, London, Ont. N6A 5C1

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tients with both rheumatoid and degenerative forms of arthritis[19,20] and have improved exercise tolerance in cases of intermittent claudication.[21] The symptoms and the number of days lost per month because of primary dysmenorrhea have been reduced in some patients by placebos.[22] Also, after 4 weeks' treatment with placebos the pain of peptic ulcer was reduced and the rate of healing was improved in 16% to 52% of patients.[23]

For decades a relatively large proportion of patients with angina pectoris responded to therapy that was pharmacologically inert.[24] In a recent double-blind study only 4% of patients with angina and angiographically proven coronary atherosclerosis had a therapeutic response to placebos equivalent to the response to propranolol.[25] Among patients with angina but no demonstrable coronary artery disease, however, 25% benefited from the use of placebos.

In trials of oral analgesics at the Mayo Clinic 39% of cancer patients found marked relief from pain when they were given placebos.[26] Another substantial placebo effect was obtained in a group of patients who had undergone extraction of impacted third molars.[27]

From a review of a series of studies on severe, steady postoperative wound pain among hundreds of patients, Beecher[28] found that placebos had given "satisfactory pain relief" (a carefully defined term) in 30% or more of cases. In summing up the results of 15 clinical studies involving 1082 patients with a variety of painful conditions Beecher[29] noted that injection of a saline solution or administration of lactose tablets was effective in an average of 35.2% of cases. The small standard error of the mean (2.2%) suggested that a common fundamental mechanism was operating that warranted further study.

In experimental studies in which pain perception rather than tolerance is usually measured, placebos are generally less effective than when pain is due to trauma or disease. Experiments conducted in 1953 indicated that starch placebos increase the pain threshold of healthy volunteers by only 4%.[30] Beecher[31] reviewed 13 studies in which healthy volunteers had been subjected to various kinds of experimentally induced pain, including radiant heat, pressure, electric shock and the application of tourniquets. He found that placebos had an analgesic effect in an average of only 3.2% of cases.

Objective measures of placebo action

Are there more objective criteria of clinical success than patients' opinions? Placebo effects are not imaginary and may involve almost any organ.[32] Measurable objective effects that can follow placebo administration include changes in gastric acidity,[33] pupil diameter[34] and serum lipoprotein levels,[35] as well as changes in eosinophil and lymphocyte counts and in serum electrolyte and ketosteroid levels that are comparable to those seen after giving large doses of adrenocorticotropic hormone.[36] In trials placebos have reduced the incidence of nausea and vomiting due to motion[37] and radiation,[38] have reduced essential tremor[39] and have lowered the blood pressure in patients with essential hypertension.[40] Placebos provided moderate to good control of blood glucose levels in 26% of diabetic patients for at least 14 days in one double-blind cooperative study.[41]

Mechanisms of action

The mechanisms that underlie the placebo response are not understood. After studying the effects of placebos and the narcotic antagonist naloxone on postoperative dental pain Levine and colleagues[27] claimed that their results were consistent with the hypothesis that placebo analgesia is mediated by the release of endorphins. This is a tempting hypothesis, but Goldstein and Gevert[42] observed that not all nonpharmacologic analgesia is due to endorphins. The dramatic analgesic effect of hypnosis, for instance, is not blocked by naloxone. Surely it is reasonable to suppose that the far lesser degrees of analgesia produced by placebos could be mediated by processes of suggestion that do not involve endorphins.

Whatever their mode of action, placebos work through the influences of the patient's mind. Indeed, the placebo effect can occur in the absence of any drug treatment, or it may be associated in various ways with genuine medication.

Influence of expectations

Beecher[28,43] contrasted the behaviour of soldiers severely wounded in a World War II combat zone, among whom only 25% said they wanted drugs for relief, with that of patients with similar wounds in civilian hospitals, 80% of whom demanded analgesics to relieve their unbearable suffering. The consequences anticipated by the patients could explain these differing reactions. To the soldiers, being wounded meant that they had survived, would be removed from combat and then would be treated well, whereas the civilians were probably worried about their families, finances and jobs.

