Commentary on "Placebo as a Treatment for Depression"

David L. Dunner, M.D.

The arguments proposed by Dr. Brown for the use of placebo for the initial treatment for depression are in many ways compelling. The response rate during placebo treatment noted in clinical trials of antidepressant pharmacotherapy in depressed outpatients is appreciable. Certainly the increase in placebo responsivity during these clinical trials in recent years is an important observation.

The causes of the increase are less clear. As noted by Dr. Brown, patients with more severe depression and patients with chronic depression have been shown to have a lessened placebo responsivity than patients with more acute depression and less severe depressive illnesses. Dr. Brown suggests that the increase in placebo responsivity may be related to fewer side effects associated with the new drugs and resulting less chance that the investigator will be able to determine drug versus placebo treatment (bias effect). An alternate explanation is that patients with depression are coming into clinical trials at an earlier stage of illness or with less severe illness than what was occurring years ago and therefore may have a greater chance of spontaneous remission over a short period of time. Indeed what seems to be a placebo response may not be a psychological response as much as a reflection of the natural history of depression. Depression tends to be a remitting illness.

Some investigators have attempted to reduce placebo responsivity in their particular clinical trial by devising complicated strategies. These strategies include blinding the time of randomization to active drug (i.e., an extended but variable placebo run in), identification of patients who may be less prone to respond to placebo by measurement of biological characteristics, and selection of patients with higher mean HAM-D scores. Placebo responsivity contributes to the expense of clinical trials and may make demonstration of efficacy of a new antidepressant more difficult. In clinical practice, however, placebo response might be a bonus since the clinician cares less about what the patient responds to than the fact that the patient is better. Thus, if of 100 patients being treated for depression, a third respond to placebo, a third do not respond and another third respond to medication, two-thirds will be responding during treatment (not necessarily because of treatment).

Treatment of depression with placebo in psychiatric practice is in many ways a compelling idea since the placebo response rate in clinical trials is high. However, I would disagree with this proposal on a number of grounds. First of all, most patients with depression are not seen by psychiatrists but instead are seen by primary care physicians. A proposal to have the initial treatment of depression with placebo is in effect a proposal for the use of placebo in primary care. The application of placebo treatment by primary care physicians would likely undermine any confidence they might have in the description of psychiatric illnesses, their course, and treatment outcome. Recognition of depression remains a serious clinical problem in primary care. Advocating use of placebo for treatment of depression by primary care physicians would likely result in a sense of futility on their part regarding psychiatric diagnosis and treating patients with psychiatric disorders.

Secondly, it is not clear that clinicians will be able to easily discern who is in the right group to apply a placebo. The misapplication of placebo to a patient who has suicidal intent might have disastrous results. If only one percent of patients during an acute depressive epi-

From the Department of Psychiatry, University of Washington, Seattle, Washington.

Address correspondence to David L. Dunner, M.D., Department of Psychiatry, University of Washington, 4225 Roosevelt Way NE, Suite 306, Seattle, WA 98105.

Received October 19, 1993; accepted February 2, 1994.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/94/$7.00

sode actually suicide, this rate might not be appreciated by clinicians but yet would be exceedingly high. A clinician cannot accurately predict who is apt to suicide and who is not during a given depression. Suicide during placebo treatment would result in significant medical-legal and ethical problems.

A review of rates of suicide/suicide attempts during clinical trials of depression shows higher rates for suicide, suicide attempts, and worsening suicidal ideation during placebo as compared with active treatment (Mann et al. 1993). Suicides during clinical trials occur in spite of patients being excluded from participating if they are thought to have a significant risk for suicide. The fact that, in spite of screening by knowledgeable investigators, some suicides occur, underscores a significant danger in use of placebo.

In psychiatric (as compared with primary care) practice most depressed patients who are seen are treatment resistant rather than never-treated first episode patients. Such patients are less likely to represent patients who might respond to placebo since they have all the characteristics associated with lack of placebo responsivity. Namely they are usually chronically depressed, usually more severely depressed, and they also have not been responding to prior treatment trials. Thus, there would likely be relatively few patients suitable for placebo treatment in psychiatric practice. Psychiatrists presumably have better knowledge regarding identification of depression, diagnosis of depression, and suitability of patients for placebo than primary care physicians, and yet the largest group who might respond to placebo would be in the primary care setting and not in the usual psychiatric practice.

Frankly, depression should be viewed as a serious medical disorder with considerable morbidity and mortality. Widespread use of placebo for treatment of depression would likely undermine efforts to provide appropriate treatment for patients whose illness is more severe.

In summary, depressed patients respond during clinical trials. Some respond during treatment with active medication and some during treatment with placebo. Patients entered into clinical trials may not represent patients who are actually seen in clinical practice in terms of their prior treatment history, course of illness, and responsivity to any treatment. The response rate to placebo treatment in clinical trials is increasing over time. Whether this increase in placebo response rate represents factors related to selection of mildly ill depressed patients who perhaps will spontaneously remit more likely during a given period of time is not clear.

Applying data regarding placebo outcome during clinical trials to clinical practice and treating depressed patients with placebo has its down sides in that it may not be easy for the primary care physician in particular to recognize who is apt to be more suicidal and might be better treated with an antidepressant. Furthermore, even with active treatment, response time is not immediate but occurs somewhere between two to four weeks after treatment is applied. Further delaying this onset time for patients who actually require treatment would seem to create ethical problems.

REFERENCE

Mann JJ, Goodwin FK, O'Brien CP, Robinson DS (1993): Suicidal behavior and psychotropic medication. Accepted as a consensus statement by the ACNP Council, March 2, 1992, Neuropsychopharmacology 8:177–183