FORUM

Placebo Effects and Research in Alternative and Conventional Medicine

A White Paper from the Placebo Working Group of the NIH Office of Alternative Medicine
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ABSTRACT The placebo effect is a very powerful and unpredictable aspect of any medical treatment. As such, it dramatically complicates efforts at convincingly demonstrating the effectiveness of specific effects in medicine, conventional or alternative. This review provides a theoretical overview of the placebo effect to assist researchers in designing trials, controlled or otherwise, so that more convincing demonstrations of specific effects can be achieved.

1. Introduction

There have been literally thousands of articles written about placebo effects; as this is written, a query on the Medical Subject Heading "Placebos" in the Medline database has over 17,000 entries while "Placebo Effect" has 820. Yet far less is known that unknown about them. In a certain sense, placebo effects are the ultimate "complementary" medical therapy in that they accompany all other medical treatments regardless of form, content, tradition or illness, from heart surgery through ayurvedic medicine and homeopathy to intercessory prayer. Our goal in this paper is the address placebo phenomena in a way to provide researchers with a theoretical approach that allows them to improve study design.

1.1. The Importance of the Placebo Effect

Differentiating between these powerful general forces and the specifics of those various therapeutic systems has long bedeviled research in medicine, whether conventional or complementary and alternative (CAM). It is true for many reasons. Placebo effects are dramatic and powerful, often swamping the specific effects of particular agents. The most thorough development of this argument is to be found in Robyn M. Dawes' recent book *House of Cards: Psychology and Psychotherapy Built on Myth* (1994). Dawes' argument goes like this:" Psychotherapy," he says," works overall in reducing psychologically painful and often debilitating symptoms. The reasons it works are unclear, because entirely different approaches may work equally well for the same problem or set of problems" (Dawes 1994: 38). He notes that there is little that can be said about how such therapy works except that those engaging in verbally oriented treatments should be "empathetic," and that those using primarily behavioral techniques should have knowledge of behavioral principles. His most dramatic claim, however, may be this one: we know, he says, "that *the credentials and experience of the psychotherapists are unrelated to patient outcomes*, based on well over 500 scientific studies of psychotherapy outcome" (p. 38; italics in original). Modestly trained therapists who are empathic, or who understand behavioral principles, or both, are just as helpful as those who are highly trained and more experienced (and expensive).

What is most remarkable is how many people are helped by such generic techniques. Many studies show up to 60% or 70% of psychotherapy patients achieving significant improvement. Other research shows that similar results exist in areas other than psychotherapy. For example, in a review of a number of medical techniques, Roberts and his colleagues have shown that it is regularly the case that 70% of patients can achieve good or excellent results with procedures subsequently shown to be ineffective in controlled trials. Among these techniques were glomectomy (removal of the carotid body or glomus) to treat bronchial asthma, levamisole for the treatment of Herpes Simplex Virus (HSV), photodynamic inactivation for treating HSV infections, organic solvents (ethyl ether and chloroform) for treating HSV, and gastric freezing for duodenal ulcer (Roberts, et al. 1993). Combining data from 32 studies showed that "for a total of 6,951 patients treated by these five methods, 2,784(40%) were reported to have had excellent outcomes, 2,049 (30%) good outcomes, and 2,098 (30%) poor outcomes" (ibid, p. 386). This finding is similar to those reported in Benson and McCallie's classic study of placebo effects in the treatment of angina pectoris. In a series of studies of treatments subsequently

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This paper is dedicated to Alan Roberts who died during its writing; he was a good scientist and a good friend. He will be missed.

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shown to be no more effective than placebo (xanthines, khellin, vitamin E, ligation of the internal mammary artery), "data from enthusiasts' studies reveal that subjective improvement was seen in 82.4 ±9.7% (mean ± S.D.).... In addition to subjective improvement, objective changes occurred: the placebo effect increased exercise tolerance, reduced nitroglycerine usage, and improved electrocardiographic results" (Benson and McCallie 1979:1427).