The expectations can thus be general in nature, but they may also be quite specific. In a study involving medical students both placebos and glyceryl trinitrate decreased the subjects' blood pressure and induced tachycardia. The changes were even greater when the students knew what substance was being administered.[44] Other medical students who had been given meperidine, 40 mg intramuscularly, were told that some of the injections had been placebos; in 33 out of 50 subsequent pain tests the meperidine showed either no effect or else lowered the pain threshold.[45]

Even without knowledge of the appropriate effects, patients find clues in characteristics of the substance administered. Lasagna[46] suggested that an extraordinarily large placebo impresses by its size and an exceptionally small one by its presumed potency, and that an injection is considered by the patient to be more effective than something taken by mouth. Blue capsules have been associated with greater sedation than pink capsules.[47] When the same dose of oxazepam was given in different colours, anxious patients responded better to green than to red or yellow capsules.[48] There is disagreement over the relation between placebo response and dosage.[47,49]

The value attached to a medication in terms of cost can be an important factor: unicorn horns, bezoar stones and mandrake roots were once highly prized; nowadays costly natural vitamin–mineral mixtures or preparations with undisclosed formulas from private laboratories are sought.

Adverse effects

Placebos do not always produce beneficial results; like other therapeutic agents, they have side effects. In a recent study on intermittent claudication 55% of patients taking a drug and 37% of those taking a placebo reported side effects.[21] Double-blind studies of new benzodiazepine derivatives and placebos as hypnotics revealed no difference in the incidence of side effects.[50]

Some adverse effects are quite dramatic. Immediately after taking a placebo capsule one patient reported that she became sick, dizzy, nauseated, blind and had numbness around her mouth.[51] Wolf[32] described overwhelming weakness, palpitations, nausea, lowered blood pressure and fainting in another patient within 5 minutes of taking a tablet, regardless of whether it was a placebo or a muscle relaxant; a second patient had a severe maculopapular rash, and a third had watery diarrhea, urticaria and angioedema of the lips.

Sick patients seem to associate certain side effects with the kinds of medication prescribed for symptomatic relief of their conditions. Placebo side effects often resemble those that could be expected with the particular active drug under investigation.

Among 67 placebo-controlled drug studies involving 14 medications and more than 3500 subjects, central nervous system depression occurred in 6.6% of all the subjects but in 8.0% of those given placebos in controlled trials of analgesics or tranquillizers.[52] Vomiting occurred in only 0.4% of all the subjects but in 8.5% of those who took placebos in the course of a trial with estrogens. Among the 38 types of side effects recorded during placebo administration depression, manifested as drowsiness, was the most frequent, occurring in over 6% of all subjects. Headache was next, followed by stimulation, manifested as nervousness and insomnia. Drowsiness, fatigue, ataxia and mental confusion occurred twice as frequently as central nervous system stimulation.

There may be other reasons for side effects to appear with placebo treatment. Some patients may find compensations in illness and wish to preserve their complaints; hence, they may be inclined to see negative pharmacologic effects.[53] The emergence of side effects has also been viewed as a communication of disappointment with the drug therapy.[54]

Adverse effects occur in healthy volunteers too. Hamilton, Philp and I[55] found that three quarters of a group of medical students experienced side effects when it was suggested to them that they were participating in the clinical trial of a new psychoactive drug, although they received only a placebo. Their most frequent symptoms were related to depression and sedation. They also reported restlessness, excitation, tremors, headache and bradycardia. Similarly, among medical students who were conditioned to expect sedative or stimulant effects but who all received placebos, sedative effects were more common than stimulant.[47] In 40 healthy geriatric subjects Salzman and coworkers[56] elicited many symptoms by giving placebos: fatigue, drowsiness, impairment of vision and hearing, cramps in the arms and legs, and nasal congestion.

