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Optimizing patient expectancy in the pharmacologic treatment of major depressive disorder

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Abstract

Background. Patient expectancy is an important source of placebo effects in antidepressant clinical trials, but all prior studies measured expectancy prior to the initiation of medication treatment. Little is known about how expectancy changes during the course of treatment and how such changes influence clinical outcome. Consequently, we undertook the first analysis to date of in-treatment expectancy during antidepressant treatment to identify its clinical and demographic correlates, typical trajectories, and associations with treatment outcome.

Methods. Data were combined from two randomized controlled trials of antidepressant medication for major depressive disorder in which baseline and in-treatment expectancy assessments were available. Machine learning methods were used to identify pre-treatment clinical and demographic predictors of expectancy. Multilevel models were implemented to test the effects of expectancy on subsequent treatment outcome, disentangling within- and between-patient effects.

Results. Random forest analyses demonstrated that whereas more severe depressive symptoms predicted lower pre-treatment expectancy, in-treatment expectancy was unrelated to symptom severity. At each measurement point, increased in-treatment patient expectancy significantly predicted decreased depressive symptoms at the following measurement ($B = -0.45$, $t = -3.04$, $p = 0.003$). The greater the gap between expected treatment outcomes and actual depressive severity, the greater the subsequent symptom reductions were ($B = 0.49$, $t = 2.33$, $p = 0.02$).

Conclusions. Greater in-treatment patient expectancy is associated with greater subsequent depressive symptom reduction. These findings suggest that clinicians may benefit from monitoring and optimizing patient expectancy during antidepressant treatment. Expectancy may represent another treatment parameter, similar to medication compliance and side effects, to be regularly monitored during antidepressant clinical management.

Introduction

Non-pharmacological factors, rather than the effects of antidepressant medication, appear to be responsible for much of the change observed in patients receiving antidepressants for major depressive disorder (MDD) (Rutherford and Roose, 2013). Meta-analyses of placebo-controlled randomized controlled trials (RCTs) of antidepressants submitted to the Food and Drug Administration (FDA) have reported that the placebo groups in these trials average 1.5 standard deviation units of improvement, which is 75% of the improvement shown in the antidepressant groups (Kirsch and Sapirstein, 1998; Kirsch *et al.*, 2008). Similar results were reported in another meta-analysis of 75 placebo-controlled antidepressant RCTs published between 1981 and 2000, which found a mean medication response rate of 50%, compared with a mean placebo response rate of 30% (Walsh *et al.*, 2002). Whereas it was once believed that the therapeutic effects of non-pharmacological factors were transient, more recent data show that 75% of responders to placebo in acute antidepressant trials stay well if double-blind placebo is administered in a continuation phase of treatment (Khan *et al.*, 2008). These data raise the possibility that optimizing non-pharmacological factors in antidepressant treatments could significantly improve clinical practice outcomes.

In many cases, placebo effects appear to be cognitively mediated by patient expectancy, that is, individuals' belief about whether and how much they will improve as the consequence of treatment (Stewart-Williams and Podd, 2004; Faria *et al.*, 2017). Supporting data include reports showing that antidepressant treatment effects are consistently smaller in placebo-controlled RCTs than in open studies or active comparator trials, in which patients know they are receiving an active medication for depression (Greenberg *et al.*, 1992; Sneed *et al.*, 2008; Rutherford *et al.*, 2009). Response to placebo increases with the number of treatment arms in a trial, which may be explained by the probability of receiving active medication as

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opposed to placebo increasing with the number of treatment arms (Khan *et al*., 2004; Sinyor *et al*., 2010). Recently, our group manipulated patient pre-treatment expectancy experimentally, and assessed prospectively its effect on antidepressant outcome (Rutherford *et al*., 2017). The findings showed that manipulation of expectancy at intake resulted in higher expectancy post-manipulation, which in turn resulted in better treatment outcome.

