The Role of Patient Expectancy in Placebo and Nocebo Effects in Antidepressant Trials

Bret R. Rutherford, MD; Melanie M. Wall, PhD; Andrew Glass, MS, MA; and Jonathan W. Stewart, MD

ABSTRACT

Objective: To determine whether patient expectancy plays a role in observed placebo and nocebo effects in 2 clinical trials.

Method: Data were reanalyzed from 2 fluoxetine-discontinuation studies conducted from March 1990 to September 1992 and from May 1997 to December 2002. The 673 outpatients included were aged 18–65 years with *DSM-III-R* major depressive disorder (MDD), responded to 12-week duration open treatment, and were randomized to continued fluoxetine or placebo for an additional year. Participants in 1 of the included studies received a fixed dose of fluoxetine 20 mg daily, while the second study utilized flexible fluoxetine doses up to 60 mg daily. Mixed effects longitudinal models determined whether the possible randomization to placebo at 12 weeks resulted in significant depressive symptom worsening across treatments. Correlations were computed between early symptom change (weeks 1–3 of open treatment) and postrandomization symptom change (weeks 13–16 following randomization).

Results: Participants continuing to receive fluoxetine and those switched to placebo had significantly higher mean Hamilton Depression Rating Scale (HDRS) scores immediately postrandomization compared to the final weeks of open treatment ($P < .001$ for both fluoxetine- and placebo-treated patients). In both studies, early HDRS change was significantly correlated with postrandomization HDRS change for patients receiving fluoxetine ($r = -0.46$, $P < .001$) as well as placebo ($r = -0.48$, $P < .001$).

Conclusions: The possibility of receiving placebo following 12 weeks of open fluoxetine was associated with significant symptom worsening in 2 large fluoxetine discontinuation studies. Worsening depression scores following randomization were significantly associated with the degree of improvement participants experienced during weeks 1–3 of open treatment. These results suggest that treatment changes influence patients' expectations of improvement, which, in turn, affect their depressive symptoms.

J Clin Psychiatry 2014;75(10):1040–1046

Submitted: *September 16, 2013; accepted December 31, 2013.*
Online ahead of print: *June 10, 2014 (doi:10.4088/JCP.13m08797).*
Corresponding author: *Bret R. Rutherford, MD, Columbia University College of Physicians and Surgeons, Department of Psychiatry, New York State Psychiatric Institute, 1051 Riverside Drive, Box 98, New York, NY 10032 (brr8@columbia.edu).*

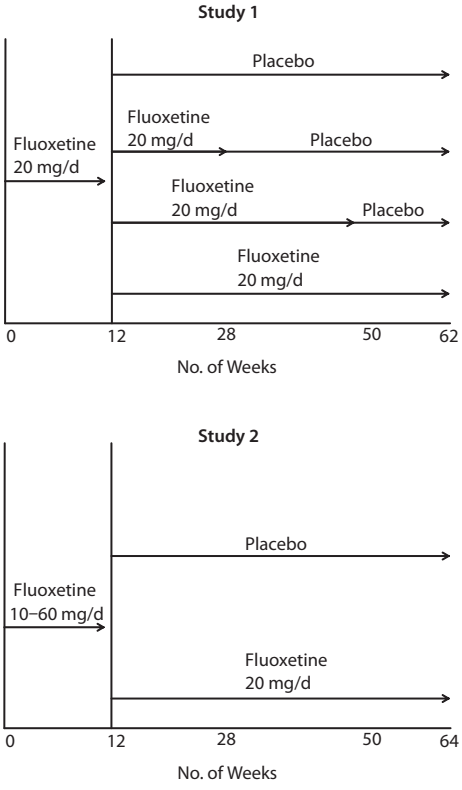
The probability of receiving placebo as opposed to active medication influences treatment outcome in antidepressant clinical trials.[1–4] Medication response rates are lowest in drug-placebo trials (51.7% response) and increase in drug-drug-placebo trials (57.7% response) and drug-drug trials (65.4% response).[5] Moreover, antidepressant trials comprising a greater number of active treatment arms have increased placebo response and decreased drug-placebo differences.[6,7]

Such marked differences depending on trial design (ie, placebo-controlled vs active comparator) imply that a medication's pharmacologic effect is only 1 contributor to symptom change. Nonpharmacologic mechanisms also contribute to outcome, including spontaneous improvement and worsening, a patient's expectation of benefit from the treatment, therapeutic effects of the treatment situation, positive life events, and sources of measurement error and bias. The relative contributions of these nonpharmacologic factors may change across different treatment settings, resulting in different observed medication responses. While the pharmacologic effects of a medication can be estimated from the differential response between drug and placebo, elucidating the role of various sources of "placebo" effects is more complicated because studies have not been designed to isolate them.