These data indicate that, when dealing with a broad range of medical problems (and always within the bounds of human mortality), some 2/3 or more of patients can be expected to experience substantial improvement when patient and therapist believe in the treatment provided, regardless of what it is.

2. Measuring Specific Effects of Medical Interventions

It is of course also the case that medicine offers many examples of *specific* treatments that predictably and reliably add to these outcomes based on general factors. Aspirin routinely relieves more headaches than placebo; H_2-receptor antagonists like cimetidine routinely hasten the healing of gastric ulcer compared with placebo (Legerton 1984). *A primary goal of medical research —conventional or alternative —should be to increase the number and effectiveness of these specific dimensions of therapy.* Given the high levels of general effectiveness in medical treatments, highly controlled trials are needed to construct such demonstrations. The idea is not to "eliminate" the general factors in treatment; that would be as impossible as it would be undesirable. Rather, the idea is convincingly to demonstrate that the particulars of a certain treatment — this acupuncture point for headache, that sort of massage for indigestion — improves the outcome of acupuncture or massage for illness.

2.1. Publication Bias

Much of what we know about such non-specific and placebo effects comes from published data on placebo-controlled trials. Yet there is good reason to believe that there is publication bias in the medical literature. Dickersin and Min (1993) have shown that a larger proportion of controlled trials showing statistically significant differences are published than those which do not show statistical significance. For example, among 200 randomized controlled trials examined, 109 had significant results; 98.2 percent of these were published. Ninety-one of the 200 had non-significant differences between the groups which were compared;only 85.7 percent of these were published. Thus, if we examine only the results of published trials, one may get an overly optimistic impression of specific effects. This may not be the case in complementary medicine, however, depending on which journals are examined, as it is possible that both positive and negative publication bias occurs in different journals.

2.2. The Size of the Placebo Response

In placebo controlled trials, there are two reasons why a study might have non-significant results. First, the drug effectiveness rate may be low. Second, the placebo effectiveness rate may be high. Consider the two trials described in Table 1.

Table 1. Two Double-Blind, Placebo Controlled Trials of Cimetidine for the Treatment of Ulcers

N	Drug group healed (Cases, %)	Placebo group healed (Cases, %)	Chi-Square	Reference
67	29/33 (88%)	27/34 (79%)	0.875, n.s.	Malchow, et al. 1978
76	36/39 (92%)	16/37 (43%)	21.1, $P<0.01$	Hetzel, et al. 1978

Both trials are of cimetidine for endoscopically diagnosed ulcers. The drug group healing rates are about the same (88% and 92%), and both are high. The placebo group healing rates, however, are quite different (79% and 43%). The first trial listed was not statistically significant while the second was; the factor which determined the statistical significance of one and not the other is the variation in placebo effects, not the drug effects. Dickersin's work suggests that trials like the first one listed, with high placebo effectiveness rates, are less likely to be published than ones with lower placebo effectiveness rates. This means that in meta-analyses, we are likely to underestimate placebo rates unless we can include all trials, published and non-published.

2.3 Variation in the Placebo Response

To control for effects of such magnitude and subtlety is a challenging proposition. Consider these aspects of the healing process to see why.

The work by Dawes, by Roberts and his colleagues, and by Benson and McCallie comes to conclusions quite different from what medical people normally believe to be the case. It is very common, for example, for physicians and others to report that the "placebo effect" occurs in 32% of cases. This is apparently based on a very common misreading of

Beecher's famous *JAMA* paper of 1955. But many physicians and nurses also understand placebo effects to be much lower even than that; in a study at two university hospitals, the mean and median response of 60 physicians was that 20% of patients could be expected to "respond to a placebo injection with adequate relief of pain the day after abdominal surgery." The response of 39 nurses was even lower with 61% asserting that no patients or only 5% of patients would so respond (Goodwin, Goodwin and Vogel 1979:107). Indeed, the number of such satisfactory placebo responses for pain is often much higher than either estimate, in various studies ranging from 30% to 60% or even more (see, e.g., Liberman, 1966, where there were 101 placebo responses in 153 opportunities — 66% — for 51 women given saline injections or other placebos during and after childbirth).