These results suggest that expectancy improving interventions should be investigated as a means of improving patient outcome in clinical treatment, but there are still open questions that need to be addressed before adequate intervention strategies can be developed. First, prior studies have analyzed the influence of pre-treatment (just before medication is administered) expectancy scores on antidepressant outcome. Little is known about the course of expectancy during antidepressant treatment, or whether changes in expectancy are a cause or effect of ongoing symptomatic change. Second, the optimal level of expectancy to realize maximal symptom reduction during antidepressant treatment is unknown: is a 'realistic' view preferable, where patients' expectancy is titrated to their current symptom severity (i.e. incremental, gradual improvement), or would greater symptom change result from maximizing expectancy to the extent possible, even if the expected outcome would amount to a dramatic improvement over current illness severity? Obtaining data on these questions could influence clinical practice by making intra-trial expectancy an important variable to measure and manage during treatment (similar to compliance or therapeutic alliance), and could provide a template to guide future strategies to optimize expectancy.

We focused on the above questions in the present study as part of our ongoing efforts to translate expectancy related research from RCTs to clinical practice. Data from two similarly designed, acute, outpatient RCTs of antidepressant medication for adult outpatients with MDD were combined to investigate the course of intra-trial expectancy and its influence on clinical outcomes. We were interested in determining (a) whether baseline patient clinical and demographic characteristics predict expectancy levels and trajectories of change throughout treatment, (b) whether distinct trajectories of change in patient expectancy could be identified during the course of antidepressant treatment, (c) whether expectancy levels during treatment drive depressive symptom change, and (d) what levels of expectancy (in relation to actual current symptom severity) are associated with the greatest symptom change during treatment. We hypothesized that distinct expectancy trajectories are identifiable in the data, that trajectories of increasing expectancy drive greater symptom change, and that higher expectancy results in greater subsequent symptom change.

Method

Sample

We combined data from two antidepressant trials conducted at the Adult and Late Life Depression Research Clinic at the New York State Psychiatric Institute (NYSPI). The trials were approved by the NYSPI Institutional Review Board and had similar eligibility criteria, except that in study 1 participants were aged 24–65 years, whereas patients in study 2 were 60–90 years old. Patients met Diagnostic and Statistical Manual IV (DSM-IV) criteria for non-psychotic MDD, had a baseline 24-item Hamilton Rating Scale for Depression (HRSD) score $\geqslant$16, and were willing to and capable of providing informed consent and complying with study procedures. Patients were excluded for current comorbid Axis I DSM IV disorders (other than nicotine dependence, adjustment disorder, or anxiety disorders), diagnosis of substance abuse or dependence in the preceding 12 months, history of psychosis or mania, significant suicidality as measured by an HRSD suicide item >2, or Clinical Global Impressions (CGI) score of 7 at baseline, history of allergic/adverse reaction or non-response in the current depressive episode to the study medication, or acute, severe, or unstable medical illness.

Clinical trial design

The clinical trials contributing data to the below analyses were designed to investigate the influence of *pre-treatment* patient expectancy on antidepressant response. Details of one of the trials have been previously published (Rutherford *et al*., 2017), and the second trial used a similar design in an older patient population. Briefly, each 8-week duration antidepressant clinical trial randomized participants to antidepressant medication or placebo, with an unequal allocation strategy of 4:1, so that most patients received medication (citalopram or escitalopram). Patients were initially evaluated at a baseline visit, returned 1 week later for a week 0 visit at which they were randomized and given either medication or placebo, and then returned for eight weekly visits. The 24-item HRSD was administered at every study visit, and patient expectancy was measured at baseline and at weeks 0, 4, and 8.

To assess expectancy, we used a modified version of the Quick Inventory of Depressive Symptomatology (expectancy QIDS, or eQIDS), in which participants were instructed to answer the standard QIDS-16 Self Report form based on how they believed they would feel at the end of the 8-week treatment period, rather than recall their actual symptom levels over the preceding 7 days. At week 8, the instructions were to rate the eQIDS based on their expected level of symptoms 1 month after the end of treatment. To enhance clarity, we reverse-coded the eQIDS, so that higher scores represented higher expectancy levels in all analyses except those focusing on the gap between expectancy and actual severity. Since the analyses focused on the role of expectancy during antidepressant treatment, all analyses were conducted on medication-treated participants, excluding those receiving placebo.

