See article beginning on page 66.

Questions Raised by the Failure of a Trial of Short-Term Psychodynamic Therapy Versus Pharmacotherapy for Major Depressive Disorder

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In this issue of the *Journal of Clinical Psychiatry,* Barber and colleagues[1] report results of a randomized clinical trial comparing short-term psychodynamic psychotherapy, antidepressant medication, and placebo for the treatment of patients with major depressive disorder (MDD) according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, criteria. Although it was a "failed" study, it was a study of very high quality. The Rating Scale for Quality of Trials of Psychodynamic Psychotherapy (RCT-PQRS) is a measure recently developed by me, Barber, and others[2] to assess the following 6 aspects of psychotherapy study design: (1) description of subjects, (2) definition and delivery of treatment, (3) outcome measures, (4) data analysis, (5) treatment assignment, and (6) overall quality of study. In my assessment, the current study achieved a total score of 36 on the RCT-PQRS, indicating very good quality. Among the exceptionally rigorous aspects were the use of investigators and therapists having a balance of allegiances and the consideration of adverse effects.

The authors of the current report, as well as the editors of the *Journal of Clinical Psychiatry*, are to be commended for publishing a failed study. It seems as though not only the pharmaceutical industry but also the psychotherapy research community have had a "file drawer" problem, ie, studies that do not find a pharmaceutical medication or a psychotherapeutic intervention more efficacious than placebo often go unpublished. This issue has been highlighted by Cuijpers et al[3] in a recent meta-analysis that concluded that the beneficial effects of psychotherapy for depression have been overestimated based on publication bias.

Among the explanations offered by the authors for the failure of the study was the power of the study to detect meaningful differences across treatment groups. This study suffered from a modest sample size and an unusually high rate of attrition (35%). The latter may be an important part of the explanation for the low response and remission rates found in this study compared to most studies of major depression. Patients dropping out early in the course of treatment are less likely to be responders or remitters. Not addressed in the discussion of the current study is chronicity of depression. With the mean duration of current major depression of 40 months, a large proportion or even a majority of the subjects in the study may have had chronic forms of MDD. Our own work[4] and another recent meta-analysis by Cuijpers and colleagues[5] support the notion that psychotherapy treatments have not fared particularly well in chronically depressed populations. However this finding would not explain the failure of the study to differentiate active antidepressant medication from placebo response.

Barber and colleagues recruited through advertisements on public transportation, free news publications, area physicians, and outpatient clinics in Philadelphia. The resulting sample yielded 52% minority and 75% low-income subjects. Minority status and gender had significant and differential effects on outcome, important findings that the authors correctly point out as warranting further study. There has been an increasing and widespread concern in our field over the failure of advances in neuroscience to produce advances in novel therapeutics. There has been a dearth of new "blockbuster" drugs over the past 15 years. Promising compounds have fallen out of development because of failed and negative trials. One concern cited as a possible explanation has been the changing nature of subjects volunteering to participate in clinical trials. Early psychopharmacology and psychotherapy research was conducted on patients recruited as subjects in clinical settings, often inpatient psychiatric units. However, there has been an increasing trend, partly based on the need to speed up drug development and satisfy sponsors, to rely on subjects recruited through advertisement and to utilize for-profit research organizations that often recycle subjects. The "job" of volunteers recruited in this manner is to have the correct diagnosis at entry into a study and to get better, ie, "respond" during the course of the trial, for which they are often amply rewarded with cash. Some feel that these factors affecting subject recruitment have contributed to the documented increase in placebo response rates[6,7] seen in clinical trials of psychiatric disorders. However, it seems unlikely that the current study failed due to this phenomenon, given the low placebo response rate.

Quoting from the discussion of the article, "Only among white women were our findings consistent with expectation, in that active treatments were more effective than placebo."[1(p71)] White women are often the most common participants in RCTs examining the efficacy of pharmacotherapy and psychotherapy for MDD.[1] Hopefully this finding should promote further investigation of personalized psychiatric treatment based on considerations of gender and ethnicity.

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