A similar complicating factor is the fact that placebo effects are highly variable — one can never know what they will be in a particular situation unless they are measured. For example, in 32 very similar double blind controlled trials of cimetidine for ulcer, placebo group healing rates (endoscopically verified) ranged from 10% to 91% (Moerman 1983). Just what accounts for such variation is not clear; regardless of origin, it is important to measure how much non-specific effectiveness is occurring in any particular circumstance, and to expect the unexpected.

In addition, Kleijnen and his colleagues underscore thie notion in their recent review of a series of trials to determine the nature of the interaction between specific and non-specific effects. While the trials they reviewed showed that " specific effects can be modified by non-specific effects,... [the interactions are] sometimes synergistic, and at others antagonistic, so the implicit additive model of the randomised clinical trial is too simple" (Kleijnen, et al. 1994).

2.4 Other Complicating Factors

Non-specific effects, therefore, come from a variety of circumstances and are very diverse. In a useful review, Roberts notes 8 general dimensions of the healing process (Roberts 1995:7). We will very briefly consider some of them here.

2.4.1. Spontaneous Recovery, Fluctuations of Complaints, and Regression to the Mean

Spontaneous recovery and **fluctuating severity of symptoms** can be very important but highly counterintuitive. Generally, people seek out medical treatment when they are ill, or when their symptoms are worse rather than better. Often, either due to the body's homeostatic abilities or to fluctuations in severity, those symptoms will approach their normal state regardless of what is done. A similar phenomenon, **regression to the mean**, occurs when a group of people with extreme values for some parameter are selected for study or treatment. After a while, the average value of that parameter in the selected group will be lower, because random fluctuations towards the more normal values will occur. People with values for this parameter just below the cut-off value, in whom the random fluctuations might be randomly higher, were not selected for inclusion in the group; therefore the study group might appear to be "better" due to treatment while the "improvement" is simply due to random changes. These phenomena can occur in people who have not sought treatment.

An Australian study of hypertension found several thousand subjects through a large screening program. People with diastolic blood pressure (DBP) greater than 95 mmHg, or systolic blood pressure greater than 200 mmHg were entered into the study. One subgroup of 237 patients continued to have their blood pressure checked every 4 months, but received no drugs or placebos. Their mean DBP dropped from 101.5 to approximately 80 in a period of 32 months where it stabilized; the mean pressure stayed at about 80 (plus or minus 1) for the next 24 months (MCATTMH 1982:187). This is probably a demonstration of regression to the mean or spontaneous recovery; whatever may cause mild hypertension is apparently, for many people, transient (but see below for alternative interpretations of this study). Were one to neglect such phenomena, any treatment would look good.

2.4.2. Measurement Bias

Medical treatments often involve relationships, and many people like to be nice to one another. The **"demand characteristics"** of the situation are the social elements of the treatment situation which lead both patients and healers to report better results than may have actually occurred in order to please one another. Patients are often under a good deal of pressure to get better quickly when they are sick — these pressures can be personal, relational, financial, or structural. Some birthing centers now send mothers home the same day they have given birth. Under such a situation, it is in a patient's best interests to "feel good" even if she doesn't. But the good report will be written down as data (and will support the decision to make such early releases).

3. Non-specific Factors — What Are Their Components?

Conditioning may play a role in the placebo effect; people may be able to learn how to feel better (Voudouris, Peck and Coleman 1990). Since conditioning requires prior learning, this factor can only be a part of the overall placebo process; large claims are unwarranted. Conditioning may play an important role in efforts to enhance the placebo effect.

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Various **psychophysiologic states** and their fluctuations may also affect the outcome. "Just talking to a healer can reduce anxiety about symptoms and their consequences. 'Take two aspirin and call me,' can be reassuring" (Roberts 1995). Doctor and patient **expectations** may amplify the preceding factors.

There may also be additional, or parallel, **direct placebo effects**. There is evidence from Levine's work that placebo analgesia involves the production of endorphins; in his study, the opiate antagonist naloxone reversed placebo analgesia (Levine, Gordon and Fields 1978). But this research remains controversial, and has been only partially replicated. This issue has been reviewed by Grevert and Goldstein (1985); recent work has been undertaken in the area by Fields (m.s.).