Statistical analyses

Relationship of baseline patient characteristics with expectancy

Because of lack of knowledge of clinical and demographic characteristics of patients predicting baseline expectancy levels and trajectories of change in expectancy throughout treatment, we used data-driven approaches, capable of evaluating the contributions of multiple predictor variables and their interactions, in the search for potential predictors (e.g. Cohen and DeRubeis, 2018; Zilcha-Mano *et al*., 2018). To investigate relationships between clinical and demographic characteristics and patient expectancy, we conducted decision tree analyses (Hothorn *et al*., 2006a) with the R 'party' package (Hothorn *et al*., 2006b), using random forest variable selection (Strobl *et al*., 2009) and Monte Carlo simulation for multiple-testing adjustment (Strasser and Weber, 1999). As potential predictors of expectancy we used: age, sex, education, age at first MDD episode, anxiety and depression symptom severity [assessed with the Hamilton Anxiety Ratings Scale (HARS) as well as the QIDS, CGI, and HRSD scores at intake], the length of the current episode (in weeks), and family history of depression

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and bipolar. Baseline expectancy and expectancy slope during antidepressant treatment were examined in separate models.

Expectancy trajectories and their associations with clinical outcome

We conducted cluster analysis to detect homogeneous subtypes or groups of similar individuals within the larger, heterogeneous sample. Clusters were constructed based on two expectancy difference scores calculated from the three post-baseline eQIDS time points (from week 0 to 4, from week 4 to 8) as the criteria for similarity *v.* dissimilarity. The sample was cluster analyzed with the *k*-means common agglomerative clustering method (SPSS K-Means; SPSS Inc., 2007), using squared Euclidean distances. Next, we tested the association between expectancy cluster assignment and patient-specific trajectories of HRSD scores across treatment, using eQIDS trajectory cluster membership, time, and their interaction, with intercept and time as random effects. The dependent variable was weekly HRSD measures, from week 0 to 8. A significant interaction between trajectory assignment and time in predicting the level of HRSD means that the HRSD trajectories for each cluster are not identical.

Testing the relationships between in-treatment expectancy and subsequent depressive symptom reduction

The data were hierarchically nested, with sessions within individuals. To account for the non-independence of the data and to prevent inflation of the effects (Krull and MacKinnon, 2001; Laurenceau and Bolger, 2012), we used the SAS PROC MIXED procedure (SAS, 2003), with level 1 as the session level and level 2 as the patient level. To disentangle between-patients and within-patient effects of expectancy on outcome, we followed the recommendations suggested in the literature (Wang and Maxwell, 2015), centering expectancy on the individual patients' mean. This procedure yielded independent coefficients for within-patient and between-patients effects (Bolger and Laurenceau, 2013). Both the within- and between-patient components of expectancy were entered simultaneously as predictors. To establish a correct temporal relationship, aiming to approach causality with a rise in expectancy as a predictor of symptom reduction, we used within-patient changes in expectancy (at time T) to predict subsequent changes in HRSD (from time T to $T+1$). The same procedure was followed to examine the ability of HRSD to predict subsequent changes in expectancy.

Identifying the optimal expectancy level for successful treatment as a function of symptom severity

To identify the optimal expectancy for a given level of symptom severity to predict subsequent HRSD reduction, we applied the dyadic score model (Iida *et al.*, 2018), based on the multilevel model reported above, with observations nested within patients, using the SAS PROC MIXED procedure. The dependent variable was differences in HRSD scores from time T to $T+1$. Based on the literature on the dyadic score model (Iida *et al.*, 2018), the following predictors were used: (a) the average score of expectancy (eQIDS) and depressive symptoms (QIDS) at time T [i.e. (eQIDS + QIDS)/2], (b) a quadratic term formed by squaring the average score at time T [i.e. ((eQIDS + QIDS)/2)^2], (c) the difference score between expectancy and symptoms at time T (i.e. QIDS − eQIDS, calculated so that higher scores denote an expectation of symptom improvement, and therefore greater levels reflected a more optimistic view), (d) a quadratic term formed by squaring the difference score at time T [i.e. (QIDS − eQIDS)^2], and (e) the interaction between the average and the difference scores. To minimize the potential effect of auto-regression between the predictor and outcome, we used the QIDS to assess symptom severity interplay with the eQIDS, and subsequent change in HRSD to measure treatment outcome.

Results

Participant characteristics

The demographic and clinical characteristics of the patients for the pooled sample, divided by studies, appear in Table 1. As shown, application of the selection criteria resulted in a severely depressed sample of outpatients, clinically similar to most RCT samples.

