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Patients' treatment expectancies in clinical trials of antidepressants versus psychotherapy for depression: a study using hypothetical vignettes

Brandon A. Gaudiano[a,b,*], **Jessica A. Hughes**[c], and **Ivan W. Miller**[a,b]
[a]Alpert Medical School of Brown University, Providence, RI, USA
[b]*Butler Hospital, Providence, RI, USA*
[c]*University of Tennessee, Knoxville, TN, USA*

Abstract

Previous research on patients' expectancies for improvement in clinical trials typically has been conducted after patients have already agreed to participate in a study. Depressed patients (n = 55) read 3 vignettes describing hypothetical clinical trials of antidepressant vs pill placebo, antidepressant vs antidepressant, and psychotherapy vs psychotherapy. Patients reported greater overall acceptability for psychotherapy over antidepressants. Patients had significantly greater expectancies for symptom reduction in either active comparator (medication or psychotherapy) compared with the placebo-controlled design. They also reported greater anticipated improvement and willingness to participate in the psychotherapy trial compared with either medication trial design. Patients' differential expectancies based on study design could lead to different patient populations being selected for these studies and influence clinical improvement.

The placebo effect in clinical trials for depression is an important issue that requires further study. Research shows that a substantial proportion of response observed in clinical trials of antidepressant medications is replicated in the pill placebo conditions [1,2]. Research on psychotherapy for depression also has shown that a variety of interventions that appear different nevertheless produce similar outcomes, suggesting that the unique features of these therapies are unlikely to be responsible for the majority of the improvement observed [3]. Better understanding the placebo response in clinical trials may help to improve future studies of depressed patients and thus lead to promising new therapies [4].

Patients' expectancies for improvement are important factors related to the placebo effect in clinical trials of adults with depression [5,6]. Numerous studies show that treatment expectancies are predictors of both pharmacotherapy and psychotherapy response in depression. For example, findings from the Treatment of Depression Collaborative Research Program study indicated that less positive treatment expectancies predicted poorer response across both the psychotherapy and pharmacotherapy conditions [7]. In another antidepressant study, 90% of depressed patients who reported high expectancies for improvement at the start of the study responded to treatment, compared with only 33% of those who expected the medications to be "somewhat effective" [8]. Expectancies likely exert their effects on outcome through indirect pathways. For example, Gaudiano and Miller [9] showed that the relationship between bipolar patients' initial expectancies for

* Corresponding author. Butler Hospital, Psychosocial Research Program, 345 Blackstone Boulevard, Providence, RI, USA. Tel.: +1 401 455 6457. Brandon_Gaudiano@brown.edu (B.A. Gaudiano)..

improvement and time remaining in treatment was mediated by the therapeutic alliance with their psychiatrist.

Expectancies are influenced by a number of variables, although little past research has directly assessed the study design itself as a significant factor. Intriguing evidence comes from meta-analyses showing that response rates in antidepressant trials are higher in active comparator studies (medication vs medication) compared with placebo-controlled studies (medication vs placebo) [10,11]. In addition, Zimmerman et al [12] showed that depressed patients participating in an antidepressant trial with an extension design (ie, treatment responders are continued on their initially assigned condition, either placebo or drug) showed lower relapse rates compared with patients in placebo substitution designs (ie, treatment responders are randomly assigned to either antidepressant or placebo). One explanation is that patients who perceive a greater likelihood of being assigned to a placebo condition have poorer outcomes due to diminished expectancies for improvement based on the study design. In a recent study [13], patients' expectancies for improvement were measured before and after randomization to either a placebo-controlled (placebo vs escitalopram) or comparator group (citalopram vs escitalopram) antidepressant study. As expected, group assignment predicted change in the magnitude of expected improvement, indicating that patients who knew that they may receive a placebo expected less improvement.