Similarly, there is evidence to suggest that the quality of human relationships and social support — or changes in them — can affect immune processes. Over the last ten years, evidence from the fields of neuroendocrinology, neuroimmunology, neurobiology and behavioral medicine has accumulated to show that higher perceptual centers and limbic emotional centers are capable of modulating virtually all arms of the immune system (Ader 1991). Thoughts, perceptions, or expectations may activate one of the two main neuroimmunomodulatory (NIM) pathways — the neuroendocrine and autonomic — producing changes in neuropeptide production and autonomic function (Blalock 1994; Cechetto and Saper 1990). These NIM pathways can then bring about an alteration in the immune response either directly via the neuropeptide receptors on leukocytes or by modulating autonomic outflow. Activation of these pathways can produce dramatic changes in immunity and may, in some circumstances, be as powerful as a direct pharmacological action. For a helpful review of some of the issues in this area, see (Watkins, 1995).

In these latter cases of "direct placebo effects," it is worth noting that we are not dealing with "non-specific effects," but with "not-yet-understood specific effects." Much creative work remains to be done in this area.

4. Taking Account of Non-Specific Factors in Effectiveness Studies

Given this broad range of sources or potential sources of general healing effects, it is important to design effectiveness studies very carefully. Recall that a primary goal of normal medical research — traditional or complementary — is to increase the number and effectiveness of specific therapeutic techniques, and in what follows, we list a number of factors which should be taken into account in order to do this.

4.1. The Choice of a Control Group

As in biomedicine, placebo effects are active in any complementary therapeutic system. How to control for such effects in order to determine the character of the putatively effective specific elements of the treatment system is sometimes relatively straightforward, but sometimes not.

4.1.1. Placebo Control Groups

At least in principle, it is easy enough to imagine how to construct a double blind experiment in homeopathy. An excellent example of this is a series of trials by Reilly and colleagues carried out in Glasgow. Patients with allergic rhinitis, or asthma, were treated with highly diluted (30 c, 1 part in 10^{60}) homeopathic preparations of grass pollen, or with identical appearing placebo tablets. "Patients taking [the] homeopathic preparation showed a greater reduction of symptoms than those taking [the] placebo. This difference was reflected in a reduced need for antihistamines, increased in significance when adjusted for pollen count and time of season, and was confirmed by the doctor's assessments" (Reilly, et al. 1994). For another example, see the study of the effect of highly diluted homeopathic drugs on healthy volunteers by Harald Wallach where "single-case evaluations showed differences between the two experimental phases for 21 [of 47] subjects. Group evaluation showed no clearcut differences" (Wallach 1993: 851).

But consider another sort of therapy. Relf has collected a series of studies which indicate that there can be positive health consequences for people who are in contact with plants (Relf 1992). For example, Roger Ulrich "compared the hospital records of matched pairs of gall bladder surgery patients who had window views of either a small stand of trees or a brick building wall. He found that patients with the views of trees had shorter post-operative hospital stays, required fewer potent pain drugs, and received fewer negative staff evaluations about their conditions than those with the wall view" (Ulrich and Persons 1992:101). Such research has suggested to some a form of therapy based on gardening, or "horticulture therapy." Horticulture therapy has been used at the Menninger Foundation in Kansas since early in this century (Mattson 1992). It makes good sense to think that spending time in a garden planting, weeding, pruning and so on might be good for sick people. Azar and Conroy (1992) consider the methodological problems of attempting to demonstrate such a proposition. They note that there would be serious problems in randomly assigning patients to such a program or its control. And unlike the case of homeopathy, it is hard to imagine what "placebo gardening" might be; that is, it is very difficult to imagine an alternate activity with which gardening might be compared.

Indeed , these authors decided that "Due to the difficulties in establishing [such] a control group in a hospital setting, we have temporarily suspended our desire to conduct a true experimental study" (ibid., p. 170).