Relationship of baseline patient characteristics with expectancy

The random forest analysis identified baseline QIDS as the strongest predictor of baseline (pre-treatment) expectancy, such that patients with more severe symptoms showed lower expectancy. Figure 1 shows the resulting variable importance plot for baseline expectancy. By contrast, the random forest analysis failed to detect any robust pre-treatment predictors of the in-treatment expectancy slope during the 8 weeks of treatment. Repeating the analyses including baseline expectancy yielded the same results.

Expectancy trajectories and their associations with clinical outcome

A model with three trajectory classes best fit the data, where 26% of patients were assigned to the first class, demonstrating a dramatic increase in expectancy, 38% of patients were assigned to the second class, demonstrating a low steady expectancy, and 36% of patients were assigned to the third class, demonstrating an upward trend followed by a downward one. The mean eQIDS trajectories of the three classes are shown in Fig. 2.

A significant interaction was found between expectancy trajectory class assignment and week in predicting HRSD from week 0 to 8 ($F_{2,788} = 43.09$, $p < 0.0001$), indicating that the expectancy trajectories significantly differed in HRSD change across treatment. Expectancy trajectory 1 (consistently increasing expectancy) showed the fastest change in HRSD ($B = -2.00$, $t_{(788)} = -14.01$, $p < 0.0001$), followed by trajectory 2 (low steady expectancy; $B = -0.70$, $t_{(788)} = -5.91$, $p < 0.0001$), and trajectory 3 (increase followed by decrease; $B = -0.31$, $t_{(788)} = -2.54$, $p = 0.01$). The findings were similar when controlling for the baseline HRSD level.

Testing the relationships between in-treatment expectancy and subsequent depressive symptom reduction

Baseline expectancy, as measured by the pre-treatment eQIDS score, was not a significant predictor of HRSD mean reduction in symptoms from one time point to the next during treatment ($B = 0.04$, S.E. = 0.09, $t_{(103)} = -0.47$, $p = 0.63$), indicating that higher pre-treatment expectancy was not associated with decreasing depressive symptoms from 1 week to the next during treatment. Mean level expectancy was also not a significant predictor of decreasing depressive symptoms from 1 week to the next during treatment ($B = 0.16$, S.E. = 0.10, $t_{(104)} = 1.51$, $p = 0.13$), indicating that general individual differences between patients in expectancy were not associated with decreasing depressive symptoms during treatment. In-treatment expectancy, however, was a significant predictor of subsequent symptom reduction ($B = -0.45$, S.E. = 0.14, $t_{(97)} = -3.04$, $p = 0.003$). Increased eQIDS

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Table 1. Clinical and demographic characteristics of included patients

Characteristic	Trial 1 ($N = 47$)	Trial 2 ($N = 81$)
Age (years)	43.25 ± 11.18	70.25 ± 7.50
Gender (% male)	42.6	38.3
Ethnicity (% Hispanic)	19.1	13.6
Race		
% White	51.1	66.7
% African-American	33.3	16.0
% Other	15.6	17.3
Baseline 24-item HRSD	25.9 ± 4.89	23.95 ± 5.62
Baseline QIDS SR	20.37 ± 5.98	17.06 ± 5.33

HRSD, Hamilton Rating Scale for Depression; QIDS SR, Quick Inventory of Depressive Symptomatology Self Report.

values at one time point (i.e. at time T relative to the patient's general expectancy level) were associated with decreased HRSD scores at the next time point (i.e. from time T to $T + 1$). Similarly, increased HRSD values at one time point were associated with decreased eQIDS values at the next time point ($B = -0.24$, S.E. $= 0.07$, $t_{(111)} = -3.46$, $p = 0.0008$). The associations between in-treatment expectancy and HRSD scores support a causal bi-directional relationship, in which greater patient expectancy is both the product and the predictor of symptom reduction.