Since clinical trial participants become aware of the probability of their receiving active medication versus placebo during the informed consent discussion, it has been suggested that patient expectancy may in some cases explain the relationship between study design and antidepressant response.[8,9] The induction of positive expectancies about treatment outcome has been shown to significantly improve antidepressant response[10] and is hypothesized to be a primary mechanism of placebo effects in clinical trials.[11] Conversely, information that generates negative expectancies may lead to worsening (ie, nocebo effects).[12] Informing patients about possible side effects of drug administration has been shown to increase the occurrence of these side effects,[13,14] and diminished medication effects are observed when delivered by neutral clinicians compared to positive clinicians.[15]

To differentiate the contribution of patient expectancy from other factors that may influence antidepressant response, we reanalyzed data from 2 large, multicenter discontinuation trials treating participants having major depressive disorder (MDD) with fluoxetine for 12 weeks followed by randomized continuation treatment with either fluoxetine or placebo.[16,17] Reasoning that changes in depressive symptoms caused by patient expectancy would occur in the initial few weeks following a change in treatment,[18] we evaluated symptom change (1) at the initiation of open fluoxetine treatment and (2) at possible randomization to placebo at 12 weeks. We hypothesized that due to a decrease in patient expectancy, depression scores would significantly worsen in the 4 weeks following randomization for patients receiving continued fluoxetine as well

Figure 1. Design of 2 Fluoxetine Discontinuation Studies Investigating Depression Relapse in Subjects After 12 Weeks of Open Treatment



as those switched to placebo. Furthermore, we predicted that individuals who experienced substantial improvement during the first 3 weeks of open treatment with fluoxetine would be the same individuals to experience significant worsening following the 12 week randomization time point (ie, from weeks 13–16). We complemented our investigation of these primary hypotheses with follow-up analyses aimed at ruling out spontaneous improvement/worsening, positive life events, and rater bias as explanations of the observed patterns of symptom change.

METHOD

Sources of Data

Data from 2 clinical trials examining the efficacy of fluoxetine in preventing depression relapse during continuation/maintenance treatment were sequentially analyzed. Study 1 initially treated MDD patients with open fluoxetine 20 mg/d for 12 weeks, then randomized remitters to continued fluoxetine treatment versus placebo substitution at 1 of 3 time points (Figure 1).[16] The study was conducted from March 1990 to September 1992. Study 2 was designed as a replication study and utilized a similar design, with the primary exceptions that remitters to open-label fluoxetine were randomized 1:1 to continued fluoxetine or placebo (see Figure 1) and medication dose was titrated to 60 mg/d.[17] This study was conducted from May 1997 to December 2002. See previous articles for full details.[16,17,19–21]

Clinical Points

- The information provided to patients at the outset of treatment may influence their response to antidepressants.
- Patients' expectations of improvement appear to influence not only placebo response but also medication response.
- The most clinically effective treatment strategy may be to present active medication in a manner that enhances patients' expectations of improvement.

Subjects

Study 1 enrolled outpatients aged 18–65 years who met *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised (*DSM-III-R*)[22] criteria for MDD for at least the 1 month preceding study participation. Subjects were also required to have a modified 17-item Hamilton Depression Rating Scale (mHDRS)[23] score ≥ 16 (described below). Exclusion criteria were acute, severe, or unstable medical problems; pregnancy or lactation; serious suicide risk; history of psychosis, mania, or organic mental disorder; substance use disorder within the past year; previous fluoxetine treatment for ≥ 3 months in a previous episode; or nonresponse to 8 weeks of fluoxetine treatment at a dose ≥ 20 mg during the current episode. Study 2 used similar selection criteria, except no minimum mHDRS score was required for study entry and subjects were excluded for substance use disorder within the previous 6 months (rather than 1 year).

Study Assessments

A modified form of the HDRS was used in which hypersomnia and hyperphagia were substituted for insomnia, anorexia, and weight loss items in patients with reverse neurovegetative symptoms. Subjects in whom the mHDRS was used for eligibility continued to use the reverse vegetative items throughout the study, whereas patients who presented with insomnia, anorexia, and weight loss used the standard neurovegetative items for the duration of the study.