It is important to recognize that just because there is no obvious control for a particular therapy does not mean the procedure is not a good one. The great majority of surgical procedures are not subjected to controlled trials (the few that are usually show dramatic levels of placebo effectiveness — for a review, see Moerman 1991). Other standard medical interventions rarely studied in controlled trials include things like physical therapy — what would you use for placebo exercise? And even an obvious control is not a guarantee of clear findings. An analysis of 31 double-blind placebo-controlled trails of cimetidine for the treatment of ulcers showed that 12 of them did not show statistically significant differences between drug guoup and control group. Moreover, in the aggregate, after 4 or 6 weeks of therapy, 46% of placebo treated patients showed healed ulcers on endoscopy. However, 77% of cimetidine treated patients showed endoscopic healing after the same period. The average 4~6 week drug healing rate in both the significant and non-significant trials was the same (78% and 76% respectively). However, the placebo healing rates differed; in the significant trials, the placebo healing rate averaged 38% while in the non-significant trials, it was 58%, swamping the effectiveness of the drug in those trials (Moerman 1983). There is little doubt that cimetidine speeds ulcer healing, but this was not evident in a dozen double blind trials.

4.1.2. Active Control Groups

Again, it is not always necessary, desirable or ethical to compare a treatment against placebo. Cimetidine has been replaced by ranitidine as the most widely used histamine H_2 receptor antagonist in the treatment of ulcers. Ranitidine may or may not be marginally more effective in speeding ulcer healing than cimetidine; but the newer drug needs to be taken only once a day where cimetidine typically had to be taken 3 or 4 times a day. A number of ranitidine trials were not done against placebo, but against cimetidine (see, for example, Dixon, et al., 1993). The rational choice for one specific therapy as opposed to another may be made not on its increased effectiveness, but for other reasons such as fewer side-effects, reduced dosage, lower cost, or enhanced patient convenience. Many complementary therapies, such as botanicals, might be more ethically and efficiently evaluated by doing direct comparative trials with conventional treatments rather than multiple trials with placebo.

4.1.3. Three Arm Studies

In cases where there are substantial levels of general effectiveness in treatment, it may be useful to consider doing three-arm trials where one group receives "no treatment." In many such trials, "untreated" patients do substantially better than they reported doing before the study began; but often placebo treated patients do better than untreated patients. There is a serious challenge here, however, in that it is very difficult conceptually as well to define a "no treatment" condition. The simple fact of diagnosing a condition, and thereby reducing the patient's sense of ambiguity can have a therapeutic effect (Brody and Waters 1980). In a recent case of my experience, a young healthy woman began to experience severe and frequent nausea and vomiting. She was not pregnant; several specialists could find no evident cause for the problem. The patient was increasingly depressed by the lack of a sense of "what to do." A brain tumor was suspected and an MRI was ordered. When the results were reported back as negative, the patient began to cry, more upset than ever; she preferred a brain tumor to ambiguity.

The difficulties are will illustrated by a study by Kewman and Roberts of biofeedback for migraine headache, summarized here:

> To assess the relative contribution of specific and nonspecific effects of skin temperature biofeedback upon migraine headache, 11 migraine patients were taught to increase the temperature of their hand. Training to decrease the skin temperature of the hand served as a control for 12 other migraine patients. An additional 11 control subjects were not trained but kept records of migraine activity. Under carefully controlled double blind procedures, migraine patients who learned to raise finger temperatures showed statistically significant and clinically therapeutic improvement during a 6-week follow up period. However, they were not significantly better than those trained to lower finger temperature, those who did not meet a learning criterion, or those receiving no training. While these groups did show some significant improvement when compared to subjects who learned to decrease finger temperature, the results are most parsimoniously explained through nonspecific rather than specific factors. The necessity of using double-blind procedures in evaluating therapeutic effectiveness is again stressed. (Kewman and Roberts 1980:327).