Depressed patients have documented preferences for certain treatments and the overall acceptability of various treatments also differs among patients. Although the acceptability of psychiatric medications has increased over recent years [14], surveys still indicate greater acceptability for counseling or psychotherapy over medications [15]. Furthermore, van Schaik et al [16] conducted a meta-analysis of patient's preferences/acceptability for treatments of depression and showed that patients preferred psychotherapy or counseling over antidepressants from 5% to 66%. Preferences for psychotherapy were predicted by female sex, former experience with psychotherapy, and middle-class status. Prior experience with psychotropic drugs and older age were predictors of antidepressant preference. Similar to the effects of treatment expectancies, recent research suggests that patients' treatment preferences influence their engagement and treatment adherence (eg, attendance, therapeutic alliance), which then can affect clinical improvement [17,18].

Recently, Rutherford et al [10] conducted a survey to assess the effect of study design on expectancies for improvement. In the study, 77 undergraduate students read hypothetical vignettes describing either a drug comparator (ie, drug vs drug) trial or a placebo-controlled trial for a rash treatment. Respondents rated their expectancies for improvement significantly higher in the active comparator trial. However, it is unclear if these effects apply to psychiatric patients and across different types of treatment. In the current study, depressed patients rated expectancies for improvement after reading three vignettes describing hypothetical clinical trials: antidepressant versus placebo, antidepressant versus antidepressant, and psychotherapy versus psychotherapy. First, we hypothesized that patients would rate expectancies for improvement higher in the active comparator medication trial compared with the placebo-controlled trial. Second, we hypothesized that patients would report higher expectancies for improvement in the psychotherapy trial versus either of the medication studies.

1. Method

1.1. Sample

Participants were 55 patients treated at inpatient or partial programs at a free-standing psychiatric hospital in the United States. A potential advantage of using hospitalized patients

is that they tend to have previous experience with depression treatment, which is useful for examining the effects of treatment history. In addition, many patients who enroll in clinical trials are not treatment naïve, and this could affect expectancies. In addition, hospitalized patients have a similar level of depression, which better controls for severity of illness. Inclusion criteria were (1) chart diagnosis of a depressive disorder, including major depressive disorder, dysthymia, or depression not otherwise specified; (2) age above 18 years; and (3) ability to speak and read English sufficiently to complete study procedures. Exclusion criteria were (1) the following chart diagnoses: bipolar disorder, psychotic disorder (eg, schizophrenia), mental retardation, or a cognitive disorder (eg, dementia), or (2) involuntary hospitalization. Mean age of the sample was 40.1 (SD, 13.7) and mean years of education completed was 13.0 years (SD, 3.2). A total of 56.4% of the sample were women, 92.2% were white, 3.6% were Hispanic, 29.6% were currently married, 46.6% earned an annual income of less than $30,000, and 66.6% identified themselves as Christian. Their mean Beck Depression Inventory II score was 29.4 (SD = 14.2), which is in the severe range. The study participation rate (consented/approached) was 75.6%.

1.2. Study vignettes

Participants read 3 brief vignettes describing the following designs of hypothetical clinical trials of novel treatments for depression: antidepressant medication vs pill placebo, antidepressant medication A vs B, and psychotherapy A vs B (see Table 1). Consistent with the previous study by Rutherford et al [10], we chose a vignette presentation as it would have been impractical for participants to read three separate, full consent forms. Given that our aim was to study the effects of study design in general, we did not specify specific medications or psychotherapies. In addition to study design, the vignettes also described other standard information regarding participation in the clinical trial that is commonly presented in consent forms. The following characteristics were held constant across the vignettes: (1) randomization, (2) blinding, (3) study duration, (4) number of treatment visits, (5) treatment provision free of cost, and (6) debriefing after study completion. In other words, all study elements were the same other than the description of the study treatment conditions. Elements of the trial were explained using simple language as is common in patient consent forms. Vignettes were comparable in length, reading level, and wording. We did not include an “active” psychotherapy vs “placebo” psychotherapy study design because it would have been difficult to describe the treatments in a way that would permit blinding to treatment assignment, which is an important methodological feature of these trials related to expectancies. Furthermore, the concept of “placebo” psychotherapy is considered to be an inaccurate label and not directly comparable to a pill placebo condition [19].