Identifying the optimal expectancy level for successful treatment as a function of symptom severity

As shown in Table 2, the difference score between a patient's expectancy (eQIDS) and depressive symptoms (QIDS) at time T significantly predicted HRSD symptom reduction from time T to $T + 1$, whereas average eQIDS and QIDS scores were not significant predictors. The absence of a significant quadratic term for eQIDS − QIDS scores suggests that the association is linear rather than curvilinear: the greater the gap between current

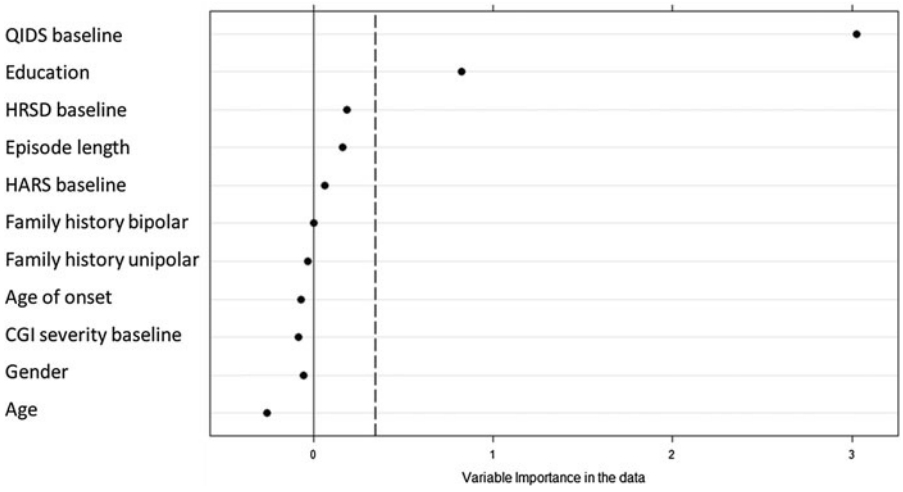

Fig. 1. Variable-importance plot for the model-based recursive partitioning trees. The horizontal axis represents the average increase in classification accuracy gained by using the given variable in the 'real' data compared with using it after it was permuted (i.e. 'mixed up' or fake). Positive values indicate that a variable not only predicts patient-specific expectancy at baseline outside of a given sample, but that it performs better than random noise. The dashed line represents the random noise of all potential moderator variables, and is constructed using the absolute value of the worst predictor.

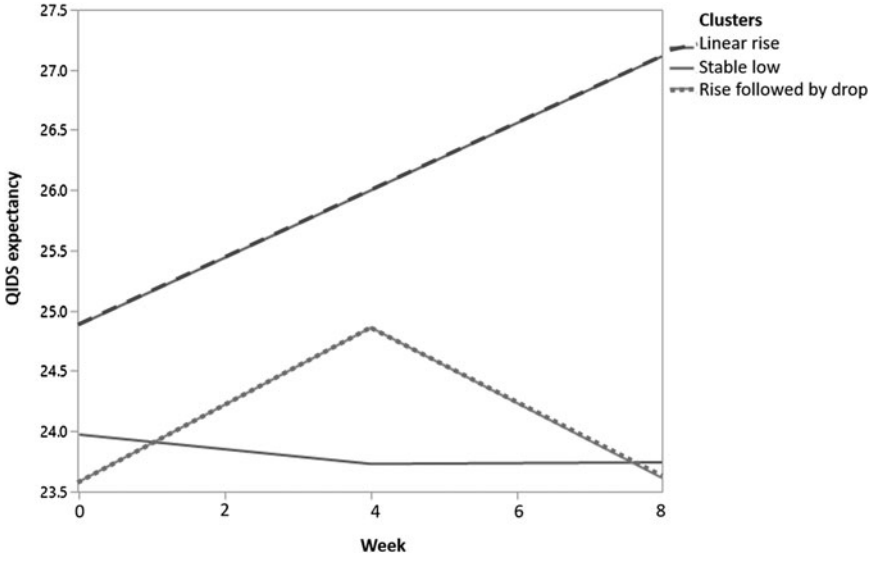

Fig. 2. Expectancy development patterns identified across treatment.

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Table 2. Slope estimates for the ability of the interplay between expectancy and symptom severity to predict subsequent symptom reduction over treatment

Effect	Slope estimate	S.E.	*t* Value	*p*
Intercept	−1.19	1.67	−0.72	0.47
Average	0.40	0.28	1.39	0.16
Differences	0.49	0.21	2.33	0.02
Average quadratic	−0.004	0.01	−0.35	0.72
Differences quadratic	0.004	0.01	0.41	0.68
Average × differences	−0.03	0.01	−1.86	0.06

expectancy and current depressive severity (i.e. the more optimistic the patient), the greater the subsequent symptom reduction observed (see Fig. 3).