Open-Label Treatment With Fluoxetine

In study 1, subjects whose depression persisted (ie, mHDRS remained ≥ 16) following a no-treatment observation week began 12 weeks of open-label fluoxetine 20 mg/d. *Remission* at the end of the open-treatment period was defined as 3 consecutive weeks with both an mHDRS ≤ 7 and failure to meet *DSM-III-R* criteria for MDD. Open treatment was similar in study 2, with the exception that target fluoxetine doses were 10 mg/d for the first week, 20 mg/d for weeks 2–4, 40 mg/d for weeks 5–8, and 60 mg/d for weeks 9–12 (increases occurring only if the patient had not remitted and tolerated the medication well). In study 2, sustained remission was not required for patients to be randomized; instead, *responders*, defined as a Clinical Global Impressions-Severity of Illness scale[24] score of 1 or 2 at 12 weeks, moved into the continuation phase of the study.

Randomization and Continuation Treatment

In study 1, subjects whose depression met remission criteria after 12 weeks of open-label treatment were randomly assigned to 1 of 4 groups: (1) placebo for 50 weeks; (2) continued fluoxetine for 14 weeks, followed by placebo for 36 weeks; (3) continued fluoxetine for 38 weeks, followed by placebo for 12 weeks; or (4) continued fluoxetine for 50 weeks (see Figure 1). In study 2, responders to open-label fluoxetine were randomized to 52 weeks of treatment with placebo or continued fluoxetine at the dose to which they had remitted (see Figure 1). Subjects who met criteria for MDD for 2 consecutive weeks or who had an mHDRS ≥ 14 for 3 consecutive weeks were considered to have relapsed and were removed from the study. Fluoxetine discontinuation was associated with a significantly increased risk of depression relapse at endpoint in both trials (study 1: hazard ratio for relapse = 2.22; 95% CI, 1.62–3.05; study 2: hazard ratio for relapse = 1.73; 95% CI, 1.20–2.51). In study 1, 42% of fluoxetine-treated patients compared to 19% of placebo-treated patients remained in remission by 62-week follow-up, while in study 2, 54.1% of participants in the fluoxetine group and 28.0% of those in the placebo group remained well at 52-week follow-up.

Data Analysis

Since the primary goals of this analysis were to investigate postrandomization changes in mHDRS scores and the correlation of these scores with early improvement, analyses were focused on data from the open-label treatment period (weeks 1–12) and the first 4 weeks following randomization (weeks 13–16). Analyses for study 1 and study 2 were identical.

To determine whether mHDRS scores significantly increased following randomization, a longitudinal mixed effects model was fit to the repeated mHDRS scores over time within patients. This model included a categorical week indicator, a group indicator that was nonzero in weeks 13–16 for those individuals randomized to placebo, and an interaction of group with weeks 13–16 to allow for different mean values postrandomization in the 2 groups.[25] A random intercept was included to account for correlation within individuals over time, and estimates were obtained by restricted maximum likelihood. Weekly estimated mean values and associated 95% confidence intervals (CIs) were calculated to facilitate interpretation.

Next, to test whether early improvement during open-label treatment with fluoxetine (ie, mHDRS decreases during weeks 1–3) predicts significant symptom worsening following randomization, we fit a piecewise linear longitudinal mixed effects model to the repeated mHDRS scores, with change points allowed at weeks 3 and 10 as well as random intercepts and slopes for individuals. Week 10 rather than week 12 was selected to more conservatively identify change following randomization, since mHDRS scores at weeks 11 and 12 may have been subject to rater bias (ie, the desire to have patients meet remission criteria and be randomized at week 12). This modeling produced individualized linear trajectories (slopes) between each knot based on best linear unbiased predictors.[26] "Early mHDRS change" (a subject's modeled mHDRS at week 3 minus mHDRS modeled at week 0) was tested for correlation with "postrandomization mHDRS change" (a subject's modeled mHDRS at week 16 minus modeled mHDRS at week 10). Additionally, the percentage variability in postrandomization mHDRS change explained by early mHDRS change and randomization group, respectively, was assessed by using regression. Finally, mean trajectories associated with individuals demonstrating very high and very low changes in their mHDRS postrandomization were estimated.