This study shows how hard it is to have a "no treatment" group: keeping diaries is apparently a very effective therapy for migraine — it is the one thing all the groups in this study did, and they all showed improvement. Diary keeping was fairly elabo-

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rate. Subjects had two types of diary forms. Instructions were included, and patients were called on the phone to answer questions about the record keeping. "The form included such items as a symptom checklist; time of headache, a rating of impairment, and a listing of the amount and kinds of medication taken" (p.331). Subjects mailed or personally returned the forms. "Approximately every 10 days all subjects were reminded by phone or in person to keep filling out and sending in the diaries. At that time, they were also provided encouragement for their efforts and any procedural questions were answered by one of the undergraduate assistants" (p. 331 - 2). One might suggest that diary keeping is a sort of minimal form of psychotherapy — silent talk with a very quiet and accepting "listener," a notebook.

This study is an absolute model of rigor in design and should be closely consulted by anyone who has to design a sublte experiment*. It also raises some interesting questions. The results have been replicated several times showing one way or another that the details of the biofeedback process do not affect the outcome and that the effectiveness of the process derives from the nonspecific elements of the therapy. *This does not say that the procedure itself is not a valid and useful one*. Indeed, biofeedback is quite popular throughout the United States. One might say that the metaphors and behaviors of biofeedback training are useful and meaningful ways for many people to organize an approach to a series of unwanted illnesses — headache, insomnia, "stress" and so on. Diary writing might offer similar benefits (Pennebaker 1993), but is not nearly as popular.

In a recent paper, Ernst and Resch (1995) have reviewed a series of studies with both placebo treatment groups and "untreated" control groups. They conclude that these studies show that a clear distinction should be made between the two sorts of groups, that doing so often reduces the size of the "placebo effect," but does not eliminate it. This can provide a technique for gaining a much more compelling understanding of the general dimensions of any therapeutic procedure.

4.1.4. These Matters Are Often Unclear

These factors often seem to grade into one another. Consider again the Australian study of hypertension discussed above where the untreated control group seemed to show spontaneous recovery (MCATTMH 1982). It is conceivable that the diagnosis of high blood pressure or the continued attention to and repeated measurement of blood pressure (like diary writing by migraine sufferers) could have influenced the patients, that the hypertension would have stayed high or even increased without the treatment the patients received. That is, the drop in hypertension could have been a direct result of the fact of treatment, a direct placebo effect, and not spontaneous recovery. The only way to know would be to compare these patients with a similar group with moderate hypertension whose blood pressure was checked again only once 4 years later. If this "control group for the control group" showed a decline in blood pressure too, one would conclude that this was spontaneous recovery; if it did not show such a decline, then one could conclude that there was a direct placebo effect, or that this is a "measurement effect": familiarity with the measurement procedures could reduce "doctor's office hypertension," originally caused by the experiment itself. It is unclear how one would differentiate between these two latter possibilities at the same time that it is abundantly clear that these sorts of changes are subtle and complex. But it is also the case that whichever of these three possibilities is correct (and it could be a combination), none gives comfort to those who claim success for their specific agents while treating moderate hypertension.

4.2. Blinding

It is important to be particularly careful about the concealment of treatment allocation and the blinding. Blinding is a control for expectation bias on the part of both healer and patient. As such, it should be decided how it is to be carried out, and uniformly applied. In some trials, it may be useful to include a segment asking therapists and patients about their treatment; if participants guess treatments correctly at more than chance would allow, this should be factored into the analysis. Blinding is problematic in many studies, but it can usually be managed. Classic examples are the studies of bilateral internal mammary artery ligation where the surgeons were not blinded, but the cardiologists following the patients were (Dimond, Kittle and Crockett 1960; Cobb, Thomas, Dillard, Merendino and Bruce 1959). In some circumstances, it may be worth developing "active placebos" which mimic the detectable but nonspecific elements of the therapy under test in order to make a more realistic control. A trial which utilized an active drug, an inert placebo, and an active placebo could be very interesting, and, were it to show significant effect of the active element, would be very convincing. An additional question is whether or not blinding itself results in different effects in the placebo and active treatment groups (the so-called compensatory placebo effect): If true, and not adjusted for, this could increase placebo effects in the placebo group resulting in lower apparent specific effects in the active treatment group. Pilot studies of blinding techniques for both patients and analysts as well as for various types of active placebos should be carried out by investigators and funded by the NIH.

