Commentary on "Placebo as a Treatment for Depression"

Ellen Frank, Ph.D.

This commentator's initial response on reading the abstract for "Placebo as a Treatment for Depression" was that Dr. Brown was suggesting something rather odd. Reading on, it became clear that the author was suggesting *openly* offering patients placebo tablets as a treatment for major depression. This seemed patently absurd. Perhaps Dr. Brown jests? However, reading on still further we discover that Dr. Brown is serious about his proposal and has thought carefully about why, to which patients, and in what way he would offer placebo tablets as a first-line treatment for depression. He notes several possible advantages from such a treatment approach, including reduced wear and tear on the body and, perhaps, a decreased propensity to relapse. In the end, a reader who has not thought carefully about the *reasons* for the ever-increasing placebo response in trials of major depression would conclude that Dr. Brown's proposal actually makes some sense.

What are problematic here, however, are the conclusions that Dr. Brown draws from the available literature on the topic of placebo response. Interpreted in another way, this literature leads to different conclusions and different treatment recommendations for the mildly to moderately depressed individual. What follows are: (1) alternative interpretations of the placebo response literature examined in Dr. Brown's review and (2) alternative treatment recommendations based on that reinterpretation.

Dr. Brown is correct in pointing out that there has been a gradual increase in placebo response in depression studies over the past 30 years, with some recent studies showing rates as high as 50%. However, there are a number of other possible explanations for this shift in addition to the lower side-effect profile of the newer antidepressant drugs. First, many of the earliest studies of antidepressant response (which demonstrated some of the lowest placebo response rates in the literature) were carried out in inpatient as opposed to outpatient samples (Hollister et al. 1964; Raskin et al. 1970,1974). With the increasing trend to treat depression on an outpatient basis, more and more studies were conducted in less severely depressed outpatient populations. Since severity of illness has been shown to be among the best predictors of placebo response (Elkin et al. 1989), it seems logical that as more mildly to moderately depressed patients were included in efficacy trials, the placebo response rate would drop. A second important shift over the period in which these studies were conducted has been one in the direction of increasing sophistication with respect to what the pharmacotherapist does in addition to providing medication. In the three decades since the first trials of antidepressants were conducted, clinicians have learned the value of providing the patient with substantial amounts of information about depressive illness including the constituent symptoms of the syndrome, the time course of recovery, and the generally good prognosis. Clinicians have also learned the value of providing a supportive clinical environment, empathy, and optimism. Indeed, this type of good practice in the treatment of depression has been codified in at least two treatment manuals (Fawcett et al. 1987; Frank et al. unpublished). As Dr. Brown correctly concludes, "placebo treated subjects in double-blind clinical trials receive much more than an inert capsule" and, as time has progressed, subjects have received more and more of the nonspecific factors including expectation of improvement, clinician enthusiasm, the opportunity to verbalize distress, the mobilization

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of hope, empathic attention, and relatively unconditional positive regard at a time when they are feeling worthless and self-blaming. Finally, and perhaps most important, these subjects are generally exposed to a theoretical model of depressive illness that frees them from a sense of responsibility for creating their own distress. Particularly in a disorder that is so apparently sensitive to changes in expectations (Brown et al. 1992; Brown 1993), social support (Brown et al. 1986; Andrews and Brown 1988; Henderson and Brown 1988), and empathy (Battegay 1987; Burns and Nolen-Hoksema 1992) one might expect these nonspecific factors therapeutically to exert a substantial effect, especially in the milder and more moderately ill cases.

Dr. Brown states that he is unaware of any studies that have directly compared the effectiveness of pill placebo with passage of time alone. Although there has been no study that made this specific comparison, the Weissman, Prussoff et al. (1979) study, which included a treatment on demand condition, is instructive in this regard. Outcome for patients in this condition (which gave them phone access to a psychiatrist at any point during the 16-week trial on a PRN basis) suggested that this was not as effective in the reduction of depressive symptoms as a regularly scheduled visit with a physician treating the patient with a pill placebo, even in the era prior to the development of manuals for clinical management conditions. This still does not address the question of whether there is something about the ingestion of a pill that adds to the efficacy of the regular contact with a physician. Dr. Brown argues that this effect grows out of the pill's symbolic value, related as it is to both the physician's healing power and the positive experiences that patients may have had in the context of other illnesses that were treated with medication. This raises the question of whether it is actually the pill ingestion that leads to the effect or whether those patients who are adherent to a treatment regime as prescribed by a physician (even if that regime involves nothing more than pill placebo) may not, at the same time, be doing other health-promoting things that enhance the chances of recovery. Not well-studied is the question of whether, once a patient takes the active decision to address his or her depressive illness through a course of treatment, that patient makes other health promoting life changes as well.

Another unresolved issue is the extent to which the results that Dr. Brown quotes are equally true for a full *remission* of depression as compared with a *response* (Frank et al. 1991). It is certainly the case that under conditions of good clinical management one often sees a *response*, usually defined as a 50% reduction in Hamilton Rating Scale score or a two-point change on the CGI, in patients treated with pill placebo. It is less clear that such treatment will bring about a clinical remission (e.g., Hamilton ≤ 6 or 7 for three or four consecutive weeks). Indeed, it seems likely that were a sustained remission required, the differences between active compound and pill placebo would be greatly magnified.

There is an important question raised by the increasing level of placebo response among moderately depressed patients. These studies demonstrate the tremendous value of the nonspecific aspects of treatment when provided by an empathic, sensitive *physician*. Since all of the studies that have demonstrated this increasing placebo response, to my knowledge, have required that the treating clinician be a physician, I think it remains an empirical question whether similar provision of information, hope, empathy, and reassurance by a non-physician mental health professional will have a similarly positive effect.

I would argue that we could consider a modification of Dr. Brown's suggestion: examining the question of whether patients *not provided a pill* (placebo or otherwise) but offered *all of the other aspects of a good clinical management* of depression would not be as likely to respond during the first six weeks of treatment as those given pill placebo. This would permit evaluation of the six-week wait-and-see approach that Dr. Brown suggests without the awkward necessity of openly explaining to patients that they are being given a pill with no known curative properties other than psychological ones.

What should also be considered is whether what might properly be termed very brief (both in terms of session length and number of sessions) psychoeducation/support is an effective treatment for mild to moderate depression, since that is what I believe patients in the placebo arms of most of the recent trials have received. We have been conditioned to think of psychotherapy, even brief psychotherapy, as something that occurs in 45 to 50 minute chunks scheduled at least weekly for at least 12 to 20 weeks. However, much lower "doses" may be effective. In our own work, we have demonstrated the efficacy of monthly 45-minute sessions in preventing recurrence of depression in a highly recurrence-prone population (Frank et al. 1990). Gath and coworkers (1991,1992) working in a primary care setting have demonstrated the efficacy of only four sessions of problem-solving-oriented counseling in relieving acute symptoms of depression. Rather than asking patients to swallow Brown's placebo story, perhaps what we should be doing is refining our techniques for providing education and support to depressed patients and seeing how quickly and efficiently those techniques can bring about remission of milder depressive syndromes.

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