Additional Analyses

In contrast to patient expectancy, fluctuation in a patient's natural course of illness is likely to occur randomly throughout treatment. To test whether some individuals randomly improved or worsened (as opposed to change being linked specifically to study events), we identified subjects having low mHDRS (≤ 7) in weeks 4–6 and examined their mean mHDRS scores in weeks 8–10. A finding of no change during this interval in this highly selected group would suggest postrandomization changes are indeed specific to the randomization time point and not due to random fluctuation.

To determine whether early improvement and post-randomization symptom increase might be caused by rater bias (ie, baseline score inflation or prerandomization score deflation), we inspected the distributions of mHDRS scores of included subjects in each study at baseline and just prior to the week 12 randomization. Peaks in the distributions at mHDRS score thresholds would indicate possible rater bias, while a normal distribution of scores would make rater bias less likely.

RESULTS

Characteristics of Randomized Patients and Response to Treatment

In study 1, 395 patients remitted during open-label fluoxetine (51.0% of subjects treated openly) and were randomized in the continuation phase (299 received fluoxetine, while 96 were switched to placebo). In study 2, 278 of the 570 subjects (48.7%) who began open-label treatment were randomized (139 to continued fluoxetine and 139 to placebo). Clinical and demographic characteristics of randomized subjects are presented in Table 1. Subjects continued on fluoxetine treatment did not differ from those randomized to placebo on any of the characteristics.

Postrandomization mHDRS Change

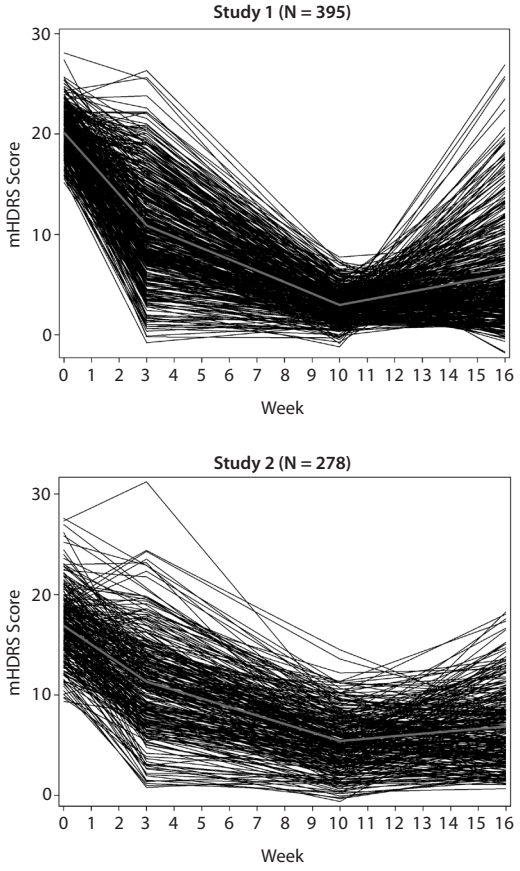
Individual trajectories of mHDRS scores over the first 16 weeks of study 1 and study 2 are shown in Figure 2. In both studies, individuals remaining on fluoxetine had significantly higher mean mHDRS scores postrandomization (ie, weeks 13–16) than immediately prior to randomization (ie, weeks 10–12). Mean mHDRS scores increased in study 1 (n = 299) from 3.3 prerandomization to 5.0 postrandomization ($t = 7.9$,

Table 1. Characteristics of Randomized Subjects in Fluoxetine Discontinuation Studies[a]

	Study 1		Study 2	
Characteristic	Fluoxetine (n = 299)	Placebo (n = 96)	Fluoxetine (n = 134)	Placebo (n = 135)
Age, mean ± SD, y	39.6 ± 10.2	40.0 ± 10.5	39.8 ± 11.3	38.5 ± 11.1
Male sex, %	34.4	20.8	50.0	31.7
Baseline mHDRS score, mean ± SD	20.7 ± 3.5	21.5 ± 3.7	17.7 ± 5.1	17.2 ± 4.5
mHDRS score at randomization, mean ± SD	2.9 ± 2.2	2.7 ± 2.3	4.8 ± 3.0	5.3 ± 3.5

[a]Age and gender data were available only for a subset of subjects in study 2: n = 82 in each group. The mHDRS data reflect the entire randomized sample.
Abbreviation: mHDRS = modified 17-item Hamilton Depression Rating Scale.