1.3. Measures

The Credibility and Expectancy Scale [20] was used to assess respondent's treatment expectancies for each study using the following questions: (1) how logical/credible the study seemed to the person (1 = “not at all logical” to 10 = “very logical”), (2) how successful study participation was anticipated to be for reducing symptoms (1 = “not at all useful” to 10 = “very useful”), and (3) the percentage of symptom improvement the person expected to achieve by the end of study (0% to 100%). The Credibility and Expectancy Scale has been shown to be reliable and valid for predicting outcomes in clinical trials [20]. We included an additional question about the patient's degree of willingness to participate in the trial (1 = “definitely not willing to participate” to 10 = “definitely willing to participate”). Consistent with the previous study by Rutherford et al [10], we analyzed each question separately because they assess different constructs.

Depression severity was assessed according to the Beck Depression Inventory II (BDI-II) [21]. The psychometric properties of the measure are well established [22]. We also asked

patients to rate the acceptability of antidepressants and psychotherapy for depression and their current use of these treatments. Based on the Treatment Options Interview [23], respondents rated the degree to which they would be willing to use (or continue to use, if already using) antidepressants or individual psychotherapy: 1 = "definitely would not" to 7 = "definitely would." Respondents also were asked whether or not they were currently receiving antidepressants or psychotherapy for depression.

1.4. Procedure

All procedures were approved by the local Institutional Review Board. Medical charts were screened by a research assistant (RA) to identify patients meeting study inclusion/exclusion criteria. After identifying a potential participant, the RA asked the treating physician for his/her permission to approach the patient about study participation. If permission was granted, the RA provided a brief explanation of the study. The RA reviewed the complete consent form with the patient and answered any questions. After signing the consent form, the patient was given an assessment packet containing the three vignettes and additional questionnaires to complete. The three vignettes were presented in counter-balanced fashion (eg, ABC, ACB, BAC, BCA, CAB, CBA) to reduce systematic bias in ratings that can be produced by having participants always read one type of vignette before another. The RA collected the completed assessment packet from the patient. Patients were paid US $15 for completing the study.

1.5. Statistical analyses

All tests were 2 tailed and α was set at .05 with effect sizes reported according to Cohen *d* statistic. Within-subjects analyses of variance (ANOVAs) were conducted to identify overall differences among vignettes to reduce Type I error. Significant ANOVAs were followed up with post hoc comparisons between vignettes. Follow-up tests were conducted and interpreted after applying the modified Bonferroni procedure by Holm [24] to examine differences between study vignettes on each expectancy question separately.

2. Results

First, we analyzed treatment use and acceptability ratings. Patients reported similar rates of current (pre-admission) psychotherapy (79.6%) or medication (87.8%) use, which were not significantly different according to the McNemar test for correlated proportions ($P = .34$). Furthermore, we compared patients' ratings of the acceptability of antidepressants versus psychotherapy. Although both were rated highly overall, within-samples *t* tests showed that patients reported a significantly higher acceptability for psychotherapy ($M = 6.62$; SD, 0.91) relative to antidepressants ($M = 6.02$; SD, 1.68), $t = 2.64$, $df = 54$, $P = .01$).

Next, we compared expectancy questions across vignettes; ANOVAs were significant for all expectancies questions across study designs, including how logical it seemed to patients to participate in the study (F = 21.32; $df = 2,53$; $P < .001$), how much success in terms of symptom reduction that patients expected based on study participation (F = 15.96; $df = 2,53$; $P < .001$), the percentage of improvement patients expected by the end of the study (F = 11.13; $df = 2,49$; $P < .001$), and patients' degree of willingness to participate in the study (F = 19.63; $df = 2,53$; $P < .001$).

See Table 2 for details. For the question assessing expected success for reducing symptoms, patients reported significantly greater expectancies in the active comparator drug study relative to the placebo-controlled drug study ($P < .05$, $d = .24$). No other differences were found between the active comparator drug study and placebo-controlled drug study. Furthermore, patients rated their expectancies on all other expectancy questions significantly

higher in the active comparator psychotherapy study relative to either the active comparator drug study ($P < .01$, $d = .51$-$.70$) or placebo-controlled drug study ($P < .001$, $d = .61$-$.76$).