All findings remain similar when controlling for the trial from which the data were derived, and when conducting all analyses on a combined dataset that includes both placebo and medication conditions.

Discussion

To the best of our knowledge, this is the first study to systematically investigate dynamic changes in patient expectancy occurring during antidepressant treatment, and to examine their relationship with clinical outcome. Our primary findings were that pre-treatment patient expectancy is dissociable from expectancy measured in-treatment. Whereas baseline depressive symptom severity is associated with pre-treatment expectancy, initial patient demographic and clinical characteristics, as measures in the present study, were unrelated to in-treatment expectancy. Three distinct trajectories of in-treatment expectancy were observed among participants in the analyzed clinical trials, and increasing expectancy during the 8-week duration trials was found to predict subsequent increased symptom improvement. Lastly, a linear relationship obtained between the gap between in-treatment expectancy and current depression severity on the one hand, and subsequent treatment outcome on the other hand, such that the greater the disparity between expectancy and current severity (meaning that the patient expects a more positive outcome), the greater the symptom reduction is.

Our distinction between pre-treatment and in-treatment patient expectancy mirrors the distinction made in recent psychotherapy process literature between 'trait-like' and 'state-like' patient characteristics (Zilcha-Mano, 2016; Zilcha-Mano, 2017). The trait-like components are the individual differences *between* patients, such as degree of general optimism *v.* pessimism, perceived locus of control, and other psychological factors. By contrast, the state-like components are the changes *within* individual patients over the course of treatment, which are crucially related to events in the treatment process. The psychotherapy literature demonstrates how critical it is to disentangle these two components for the investigation of causal relationships during treatment, as the same variable may have different effects on outcome when considered from a trait-like *v.* a state-like perspective (Curran and Bauer, 2011; Wang and Maxwell, 2015). For example, considered from a trait-like (between-patients) perspective, physical exercise reduces the risk of myocardial infarction, while from a state-like (within-patient) perspective, physical exercise may increase risk (e.g. an unfit person shoveling snow on a cold day). Only if we separate the state-like, within-patient effect, from the trait-like effect, can we indicate a causal relationship between two treatment variables. In the data analyzed here, in-treatment (state-like) patient expectancy was found to predict subsequent depressive symptom reduction, rejecting the converse possibility that expectancy is merely a by-product of whether or not treatment is working. This finding confirms and extends past reports, suggesting that patient expectancy may be a useful tool to improve psychopharmacologic treatment outcomes of depressed patients.

The finding that patients in antidepressant clinical trials tend to follow distinct expectancy trajectories during the course of treatment suggests that patient expectancy should be measured and tracked. Just as proper clinical management of antidepressant treatment calls for regular monitoring of medication compliance and side effects, patient expectancy should be measured to detect maladaptive expectancy trajectories (linked here to worse depression outcomes) as early as possible. Relatively simple and low-burden questionnaires, such as the modified QIDS used in this study, or selected items from the Credibility and Expectancy Scale (Borkovec, 1972; Borkovec and Nau, 1972) could be used for this purpose. Decreasing expectancy may alert the treating clinician to query the patient, undertake further psychoeducation about the effectiveness of the treatment being administered, and express confidence that the patients' depressive symptoms can respond positively to treatment.

To guide such expectancy enhancing interventions, we analyzed the data to determine the optimal level of expectancy for individual patients, given their symptom severity. A clinician might worry that enhancing expectancy may be inadvisable for a patient with severe symptoms, and even endeavor to dampen 'unrealistic expectations' of improvement held by a severely depressed patient (Fawcett *et al.*, 1987). Although our results must be replicated in studies manipulating in-treatment expectancy before they can be generalized to all psychopharmacologic treatments, our findings are inconsistent with concerns about unrealistic expectations. Larger differences between expected improvement and actual symptom severity produced greater subsequent symptom reduction, suggesting that the more optimistic the patient during antidepressant treatment, the better.