Figure 2. Individual and Group Trajectories of mHDRS Change in All Subjects During the First 16 Weeks of Treatment in Studies 1 and 2[a]



[a]The thin dark lines in each panel represent the measured mHDRS scores for each individual patient. All patients received fluoxetine prior to week 12, after which they may have been switched to placebo. Both patients receiving fluoxetine as well as those receiving placebo are pictured. The lighter gray lines represent the linear longitudinal mixed effects model of repeated mHDRS scores, with change points allowed at weeks 3 and 10.
Abbreviation: mHDRS = modified 17-item Hamilton Depression Rating Scale.

$P < .0001$) and, in study 2 (n = 139), from 5.5 prerandomization to 6.6 postrandomization ($t = 3.7$, $P = .0002$). Moreover, in study 1, individuals substituted to placebo (n = 96) showed a significantly larger worsening than those remaining on fluoxetine during weeks 13–16 (2.6 additional mHDRS points, $t = 6.5$, $P < .0001$), while individuals randomized to placebo in study 2 (n = 139) worsened no more on average than the group that remained on fluoxetine during weeks 13–16 (0.3 additional mHDRS points, $t = 0.79$, $P = .38$).

Further analyses suggested the changes identified during weeks 1–3 and 13–16 were not random, as subjects with low mHDRS scores during weeks 4–6 did not experience significant symptom increases during weeks 8–10 (study 1: mean mHDRS = 3.50 during weeks 4–6 vs 3.45 during weeks 8–10, $t = 0.25$, $P = .80$; study 2: mean mHDRS = 3.27 during weeks 4–6 vs 3.47 during weeks 8–10, $t = -0.66$, $P = .51$). Histograms depicting distributions of mHDRS scores at baseline and weeks 10–12 revealed no evidence of significant rater bias at study entry or in the perirandomization period.

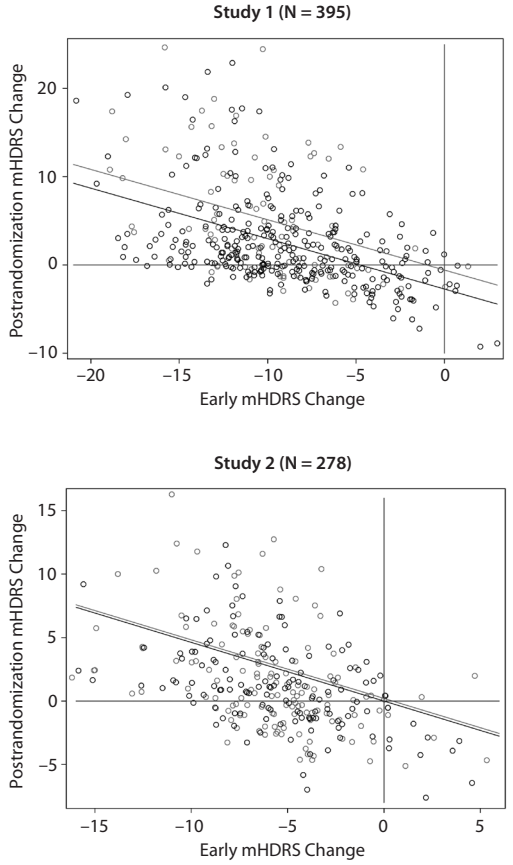
Correlation Between Early mHDRS Change and Postrandomization mHDRS Change

Figure 3 plots postrandomization mHDRS change (ie, change from weeks 10–16) as a function of early mHDRS change (ie, change from weeks 1–3) for studies 1 and 2. In study 1, the correlation of early mHDRS change with postrandomization mHDRS change was −0.46 ($P < .0001$) for subjects receiving continued fluoxetine and −0.47 ($P < .0001$) for those switched to placebo. Each additional point of mHDRS improvement in the first 3 weeks of the study was associated with a 0.57-point worsening postrandomization ($t = -10.03$, $P < .0001$), while we controlled for randomization to placebo or fluoxetine. Early mHDRS change predicted 23.8% of the variability in postrandomization mHDRS change, while treatment condition explained only 4.3% of the variability in postrandomization mHDRS change.

In study 2, the correlation of early mHDRS change with postrandomization mHDRS change was −0.48 ($P < .0001$) for fluoxetine and −0.43 ($P < .0001$) for placebo (see Figure 3). Each additional point of mHDRS improvement in the first 3 weeks resulted in a 0.46-point worsening postrandomization mHDRS ($t = -8.44$, $P < .0001$). Early mHDRS change predicted 20.8% of the variability in postrandomization mHDRS change, while treatment explained 0.2% of the variability in postrandomization mHDRS change.