We reran analyses controlling depression severity, current treatment use (antidepressant and psychotherapy), and treatment acceptability ratings, as these variables may have influenced patients' expectancies about the different studies. Although the effects were decreased in general, comparisons reported above remained significant except for one after controlling for the covariates. For the item assessing anticipated success for reducing symptoms, the difference between the active drug comparator trial and the placebo-controlled drug trial was no longer significant ($P = .89$).

3. Discussion

We found support for the hypothesis that patients have significantly greater expectancies for improvement in active comparator versus placebo-controlled drug trials. However, the difference in expected improvement found between the active versus placebo-controlled drug trial was no longer significant after controlling for current treatment use and treatment acceptability. This suggests that treatment history and acceptability can have important effects on expectancy for improvement in clinical trials. In addition, we found that depressed patients reported a generally higher treatment acceptability for psychotherapy relative to antidepressant medications, which was documented for the first time to our knowledge in a hospitalized sample. Furthermore, we demonstrated that expectancies for improvement were higher in psychotherapy studies relative to antidepressant trials. Related to this, patients also expressed a greater willingness to participate in a psychotherapy study compared with drug studies for depression. We did not include a vignette in which psychotherapy and medications were compared within the same study design because participants would not have been blinded to treatment as in the other vignettes tested, which could have confounded expectancy differences.

Differences in treatment acceptability and expectancies for improvement could lead to different patient populations being treated in clinical trials of different treatments. Researchers have previously noted that patients enrolled in antidepressant trials differ in clinically important ways from patients in routine practice. For example, Zimmerman et al [25] compared depressed patients who would or would not qualify for enrollment in a typical antidepressant study. Results showed that excluded patients have more comorbidity, suicidality, chronicity, previous episodes, functional impairment, and personality pathology. In addition to these factors, the current study demonstrated a lower willingness of depressed patients in routine treatment settings to participate in medication studies and lower expectancies for improvement compared with psychotherapy. These differences may help to explain the efficacy-effectiveness gap for antidepressants. Results from the recent STAR*D study showed that antidepressant efficacy in routine clinical practice was lower than in clinical trials [26]. Research suggests that generalizability concerns may be similar but less pronounced in psychotherapy trials. Stirman et al [27] assessed the characteristics of community outpatients and found that 80% of those with commonly studied diagnoses could qualify for a psychotherapy trial.

Patients' preference and expectancies for improvement in psychotherapy studies become more understandable when considered in the context of the outcomes depressed patients say they want to achieve from treatment. Zimmerman et al [28] surveyed 535 depressed outpatients and the three items self-rated as most desirable for determining remission were positive mental health characteristics (eg, optimism, self-confidence), a return to one's normal self, and a return to normal functioning. Uebelacker et al [29] interviewed depressed, hospitalized patients, and their most commonly self-expressed treatment goals were related

to improving their interpersonal relationships. These goals appear more amenable to and match better with treatments such as psychotherapy compared with medications. It follows that matching patients based on their preferences could lead to better outcomes. As an illustration of this, Lin et al [30] showed that matching patients to their preferred treatment (medication or psychotherapy) led to more rapid symptomatic improvement in depressed primary care patients. Another recent study in primary care demonstrated a moderate effect size advantage for patients matched compared with mismatched based on their treatment preferences [31].

Our results support the rationale for using alternative clinical trial designs that attempt to incorporate patient preferences. In the Partially Randomized Preference Trial [32], patients are first asked if they are willing to participate in randomization to the treatments. Those answering yes are then randomized as usual, whereas those who are not willing to be randomized are assigned to treatments based on their preferences. Alternately, in the Doubly Randomized Preference Trial [33] patients are first randomized to a choice condition versus a randomization condition. Patients randomized to the choice condition are assigned to treatments based on their preferences, whereas patients randomized to the other condition are assigned to treatments based on random assignment. Although there are potential methodological and statistical disadvantages to using these designs [34,35], incorporating preferences into clinical trials may improve the external validity of studies and more accurately reflect the effectiveness of treatments when they are implemented in the community [36]. Thus far, trials conducted in depressed samples using these designs have produced mixed results [18].