* The paper was presented as a Citation Award Paper at the Biofeedback Society of America meetings, San Diego, 1979.

4.3. Informed Consent

Problems may also arise in trials regarding informed consent. The issue here is not whether or not to obtain informed consent, but rather how to obtain it in an ethically and humanly satisfactory manner without seriously compromising either the general or specific dimensions of therapy. This is another area which deserves research attention by those interested in CAM research.

4.4. Adherence

Finally, there is the issue of "adherence." There is evidence from several large studies, recently reviewed by Horwitz and Horwitz (1993), showing that patients "who adhere to treatment, even when that treatment is a placebo, have better health outcomes than poorly adherent patients" (Horwitz and Horwitz 1993:1863). The beta-blocker heart attack trial (BHAT) was a large study of propranolol vs. placebo in patients who had survived a myocardial infarction (BBHATRG 1982). Propranolol patients who took more than 75% of their medication had a 3-fold advantage over patients who took less of their medication (1.4% vs. 4.2% 1-year mortality rate). Placebo patients had a similar profile: those who took more than 75% of their placebos had a 2.3-fold advantage over those who took less than that (3% vs. 7% 1-year mortality rate). These differences could not be explained by clinical severity, sociodemographic features, life stress, social isolation, or smoking (or any combination of them) (Horwitz and Horwitz 1993:1864). It apppears that "the fact (or act) of taking medication" can have a positive effect on health. Conversely, it is evident that "blind obedience " may well be worse for patients in some circumstances than " intelligent non-compliance." It is probably unwise at this juncture to try to "control" for adherence in determining the effectiveness of specific agents, but one must attempt to measure it and assess its impact on the therapeutic situation. These data also suggest that patients be involved in research studies less as guinea-pigs and more as consultants or co-investigators, much more literally "subjects in experiments" rather than "objects for investigation." How such an approach would work is clearly worth close investigation.

4.5. Negative Findings

There is always a risk of negative findings; studies must be carefully crafted so that the claims under investigation are the proper ones. Scientific studies are by their nature of small scope and reductionist. Yet massive claims are often made on the basis of single studies or small sample sizes. A study which shows no difference in outcome in headache severity after treatment with a particular homeopathic drug compared to placebo has nothing to say about the value of homeopathy, only about the use of that particular treatment. Even negative findings need not lead to such conclusions (c. f., the 12 cimetidine studies mentioned earlier). Negative findings testing a plausible hypothesis after a reasonable study ought not yield the conclusion "Biomedicine [or CAM] is nonsense," rather they should yield the conclusion "More research is needed."

5. Conclusions

The problems addressed here are important ones for Alternative Medicine. But they are also important for traditional biomedicine. As such it is our judgment that the OAM or other elements of the NIH (as well as national health organizations in other countries) should develop a program of study of placebo effects in healing via the Cochrane Collaboration, and through other ongoing medical research, biomedical and otherwise.

It is clear that primary goal of the medical research is the development of effective specific treatments. To identify and evaluate these specifics, general effects must be controlled. However, as we have noted, much of medical effectiveness, perhaps a majority of it, relies of these general or non-specific dimensions of treatment. The best treatment, or optimal treatment, is some complex combination of specific and general processes. Even though a particular specific treatment may be effective in isolation, the effect of adding it back into the general treatment milieu may result in unpredictable outcomes. Our ultimate goal ought to be formally and systematically to identify optimal therapy in complex therapeutic systems. This will involve a more complex kind of study utilizing randomized comparative trials which seek not to isolate specific effects, but to find the most efficient ways to amplify or enhance them.

Placebo effects are harmful only to dogma, not to enlightened, thoughtful, disciplined and rational medical treatment. Indeed, it can be argued that, whatever the primary effects of specific treatments on patients might be, a powerful element of their action is as a reinforcer for therapists whose commitment to the specifics of a therapeutic scheme is one of the primary agents of its effects. The healing effect of most modern medicine is general, not specific. Both elements are exceedingly important in any treatment scheme, and both should be optimized.

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