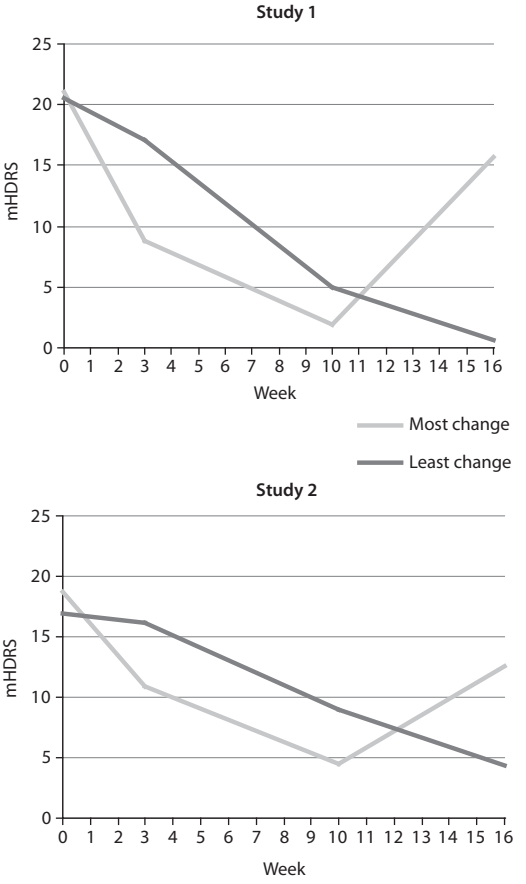
Figure 4 presents the mean trajectories for individuals on the extreme ends of early improvement in mHDRS scores and postrandomization worsening. These curves demonstrate in a different way the pattern already described, such that individuals with the steepest improvement during the first 3 weeks of open treatment are the patients with the greatest mHDRS worsening following randomization at week 12. Subjects who continued to improve postrandomization

Figure 3. Scatter Plots of Postrandomization mHDRS Change Versus Early mHDRS Change for Studies 1 and 2



Abbreviation: mHDRS = modified 17-item Hamilton Depression Rating Scale.

Figure 4. Mean Trajectories for Individuals Remaining on Fluoxetine Who Had the Highest 10% and Lowest 10% Amount of mHDRS Change Postrandomization[a]



[a]Curves are based on mean mHDRS trajectories across 29 (most change) and 30 (least change) individuals in study 1 and 14 (most change) and 13 (least change) individuals in study 2.
Abbreviation: mHDRS = modified 17-item Hamilton Depression Rating Scale.

tended to be individuals who showed only mild improvement during the first 3 weeks of open treatment with fluoxetine.

DISCUSSION

The reported analyses support the hypothesis that symptom increases and decreases immediately following treatment changes are affected by patient expectancy. Some depressed patients appear more prone to the effects of expectancy than others, since there were high correlations between likelihood of symptom change at each of 2 treatment changes. Strikingly, the postrandomization increase in mHDRS scores occurred irrespective of treatment assignment, as worsening mHDRS score following randomization was significantly associated with the degree of mHDRS improvement during weeks 1–3 of open treatment in patients continuing to receive medication as well as those switched to placebo. Analyses of study 2 paralleled those of study 1, demonstrating a remarkable consistency in findings across the 2 patient samples.

One explanation of these results is that treatment changes (eg, institution of a new treatment or discontinuation of an established treatment) influence patients' expectations of improvement, which, in turn, affect their depressive symptoms. In the studies examined, patients were informed at the start of open-label treatment that they would receive a medication known to be effective in the treatment of depression. This knowledge most likely instills a positive expectancy of improvement that may ameliorate the symptoms of depression. At week 12, participants are aware that they may be randomized to placebo, which may decrease their expectancy of continued improvement (ie, decreased placebo effect) or increase their expectation of worsening (ie, increased nocebo effect). Such expectancy effects in continuation studies of antidepressants have been found by Zimmerman et al,[27] who compared relapse rates to antidepressants and placebo in studies using a placebo substitution (ie, open acute treatment with active medication followed by randomization to continued medication or placebo) versus extension designs (ie, responders to double-blind acute treatment with medication or placebo continue taking what they responded to in continuation phase). Overall relapse rates were reported to be lower in extension studies, most likely due to a greater expectation of continued positive response in these studies where patients are aware they will continue taking the agent that made them better.

