Placebo Responsiveness Does Not Imply that Placebo Is a Sufficient Treatment

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Dr. Brown raises a provocative point regarding the treatment of major depressive disorder, namely, the use of a pill placebo prior to "active" treatment in outpatients. First, let us look at the available evidence from randomized controlled trials (RCTs). Most RCTs use a pill placebo run-in prior to randomization to either active or pill placebo treatments. Subjects with a 20 to 30% drop in symptom severity during this single-blind, placebo run-in are typically excluded from randomization. Following randomization, there is still a significant response to placebo. Using intent-to-treat metaanalyses of several hundred studies, response rates to antidepressant medications ranged from 48 to 65% in outpatients, whereas drug-placebo differences were on the order of 18 to 25% (Depression Guideline Panel 1993). Thus, 25 to 30% of outpatients respond, post-randomization, to pill placebo. The *specific effect* of medication is only 18 to 25%. Response is defined as a Clinical Global Impression (CGI) (Guy 1976) score of 1 or 2, or at least a 50% drop in Hamilton Rating Scale for Depression (HRS-D) (Hamilton 1960) score.

Generalizing these findings to clinical practice is open to question, however, since the post-randomization placebo response rates only apply to patients who did *not* show a "response" to the pill placebo run-in (i.e., a 20 to 30% drop in initial symptom severity). Secondly, many of these placebo-controlled RCTs rely on symptomatic volunteers who may be more placebo-responsive than self-identified patients.

As Dr. Brown notes, those with shorter duration (i.e., less chronic) depressive conditions appear to be more placebo-responsive than those with a more chronic history (either a longer current episode or poor interepisode recovery with recurrent episodes). Thus, chronicity rather than severity may better identify patients who specifically benefit from medication.

These data do suggest that it would be clinically useful to identify depressed patients who do not need medication. The question, however, is how? There are several logical possibilities: (1) provide a pill placebo for several weeks (as Dr. Brown suggests); (2) provide an extended evaluation (several visits over several weeks without a pill placebo); (3) use the available correlates of placebo response to select patients for (1) or (2); and (4) treat everyone but discontinue the medication in all acute phase responders following a brief continuation phase to see who relapses.

Let's consider each option. First, extended (multiple) evaluation visits with pill placebo may subserve the same function as pill placebo treatment. That is, efficacy of pill placebo over and above good clinical care/management with an extended evaluation has not been established. It is not clear whether patients who respond to repeated evaluations *without* a pill placebo are the same or different from those who respond to multiple visits *with* a pill placebo.

Secondly, a number of reports (e.g., Downing and Rickels 1973; Fairchild et al. 1986; Rabkin et al. 1987; Khan et al. 1991) suggest that those who respond initially (over 7 to 10 days) to a pill placebo run-in may be different from those who respond to pill placebo after randomization. Thus, to make a pill placebo a workable option, one would need a 4 to 6 week (or longer) trial on pill placebo. This trial length borders on the unethical since *most* outpatients with major depression *do not respond fully* to pill placebo (Depression Guidelines Panel 1993). Such an extended placebo trial would deny

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treatment to the majority who will not respond to placebo for the sake of a minority who will.

Thirdly, careful follow-up of those who do respond to a multi-week, pill placebo trial is essential, given data that over half of those who respond acutely to placebo will relapse within 12 weeks (Rabkin et al. 1986, 1987). In these cases, patients are still being seen, so *costs have not dramatically dropped*.

Finally, as HMO's and PPO's increase over the next several years, depressed patients seen by psychiatrists will likely already have had several visits and even a medication trial with a nonpsychiatrist. Practically speaking, those who would have responded to the nonspecific effects of treatment will have. Thus, both the ethics and the need for an extended pill placebo trial in such patients is highly questionable.