Limitations of the current study also should be considered. All patients were hospitalized at the time of the study and generalizability to outpatient samples is unclear; although our results are consistent with those found in non-hospitalized samples [5,13] suggesting that the effects are unlikely to be explained by setting alone. In addition, patients may have been in the hospital due to outpatient treatment failures. Nevertheless, patients reported similar rates of psychotherapy and antidepressant use and most findings remained significant after controlling for current treatment in most cases. We did not ask patients to rate the perceived helpfulness of the treatments they were currently receiving, although we would expect ratings of acceptability to measure a similar construct. It also is important to note that we assessed treatment acceptability and not preference per se, although there is considerable overlap between these constructs. Although some may argue that the use of vignettes lacks external validity, we took great care to equate all other study characteristics across vignettes, so differences can be attributed to the treatments themselves. The use of vignettes is the only practical way to study this topic in lieu of conducting costly, large-scale studies in which patients are randomized to different clinical trial designs.

We used a treatment-seeking sample and many patients choose to enroll in drug or psychotherapy studies even though they are currently in treatment or have previously received treatment for depression. Although many patients enrolled in community treatments are routinely recruited into clinical trials, we did not include information on the potential need for treatment discontinuation in the vignettes. As the aim of our study was to examine expectancies related to the treatment conditions specifically, we chose to describe only the most important and central aspects of the study design. Furthermore, given that the studies were described as hypothetical only, we wanted to present the vignettes in the most generalizable way. It also is important to note that if we had included information about treatment discontinuation, this would have been controlled across vignettes and thus would not explain differences.

In addition, we employed a within-subject design, whereas Rutherford et al [10] used a between-subjects design. It is unclear whether patients' ratings were affected by reading all three types of trial designs, although vignettes were presented in counterbalanced fashion to minimize order effects. In addition, Rutherford et al [10] reported a large effect size expectancy difference between placebo versus active comparator drug designs. The difference in expectancy for improvement found in the current study was small in magnitude and no longer significant when controlling for current treatment as we would expect this variable to affect expectancies. It is possible that the use of the non-clinical, more highly educated student sample used by Rutherford et al [10] resulted in the finding of larger expectancy differences due to participants' better understanding of the nature of the placebo condition.

Given these potential limitations and the need for further study, the next step would be to test expectancies for improvement and treatment preferences in studies of combined treatments (eg, antidepressants plus psychotherapy versus antidepressant alone) and in studies with designs directly comparing psychotherapy versus antidepressants, as they also may differ. In addition, it will be important to conduct similar studies in outpatient treatments samples and in non-treatment seeking samples to examine effects in individuals with a wider range of depression severity and potentially different treatment experiences and histories.

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Table 1

Study vignette for placebo-controlled drug study

Imagine you have been asked to be in a depression treatment study.
If you agree, you will be randomly chosen to get Drug A or placebo. A placebo is an inactive substance that does not contain medicine, like a sugar pill. We will test whether Drug X is better than placebo for treating depression.
You will have a 50-50 chance (like a coin flip) of getting either Drug X or placebo, but not both.
Both treatments may have certain risks (such as side effects) and benefits.
You will not be told which treatment you are receiving while in the study.
The study will last for 12 weeks, and you will have weekly meetings with a doctor.
The treatments will be provided to you free of charge.
At the end of the study, you will be told which treatment you received.

The other study vignettes described different conditions (drug A vs drug B or psychotherapy A vs psychotherapy B) but otherwise were identical in wording to the above (excluding the statement defining a placebo).

Table 2

Patients' treatment expectancies based on study design

Expectancy questions	Drug vs placebo	Drug vs drug	Psychotherapy vs psychotherapy
1. How logical does it seem to you to participate in the study?	5.24(3.01)[a]	5.44(2.91)[a]	7.31(2.42)[b]
2. How successful do you think participating in the study would be for reducing your depression?	4.15(2.21)[a]	4.72(2.57)[b]	6.00(2.16)[c]
3. By the end of the study, how much improvement in your depression do you think would occur?	35.20(27.43)[a]	37.60(28.97)[a]	50.80(22.93)[b]
4. How willing would you be to participate in the study if asked?	5.00(3.27)[a]	5.11(3.12)[a]	7.09(2.62)[b]

Means in the same row that *do not* share superscripts (eg, a vs b) differ at $P < .05$.