Finally, these findings must be interpreted in light of several limitations. One major limitation of the study was that the range of in-treatment expectancy available for analysis was restricted to that naturally occurring in these trials. In-treatment expectancy was not manipulated or actively managed so as to provide direct causal evidence of different clinical outcomes. The study was further limited by the relatively few number of baseline clinical and demographic variables available to predict pre-treatment and in-treatment expectancy. Future studies may benefit from including related constructs from the psychotherapy literature, such as level of hopefulness, optimism (Constantino *et al.*, 2018), openness to experiences, the belief in the ability to get better and that the depression is not one's permanent fate, as well as previous treatment experiences. The findings are also limited by the relatively small sample size, the infrequency of expectancy assessment (which ideally, should be conducted weekly), the lack of sufficient data to test therapists effect, and by the fact that the assessments are the result of secondary

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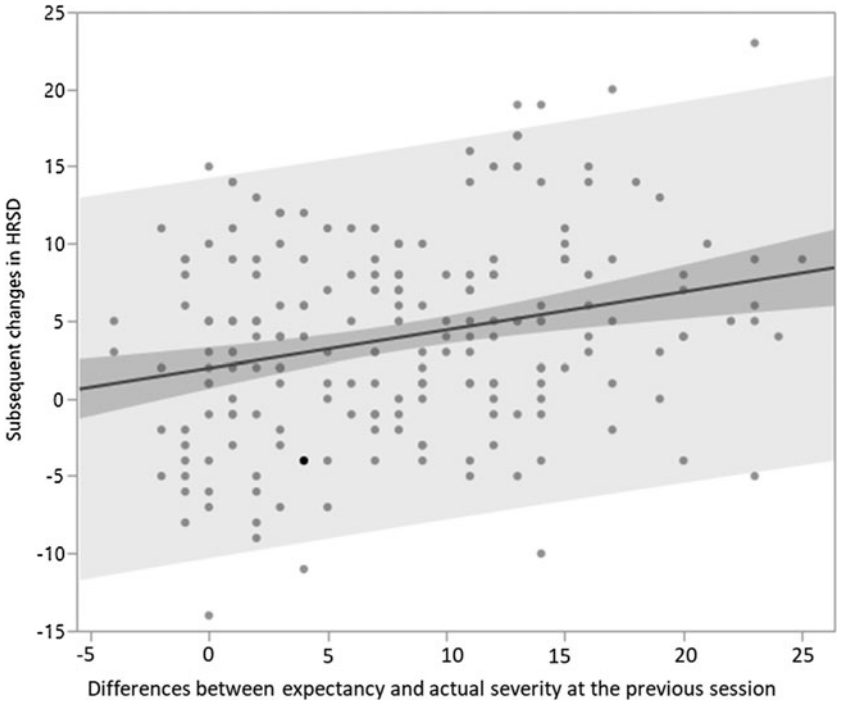

Fig. 3. Differences between expectancy and actual severity at the previous session (session *T*) as predictors of subsequent symptom reduction (from time *T* to *T* + 1). The *Y* axis refers to subsequent changes in HRSD, so that higher scores denote greater symptom reduction.

analyses of the combined data of two antidepressant trials. Future studies may use more comprehensive expectancy assessment, including traditional ones (Borkovec, 1972; Borkovec and Nau, 1972), as different measures have their own advantages and disadvantages (Constantino *et al*., 2018), and assess them weekly. Furthermore, note that additional factors may contribute to the placebo effect, including potential interactive effects between expectancy about the drug effect and the actual drug effect, and that other factors may impair the drug effect, including inappropriately prescribed antidepressants

In conclusion, despite these limitations, the present study provides a finer-grained analysis of patient expectancy during antidepressant treatment than any previous report. Prior studies focused exclusively on pre-treatment patient expectancy and did not investigate in-treatment changes. Increasing expectancy during antidepressant treatment is common, important for treatment success, and may be under the influence of the treating physician. Rather than increased expectation of improvement being a product of effective treatment, changes in expectancy may appear to drive depressive symptom change. Contrary to guidance offered to patients in clinical practice (Fawcett *et al*., 1987), what was previously viewed as 'unrealistic expectations' may actually be a powerful therapeutic ally.

Conflict of interest. None.

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