We also explored the possibility that some patients experience random mood fluctuations independent of anticipated treatment change. Such mood fluctuations appeared unlikely to explain the observed patterns, since we found no significant symptom increases or decreases at arbitrary time points not associated with changes in treatment. We also considered regression to the mean and rater bias as alternative explanations of the observed patterns of symptom change. Inflation of baseline scores in order to meet the minimum cutoff for initial enrollment might be expected to cause decreased scores during weeks 1–3.[28–30] Similarly, mHDRS scores might be artificially decreased to facilitate randomization at week 12, resulting in increased scores postrandomization once the mHDRS score restriction is released. Again, there was no evidence that score inflation or deflation by raters contributed to the observed pattern of results, since no clustering of mHDRS scores near the cutoff points was observed. To further mitigate the effects of rater bias on the present analyses, we analyzed week 10 in addition to week 12 as the change point in our linear models of mHDRS scores following randomization. Similar results were obtained across these analyses, again suggesting minimal contribution of rater bias.

Developing methods of prospectively identifying participants likely to experience expectancy effects may facilitate efforts to minimize placebo response in clinical trials, thereby making it easier to detect a signal of efficacy for a putative antidepressant over placebo. Methods of predicting expectancy effects may also allow patients to be targeted in clinical treatment with interventions designed to increase patient expectancy and improve treatment outcomes. While simplistic attempts to identify these individuals (ie, single-blind placebo lead-in periods) have generally failed to influence placebo response, these data suggest that more sophisticated methods of predicting expectancy effects should be studied.[31]

Finally, several limitations must be considered when interpreting the findings presented. Most importantly, the studies analyzed did not measure expectancy or attempt to assess expectation effects, so it is an inference that expectancy caused the observed patterns of symptom change. The role of patient expectancy in antidepressant outcome must be prospectively tested in randomized controlled trials that manipulate expectation to make firmer conclusions about its causative role. Another limitation may have been confounding expectancy effects with clinical worsening caused by the loss of therapeutic effects of fluoxetine. However, fluoxetine discontinuation would be expected to have a delayed onset owing to the long half-life of this medication.[32] Fluoxetine discontinuation also would not explain the worsening observed in the patients receiving continued fluoxetine, the magnitude of which was identical to that observed in patients switched to placebo at 12 weeks.

In summary, analyses of depression scores from 2 large clinical studies were consistent with the hypothesis that patient expectancy contributes significantly to symptom change in the first weeks following change in treatment and occurs independent of the pharmacologic effects of treatment. Following an acute period of open treatment, patients who are aware they may be randomized to receive placebo experience significant worsening in depressive symptoms, even if they actually continue taking medication. Depressed patients who experience substantial early improvement (presumably due to positive expectancies instilled by knowing effective treatment has begun) are likely to experience a substantial worsening when their expectancies are diminished. Thus, patient expectancy of improvement or worsening should be considered when interpreting the results of both acute and discontinuation antidepressant studies. Optimizing expectancy may be explored as a useful therapeutic technique in the clinical treatment of patients with depression.

Drug names: fluoxetine (Prozac and others).
Author affiliations: Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, New York.
Author contributions: Dr Rutherford had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Potential conflicts of interest: Within the past 3 years, **Dr Stewart** reports receiving honoraria from Sanofi-Aventis and Merck as well as participating on a Bristol-Myers Squibb advisory board. **Drs Rutherford** and **Wall** and **Mr Glass** have no disclosures to report.
Funding/support: Support for the design and conduct of the study was provided by a National Institute of Mental Health grant K23 MH085236 (Dr Rutherford).
Role of the sponsor: The sponsor of this study played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

