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MIND OVER MEDICINE: THE INFLUENCE OF EXPECTATIONS ON ANTIDEPRESSANT RESPONSE

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The purpose of this study is to explore how psychological factors may affect research subjects' observed response to experimental treatment

and, more specifically, to investigate whether subjects' knowing they are receiving an active medication affects response rates to antidepressants in clinical trials.

Background

Over a century ago, Freud recognized the potential influence of patients' treatment-related beliefs and expectations on their response to psychoanalysis, and he took pains to differentiate his results from such "suggestion." In the "Preliminary Communication" (Freud and Breuer 1893) he phrased this possible interpretation of observed treatment effects: "the patient expects to be relieved of his sufferings by this procedure, and it is this expectation . . . which is the operative factor" (p. 7). Psychotherapy researchers later picked up on this thread. For example, Jerome Frank (1961) famously discussed how "a patient's expectancy of benefit from treatment in itself may have enduring and profound effects upon his mental state" (p. 36). Later investigators enumerated other nonspecific treatment factors, including chance variation, spontaneous remission, health care provider attention, treatment credibility and rationale, persuasion, clinician allegiance effects, and experimental demand characteristics (Lohr, DeMaio, and McGlynn 2003).

In contrast, the fact that patients in research studies have been informed they are in an experiment and are likely to develop condition-specific expectancies about whether or not they will improve has been largely ignored by pharmacotherapy researchers. This may be explained by the use of pill placebo, which controls for many nonspecific factors in medication trials. Theoretically, a research subject's expectation of therapeutic gain was equivalent between active medication and an identical-appearing pill placebo (Gaudiano and Herbert 2005).

However, the increasing need to study the relative efficacy of medications and psychotherapeutic treatments, including psychoanalysis, now compels all researchers to more rigorously account for nonspecific factors like patient expectations. Recent studies show that the use of medications in psychoanalytic treatments is widespread: a survey studying the use of medication by candidates at the Columbia University Center for Psychoanalytic Training and Research found that 46% of respondents prescribed medication to at least one patient in analysis, and that 29% of patients currently in analysis were taking medications (Roose and Stern 1995). It would be clinically useful to know which patients are better treated with medications or psychotherapy, and which would benefit

most from combined treatment. Studying psychotherapy and medications in a single trial is complicated by the need to differentiate treatment-specific effects from nonspecific factors like patient expectations.

The Treatment for Adolescents with Depression Study (TADS Team 2004) illustrates how nonspecific factors may influence psychotherapy and medication trials. This study randomized adolescents with major depression to cognitive-behavior therapy (CBT) alone, fluoxetine alone, combined CBT and fluoxetine, and pill placebo. The authors found that fluoxetine alone had results not significantly different from those of CBT alone, and that combined treatment was significantly superior to either. The conclusion and apparent clinical recommendation was that "the combination of fluoxetine with CBT produced the greatest improvement in symptoms of MDD" (p. 816). On closer examination, it seems possible that observed differences between these conditions may have resulted from factors other than the specific effects of the treatment. One might expect patients to have different expectations of therapeutic gain in the medication and psychotherapy cells, since patients receiving psychotherapy know they are receiving active treatment, which is not the case for patients receiving a pill. Similarly, subjects in the combined treatment cell are aware they are receiving two active treatments rather than one (psychotherapy) or possibly none (neither medication nor placebo).

The objective of this ongoing study is to determine whether response and remission rates to antidepressants are different when patients do not know whether they are receiving medication (i.e., a placebo controlled trial) and when they know they are receiving active treatment (i.e., an open trial or a comparator trial between two medications). We hypothesize that response and remission rates to medications in open and comparator trials will be significantly higher than those observed in placebo controlled studies. This project has major implications for the design of combined psychotherapy and medication trials, since comparisons between the two treatments may differ based on whether or not the medication was administered in a placebo controlled fashion.

Method

Inclusion/exclusion criteria. Metaanalyses will be performed to compare response and remission rates to antidepressant medications across (1) placebo controlled and active comparator trials and (2) open and placebo controlled treatment in combined psychotherapy and

pharmacotherapy trials. A Medline search employing the search terms *depression, depressive disorder, antidepressant,* and *placebo,* in addition to the specific names of all approved antidepressants, located 4,048 candidate articles. To be included, studies must be randomized controlled trials of an approved antidepressant medication, reported in English, contain a placebo, psychotherapy, or active medication comparison condition, have an outcome measure specific for symptoms of depression (i.e., Hamilton Rating Scale for Depression, Montgomery Asberg Depression Rating Scale, or Beck Depression Inventory), trial duration of at least six weeks, and patient diagnosis of Major Depressive Disorder.

Data analysis. Outcome data from included studies will be input into the Comprehensive Meta-Analysis statistical software package (Biostat). Because most studies do not report the pre-post correlation or standard deviation of the difference in change with treatment, we are unable to use mean scale scores pre-post to make comparisons across experimental parameters without making the problematic assumption that the pre-post correlation is the same in different kinds of trials. As a result, we will examine differences in response and remission rates using an arcsine transformation for proportions, which linearizes the variable formerly bounded by 0 and 1. We will then conduct *t* tests on the transformed variables with study type as the independent variable and calculate effect sizes for the comparisons.

Results

Our group at Columbia has completed preliminary work involving metaanalyses of randomized controlled trials comparing antidepressant medications to a placebo or active comparator in geriatric outpatients with Major Depressive Disorder (Sneed et al. 2006). In placebo controlled trials, the medication response rate was 48% and the remission rate 33%, compared to a response rate of 62% and remission rate of 43% in the comparator trials ($p < .05$). The effect size for the comparison of response rate to medications in the comparator and placebo controlled trials was large (Cohen's $d = 1.2$).

Discussion

If response and remission rates to antidepressants are significantly different under double-blind conditions and when patients know they are receiving active treatment, then one must interpret studies of psychotherapy

versus medication differently depending on whether a pill placebo condition has been included. Disparate study designs may have different psychological effects on research subjects, thereby accounting for how the same medication may evoke different responses depending on the experimental context. While psychotherapy researchers have made them a focus of inquiry, such intrapsychic factors have long been neglected by pharmacotherapy researchers and may confound treatment comparisons made between studies and between cells within a single study. Investigators interested in comparing the effects of medications across different experimental settings and medications to psychotherapy may benefit from closer attention to the psychological effects of study design.

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