REPLY

Reply to Commentaries

Walter A. Brown, M.D.

Doctors Shea and Frank suggest that although patients may improve with placebo they don't truly get better or remit. Not surprisingly, as the criterion for "response" becomes more stringent, the response rate for both drugs and placebo goes down. It's not clear, however, that using remission rather than improvement as the endpoint enhances the drug-placebo difference.

What about the degree of improvement in placebo treated patients? In three separate studies of depressed patients randomly assigned to six weeks of placebo, a placebo responder was defined according to the conventional criterion of a greater than 50% improvement in Hamilton scores. In the first study (n = 125) placebo responders' mean Hamilton scores dropped from 26.5 to 7.1, in the second (n = 88) from 24.9 to 5.9 (Brown et al. 1988) and in the third (n = 241) from 27.4 to 6.1 (Brown et al. 1992). These data come from clinical trials and may not be fully generalizable to the practice setting. Nonetheless, they suggest that patients treated with placebo can experience substantial clinical change.

Doctors Klein, Rush, and Frank suggest that one or more components of the placebo treatment situation might be as effective as the entire placebo treatment package. Dr. Klein suggests that the improvement in placebo-treated patients is accounted for by spontaneous remission. If he's correct a substantial number of depressed patients might be managed by simply instructing them to report back in a few weeks. My reading of the data that edge up to this issue (low rate of remission in waiting list controls, low rate of remission during evaluation weeks preceding assignment to treatment, known effects of expectation on general treatment outcome) is that the treatment situation in itself provides benefit beyond that from the passage of time. But, since placebo treatment has not been directly compared to absolutely no treatment, the contribution of spontaneous remission to the placebo response is unclear.

There seems to be a consensus that some type of nonpharmacologic minimal intervention (wait and see, extended evaluation, limited counseling) might be sufficient management for a substantial number of depressed patients. But there is a reluctance to prescribe placebo. This reluctance seems to arise from the absence of data supporting the therapeutic effectiveness of pill ingestion per se and the assumption that a pill identified as placebo will be unacceptable to patients.

The role of pill ingestion in the placebo response is unknown. And it will remain unknown until the individual components of the placebo treatment situation are dissected and evaluated along the lines suggested by Dr. Klein. At this point, we simply don't know which components of the placebo treatment situation are the "active ingredients."

As for patient acceptance, the recent report mentioned by Dr. Delbanco (Eisenberg et al. 1993) on the use of alternative medicine strikes me as pertinent. This survey showed that one out of three adults use alternative therapies (e.g., massage, homeopathy, spiritual healing, megavitamins), and that the number of visits per year to providers of alternative therapy is greater than the number of visits to primary care physicians. Depression was among the five conditions for which people were more likely to seek alternative than conventional treatment, and 35% of the depressed patients treated by physicians sought alternative therapy as well.

Neither the FDA nor the readers of this journal would be persuaded by the "evidence" offered for the efficacy of alternative treatments. But our patients flock to these treatments—and, perhaps wisely, they don't

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tell us about it (Eisenberg et al. 1993). Clearly, our patients have different ideas than we do about what's good for them and they use different criteria in selecting treatments.

A thread that runs through alternative medicine is that the body can heal itself. A prescription for placebo treatment affirms this belief. And, although a treatment that works in a mysterious manner may be an anathema to those of us seeking rational therapies, this very mystery—and magic—may be not only acceptable but appealing to many of our patients.

As for the prescription of identified placebo sounding like something from the Wizard of Oz or depicting psychiatrists as "artful, exploitative, manipulators who take advantage of patients' gullibility," imagine this scenario. Your internist tells you that you have mild hypertension and that one of your options is to take placebo pills for two months. "We don't know how they work," your internist says, "but about 20% of the patients with your degree of hypertension get their blood pressure into the normal range with this approach. These placebo pills have fewer side effects than any other medicine I would prescribe for you and they're less expensive. If they don't work I'll recommend one of the standard medicines for you." Does this sound flaky, exploitative, artful?

Running through the commentaries is a concern that patients treated with placebo are deprived of treatment that is clearly more beneficial. Drs. Klein, Dunner, and Delbanco suspect that the clinician would be at fault if a patient suicides during placebo treatment. A recent review of psychotropic drugs and suicide (Mann et al. 1993) indicates that although in some studies patients treated with placebo as compared to those on antidepressants have a higher incidence of suicidal ideation, placebo treated patients do not have a higher incidence of suicide. These data come from clinical trials, which exclude actively suicidal patients; as I said, such patients should also be excluded from placebo treatment.

So much for the data. Neither conventional medical care nor the communities' perception of good medical care are based solely, or even largely, on data. I have no idea whether the data would be an adequate defense.

How good are our treatments in general? What is the patient treated with placebo being deprived of? Let's take antidepressants; they're the current standard against which other treatments are measured. Drug-placebo differences vary depending on the patient population, study methodology, and so on. Dr. Rush, on the basis of a large meta-analysis of placebo-controlled clinical trials, has come up with a drug-placebo difference of 18 to 25%. That's not an astonishing drug effect. Greenberg and his associates (1992) make a difficult-to-ignore case for smaller (virtually nonexistent) drug-placebo differences. They propose (and offer data supporting this) that the apparent drug effect in clinical trials arises largely from clinician bias.

But I think the apparently fragile efficacy of antidepressants results more from administration to unsuitable patients than from essential ineffectiveness. In certain samples of depressed patients drug-placebo differences can be as high as 70%. Depressed patients with long episode durations, a high degree of severity and melancholic features do not do well without antidepressant medication (Kahn and Brown 1991); their placebo response rates often are less than 20%. But these patients respond well to antidepressants. And depressed patients who show some of the "biological" features of the illness (pituitary-adrenocortical overactivity and short REM latency) fare poorly with both psychotherapy and placebo (Ribiero et al. 1993; Thase et al. 1993; Lahmeyer et al. 1993) but do well on antidepressants. My proposal is a step toward improving the precision with which we select treatments for our patients.

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