REFERENCES

1. Rutherford BR, Roose SP. A model of placebo response in antidepressant clinical trials. *Am J Psychiatry*. 2013;170(7):723–733.
2. Roose SP, Schatzberg AF. The efficacy of antidepressants in the treatment of late-life depression. *J Clin Psychopharmacol*. 2005;25(suppl 1):S1–S7.
3. Rutherford BR, Sneed JR, Roose SP. Does study design influence outcome? the effects of placebo control and treatment duration in antidepressant trials. *Psychother Psychosom*. 2009;78(3):172–181.
4. Sneed JR, Rutherford BR, Rindskopf D, et al. Design makes a difference: a meta-analysis of antidepressant response rates in placebo-controlled versus comparator trials in late-life depression. *Am J Geriatr Psychiatry*. 2008;16(1):65–73.
5. Sinyor M, Levitt AJ, Cheung AH, et al. Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials? results from pooled and meta-analyses. *J Clin Psychiatry*. 2010;71(3):270–279.
6. Khan A, Kolts RL, Thase ME, et al. Research design features and patient characteristics associated with the outcome of antidepressant clinical trials. *Am J Psychiatry*. 2004;161(11):2045–2049.
7. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? a meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol*. 2009;19(1):34–40.
8. Rutherford BR, Wager TD, Roose SP. Expectancy and the treatment of depression: a review of experimental methodology and effects on patient outcome. *Current Psychiatry Reviews*. 2010;6(1):1–10.
9. Gaudiano BA, Hughes JA, Miller IW. Patients' treatment expectancies in clinical trials of antidepressants versus psychotherapy for depression: a study using hypothetical vignettes. *Compr Psychiatry*. 2013;54(1):28–33.
10. Rutherford BR, Marcus SM, Wang P, et al. A randomized, prospective pilot study of patient expectancy and antidepressant outcome. *Psychol Med*. 2013;43(5):975–982.
11. Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. *Psychol Bull*. 2004;130(2):324–340.
12. Barsky AJ, Saintfort R, Rogers MP, et al. Nonspecific medication side effects and the nocebo phenomenon. *JAMA*. 2002;287(5):622–627.
13. Nestoriuc Y, Orav EJ, Liang MH, et al. Prediction of nonspecific side effects in rheumatoid arthritis patients by beliefs about medicines. *Arthritis Care Res (Hoboken)*. 2010;62(6):791–799.

14. Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. *Clin Pharmacol Ther*. 1987;42(3):250–253.
15. Uhlenhuth EH, Rickels K, Fisher S, et al. Drug, doctor's verbal attitude and clinic setting in the symptomatic response to pharmacotherapy. *Psychopharmacologia*. 1966;9(5):392–418.
16. Stewart JW, Quitkin FM, McGrath PJ, et al. Use of pattern analysis to predict differential relapse of remitted patients with major depression during 1 year of treatment with fluoxetine or placebo. *Arch Gen Psychiatry*. 1998;55(4):334–343.
17. McGrath PJ, Stewart JW, Petkova E, et al. Predictors of relapse during fluoxetine continuation or maintenance treatment of major depression. *J Clin Psychiatry*. 2000;61(7):518–524.
18. Quitkin FM, Rabkin JG, Ross D, et al. Identification of true drug response to antidepressants: use of pattern analysis. *Arch Gen Psychiatry*. 1984;41(8):782–786.
19. McGrath PJ, Stewart JW, Quitkin FM, et al. Predictors of relapse in a prospective study of fluoxetine treatment of major depression. *Am J Psychiatry*. 2006;163(9):1542–1548.
20. Amsterdam JD, Fawcett J, Quitkin FM, et al. Fluoxetine and norfluoxetine plasma concentrations in major depression: a multicenter study. *Am J Psychiatry*. 1997;154(7):963–969.
21. Quitkin FM, Petkova E, McGrath PJ, et al. When should a trial of fluoxetine for major depression be declared failed? *Am J Psychiatry*. 2003;160(4):734–740.
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987.
23. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
24. Guy W. Clinical Global Impressions. *Assessment Manual for Psychopharmacology*. US Department of Health, Education and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976:218–222.
25. Diggle P, Heagerty P, Liang KY, et al. *Analysis of Longitudinal Data*. Oxford, UK: Oxford University Press; 2002.
26. Harville DA. Variance component estimation. *JASA*. 1977;72:320–340.
27. Zimmerman M, Posternak MA, Ruggero CJ. Impact of study design on the results of continuation studies of antidepressants. *J Clin Psychopharmacol*. 2007;27(2):177–181.
28. Rief W, Nestoriuc Y, Weiss S, et al. Meta-analysis of the placebo response in antidepressant trials. *J Affect Disord*. 2009;118(1–3):1–8.
29. Mundt JC, Greist JH, Jefferson JW, et al. Is it easier to find what you are looking for if you think you know what it looks like? *J Clin Psychopharmacol*. 2007;27(2):121–125.
30. Landin R, DeBrota DJ, DeVries TA, et al. The impact of restrictive entry criterion during the placebo lead-in period. *Biometrics*. 2000;56(1):271–278.
31. Trivedi MH, Rush H. Does a placebo run-in or a placebo treatment cell affect the efficacy of antidepressant medications? *Neuropsychopharmacology*. 1994;11(1):33–43.
32. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry*. 1998;44(2):77–87.