Commentary on "Placebo as a Treatment for Depression"

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Dr. Brown presents a well-reasoned argument that we have an unrecognized therapeutic treatment for depression that should be added to our treatment options: pill placebo. His case is based upon the following lines of evidence: for certain patients, the placebo response rate is indistinguishable from that of antidepressants; there is no consistent evidence that the psychotherapies offer an advantage over pill-placebo; pill placebo treatment is less expensive and requires less training and qualifications. This proposal is certainly an interesting one and a compelling case is made. In the end, however, I find myself unconvinced that ". . . the initial treatment for a sizable portion of depressed patients should be four to six weeks of placebo."

First of all, this conclusion rests on the untested assumption that a placebo administered "nonblind," (i.e., with full knowledge by the patient that he or she is receiving placebo), will have the same effects as demonstrated in double-blind treatment studies. The dilemma, of course, is that the "active ingredients" of placebo include such factors as hope and expectation of improvement, which rely upon faith in a credible treatment. This problem is acknowledged: "For placebo treatment . . . to be effective both patient and clinician need to have faith in its therapeutic power." It is argued that clinicians who are informed about the evidence of response to placebo will be able to convey confidence in the therapeutic potential of placebo, thus presumably convincing the patient. However, the clinician cannot know how placebo works when everyone knows it is a placebo (as this has never been demonstrated) and thus has no evidence upon which to base his or her confidence. In fact, elsewhere in the article evidence to the contrary is noted. Fewer than 10% of depressed patients entering antidepressant clinical trials improve during one to two weeks of single-blind placebo treatment, in contrast to the sharp decrease in symptoms during the first one to two weeks of double-blind placebo treatment; this would suggest that the double-blind is critical to the placebo effect.

Even if the clinician can muster enthusiasm, how is the patient to be convinced? Essentially the patient is being asked to believe in the potency of taking an inactive pill that can have effects when it is believed to be active. The unanswered question is whether such a treatment would be perceived as credible; this of course is critical to the presumed mechanism of the "placebo" effect.

A second point concerns the interpretation of existing data in terms of "effectiveness" of pill-placebo. Does the absence in some studies of statistically significant differences between an "active" treatment and placebo mean that we want to encourage placebo treatment? Or does it mean that we want to improve our "active" treatments? This depends at least in part on how "improvement" is defined. Statistically significant differences from pre- to posttreatment is the rule, and it is clear that most patients do show some improvement in controlled trials, regardless of treatment condition. However, when outcome is defined more stringently, the picture looks quite different.

In the NIMH Treatment of Depression Collaborative Research Program (TDCRP; Elkin et al. 1989), for example, all treatment conditions (interpersonal psychotherapy, cognitive therapy, imipramine plus clinical management, and placebo plus clinical management [PLA–CM]) showed statistically significant and substan-

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tial improvement, similar to findings from other studies. Among the less severely depressed patients (pretreatment Hamilton of 14 to 19), there were no significant differences in outcome among the treatments, including placebo plus clinical management. These are certainly the type of patients that might be candidates for the proposed placebo treatment (i.e., less severely depressed, and no significant benefits demonstrated for the active treatments compared to a placebo condition). However, out of all such (*less severely depressed*) patients entering treatment, less than half of those in the "active" treatments (44 to 45%), and only 30% of those in the PLA-CM condition, reached a Hamilton of six or less by the end of 16 weeks of treatment. Even among the less severely depressed patients who completed treatment with PLA-CM, less than 40% reached this criterion of response. And if maintenance of remission is considered, the proportion of these less severely depressed patients for whom placebo treatment is associated with optimal outcome is even smaller (Shea et al. 1992).

Further, these findings must be considered in light of the nature of the PLA-CM condition in the TDCRP, which was probably close to optimal in terms of providing "nonspecifics." In addition to weekly 20 to 30 minute sessions with experienced psychiatrists who provided support and encouragement, these patients also had assessment sessions every four weeks with a trained clinical evaluator, plus the general demand characteristics of being in a study. It is certainly possible that less structured "placebo" treatments would do less well, even if credibility is not an issue.

These treatment response rates, which are not unique to the TDCRP, do not mean our existing treatments are not effective. Most patients do improve with treatment, and for many the improvement is substantial. They simply highlight the fact that when a more stringent definition of "response" (one that I think that most depressed patients would like to have) is used, it suggests there is room for improvement. I think the data argue for improving and augmenting treatment strategies, rather than accepting a less expensive placebo treatment. As one example: psychotherapy has been demonstrated to have "specific" effects in the treatment of depression, under certain conditions (e.g., Elkin et al. 1989; Frank et al. 1990; Frank et al. 1991). Further work clarifying the factors associated with such effects should help improve treatment response rates.

There can be no doubt that the "nonspecifics" of faith, hope, and positive expectations are a critical aspect of any treatment, perhaps particularly so for depression. And such factors undoubtedly play a significant role in reduction of distress. This may be enough for some patients, but if optimal outcome (in the short and long term) is the goal, the data suggest that these will be few and far between. For most patients treatment of depression is more than initial distress reduction, it is a long-term affair. Use of placebo treatment would, I think, be a waste of valuable time.

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