What about an extended evaluation (over several visits) without a pill placebo to determine whether the persistence of symptoms and disability warrants medication treatment? This practice, similar to an evaluation of milder cases of hypertension, is less complex (i.e., no pill placebo) and is more likely to be reimbursed. In theory, such an extended evaluation might reduce the inappropriate use of medication for patients who do not require it. Who might be most suited for such an extended evaluation? Clearly not those patients who are psychotic, acutely suicidal, very severely or chronically depressed, or those who have failed on recent prior treatment trial(s). One might also exclude patients with concurrent general medical disorders, since their longer term outcome of their depressions, as well as the general medical condition, seems to be poor (Keitner et al. 1991; Depression Guideline Panel 1993). However, an extended evaluation still requires that responders be followed to detect relapses.

The third option, using the correlates of placebo response to select patients for extended evaluation visits (or pill placebo), sounds fairly reasonable. However, several questions remain: (1) how predictive are these correlates (e.g., length of the current episode, etc.) in actual practice? A Receiver Operator Characteristic (ROC) (Hsiao et al. 1989) analysis with available data might provide an estimate. (2) Does it actually save money? As noted above, some placebo responders relapse shortly, which requires that all be followed up. (3) How acceptable is the practice to patients and physicians? There are no data. To recommend such a dramatic change in practice without data on its utility, cost impact, or acceptability, seems premature at present.

The fourth option, early discontinuation, likely already occurs in probably too many patients. The available continuation/maintenance phase trials in which patients are randomized to pill placebo or continue on medication reveal that roughly 30 to 50% relapse while on placebo within 6 to 12 months (e.g., Mindham et al. 1973; Paykel et al. 1976; Coppen et al. 1978; Stein et al. 1980).

Many believe, and some data suggest, that those most likely to relapse following briefer continuation treatment are those with longer current episodes, highly recurrent depressions, or poorer interepisode recovery (i.e., "double" depression) (Keller et al. 1992). Perhaps those with histories suggesting that they are less likely to relapse would be candidates for earlier termination of continuation phase treatment. However, there are no data for how this option actually works in practice, and this approach requires that all patients receive acute phase active medication.

Maybe the best solution for now is to let patients (with the benefit of some education by the practitioner) have a greater voice in whether or not they want to immediately start medication or wait for a few visits to see how persistent and disabling their symptoms are. The less severe, chronic, disabling, or recurrent the illness, the greater the role, I believe, for patient preference. The little data available suggest that for these kinds of patients, there is a lower likelihood that medication has a specific benefit over and above pill placebo. Presently, such patients are not likely to seek care initially from a psychopharmacologist, but rather initially see their primary care physicians. By providing the option of a few additional evaluation visits for such patients, practitioners have time to assess repeatedly symptom severity and associated disability, and to prepare (with educational efforts) such patients for a medication trial, if it is indicated. The dangers are (1) patients who need the medication will drop out during this extended evaluation, (2) practitioners will not specifically assess symptoms, and (3) a partial response to these visits will be judged as "good enough" so as to not require medication. Conversely, education will likely increase adherence in these patients (Depression Guideline Panel 1993) with some consequent cost savings. Once again, however, we lack direct data to evaluate this option in practice.

In summary, 25 to 35% of outpatients with nonpsychiatric, major depression respond to placebo. However, over half of the responders suffer a relapse within three months. Even for those with a good response to placebo after 16 weeks of treatment, 40% relapse within 18 months (Shea et al. 1992). Although it is logical to provide the option of an extended evaluation to a subgroup of patients (the less chronic, severe, recurrent, nonsuicidal), even those who remit require subsequent follow-up, since relapse is common. The specific costs and benefits of this option have not been established empirically.

The essence of the problem seems to be that for some outpatients with major depression (with a less chronic course of illness), the episodes are placebo responsive. Yet over time, the illness may become less and less responsive to nonspecific treatment, not unlike hypertension. The bottom line is that placebo responsiveness does *not* imply that medication is not

needed, though it does make short-term, acute phase efficacy trials more difficult. There are less intrusive options available than providing a pill placebo. These options deserve empirical evaluation before changing practice. In the interim, let's not inflict the research problem of acute phase placebo response on our patients. They're already depressed!

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