Conditioning in the doctor–patient relationship

A number of factors in the doctor–patient relationship and in drug trials may influence the therapeutic outcome of placebo treatment: the personalities of both parties, the expectations of the physician concerning the drug, the treatment setting and the doctor's verbal and nonverbal communication of therapeutic intent to the patient.[57] The provision of a checklist of possible symptoms after subjects take the placebo could be interpreted by them as a directive to be unusually introspective.[55] Heightened self-awareness could then lead to reports of treatment-induced symptoms.[56] In an investigation of placebos related to anti-motion-sickness drugs, however, the frequency of such reports decreased with repeated administration of the placebo and questioning.[58]

Some investigators have postulated that the placebo response is a conditioned reflex.[59] The stimulus would be a complex configuration comprising doctor, therapeutic setting and therapy, and the response would be learned through experience. Indeed, a placebo response can be produced in hooded rats, the strength of the response being related to the number of pairings between the active drug and the conditioning stimuli.[60]

Who will react?

Can one predict which patients will respond to placebos? Many doctors think they can, yet they fail when tested objectively. A great deal has been written on this aspect of the subject. Lasagna and colleagues[16] reported that "placebo reactors" tend to be immature, eccentric, inadequately controlled, more dependent on outside stimuli, more anxious and less rigid than other subjects. Some investigators have found that placebo reactors are older and less educated than nonreactors;[61] others have discovered the reverse.[62] One group thought placebo reactors were less likely to have a history of neurotic traits or of a hysterical or inadequate personality but were more likely to have unelaborated anxiety;[62] another concluded that strong placebo reactors are passive and unintellectual, with loose thinking and flattened affect.[63] Luoto[64] reported that "high neurotic introverts" were likely to be placebo reactors, whereas Joyce[65] found that the consistent reactors among medical students were less self-confident but more sociable and extroverted.

In women the emergence of side effects with placebos corresponds to the times in the menstrual cycle when the frequency of baseline symptoms is higher.[56] Moertel and collaborators,[26] however, concluded from their placebo-controlled studies in cancer patients that men were slightly more likely than women to react to placebos but not significantly so. Smokers were clearly less susceptible than nonsmokers. Cancer patients who had a high level of education or were professional peo-

ple, farmers or women working outside the home showed an inordinate placebo response. Patients who had had a traumatic interruption of marriage through death, separation or divorce were strikingly vulnerable. Most vulnerable to the placebo effect was the very self-sufficient individual with heavy responsibilities who was thrust into the unaccustomed dependency of a disabling illness. However, those responding to placebos also responded more readily to active drugs — a finding that corroborated the earlier work of Beecher.[29]

Actually, we should not expect to be able to identify a population of consistent placebo-reactors. The effects of placebos are characteristically much more unpredictable and inconsistent than those of drugs. Although from 30% to 50% of patients respond to placebos in a variety of situations, they are not always the same people.

Where and how well placebos are used

Goodwin and coworkers[1] observed that in the clinical situation placebos are typically given to patients who are disliked because they are suspected of exaggerating their pain or because they have failed to respond to the usual medical regimens. In such cases a positive response to placebo medication is interpreted by the physician as evidence that the pain had no physiologic basis. While overdemanding and complaining patients are, if anything, actually less likely to respond to placebos than patients well liked by the hospital staff, the former are the very ones "at risk" of being given placebo treatment.

The placebo may have done much to dignify clinical research, but Modell and Houde[53] warned that even the use of the double-blind technique does not ensure validity of the conclusions. They had given 25 patients with arthralgia either a placebo or acetylsalicylic acid and asked the patients to fill out a card and report on their treatment at the end of 2 weeks. The patients' reports indicated that there were no differences between the drug and the placebo. However, when the same doses were given and a bedside observer communicated directly with the patients, recording analgesia as it developed, the active drug was significantly more effective.

Wolf[66] observed that experimental subjects in a placebo-controlled trial face an interesting hazard. By reacting to a placebo they may arouse hostility in the physician or nurse. This is an ironic twist because their very response expresses confidence in those who care for them.

Conclusions

One can question whether the placebo is a legitimate part of the practice of medicine. To some the placebo is a form of deceit, initially of the patient but ultimately of the physician.[67] One cannot really avoid the use of placebos, however, even if they are never administered as such, for a placebo effect can arise from any therapeutic action. Thus, the physician may well be using this effect without even recognizing it.[68] What is at issue, then, is not whether the physician should make use of placebos but how the omnipresent and sometimes powerful placebo effect can best be used.

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