What Shapes Depressed Individuals' Pre-Treatment Expectation in Antidepressant Clinical Trials?

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Citation

Abstract

Objective: To examine the relationship between patients' treatment outcome expectation and a set of socio-demographic factors, clinical course variables, symptom severity, health locus of control, and Temperament and Character Inventory (TCI) dimensions.

Method: Logistic regression analyses were performed on data collected at screen and baseline interviews from 45 participants enrolled into one of two randomized placebo controlled antidepressant trials.

Results: Participants with high outcome expectations reported shorter depressive episodes and scored lower on Harm Avoidance (TCI). The data also suggest that external locus of control, gender, ethnicity/race, employment status, and the dimension of self-directedness (TCI) may have a role in shaping treatment expectation.

Conclusion: Depressed patients' treatment outcome expectations were found to be associated with depression characteristics, personality traits, locus of control, and certain socio-demographic factors. If these findings are replicated, this information can be used to identify individuals needing additional interpersonal support or motivation at the onset of treatment.

INTRODUCTION

Major depression ranks among the most common disabling conditions ([1], [2]) and therefore efforts are ongoing to not only improve access to treatment, but also to better understand who responds favorably to treatment. Among the promising biological and psychosocial predictors of treatment outcome, there has been a longstanding interest in patients' expectation of treatment as a contributing factor to response or remission ([3],[4],[5]). Expectation, or patients' subjective assessment of the likelihood of being helped by treatment, is considered a necessary element in motivating and preparing patients to take an active role in treatment and in the development of a positive treatment alliance, and therefore related to treatment outcome ([6],[7],[8],[9]). Indeed, patients' expectation of treatment has been correlated with outcomes in relation to a wide range of medical and psychiatric conditions such as chronic pain, asthma, anxiety, aggression, psychosis and addiction ([10],[11],[12],[13]), as well as in different treatment contexts, such as post-surgery recovery or chemotherapy ([14],[15]). In relation to psychiatric illnesses, studies exploring the predictive power of patients' expectations of outcome or treatment mostly involve psychotherapeutic interventions, where this construct has generally accounted for 8-15% of the outcome variance ([16],[17]).

In the realm of antidepressant drug treatment, patients' expectation has received relatively less research attention, but a few relevant studies confirm its importance. A recent 9-week study in our laboratory found that patients' pre-treatment expectation was predictive of change in core depressive symptomatology; 90% of participants who reported expecting the drug to be "very effective" responded favorably to the antidepressant, while only 33% of

participants initially expecting medication to be "somewhat effective" responded favorably ([18]). This study found expectation accounted for 17% of the variance in treatment outcome. Sotsky et al. also confirmed that patients' expectation is an important factor in understanding the variability of individuals' response to pharmacotherapy ([19]).

Despite growing recognition of the clinical importance of patients' expectations of treatment, there is little to suggest what factors determine depressed individuals' expectations of pharmacologic treatment ([3]). Several studies of patients with different psychiatric disorders suggest that pre-treatment expectation may be associated with socio-demographic characteristics such as age, education, race, gender, marital status, employment, and income ([20,21,22,23]). Patients' expectations have also been found to be related to the severity of symptoms ([11, 22, 24]), but not necessarily associated with the length of time that difficulties have been experienced ([20]). Individuals' personality traits have been hypothesized as potentially shaping beliefs that treatment will be effective; a few previous studies, using different conceptualizations of personality traits (e.g., extroversion/introversion, perfectionism, acquiescence, sociability) found some associations with patients' expectancy ([25,26,27,28]). These studies offer some guidance in approaching the question of what determines treatment expectation, but much of the research is limited in scope in terms of both the nature of correlates examined as well as a primary emphasis on psychotherapy rather than psychopharmacologic treatment.

The purpose of this study was to examine the characteristics of depressed participants regarding higher versus lower expectations of treatment in the context of a randomized antidepressant clinical trial, including demographic and illness characteristics as well as personality dimensions and health locus of control. Illness characteristics including severity, recurrence, age of onset, and duration, are all elements affecting an individual's experience of depression and the extent to which depression has impacted one's life, and hence may have a role in determining an individual's expectation of treatment. Further, as suggested above, personality traits may shape the extent to which participants believe medication will be effective ([29]). We utilized Cloninger's Temperament and Character Inventory (TCI) ([30]) to study how individuals' temperament and character dimensions are related to pre-treatment expectations. Finally, using the Multidimensional Health Locus of Control Scale ([31]), we examined the extent to which participants'

attributions of control over their health well-being are related to their pre-treatment expectation of psychopharmacologic treatment.

METHOD

Participants & Study Procedures: The study sample was comprised of 45 participants enrolled in one of two ongoing randomized, placebo-controlled clinical trials for individuals with major depressive disorder (MDD) in our research laboratory between April 2003 and October 2004. The UCLA IRB approved both studies, whose primary aim was to identify and distinguish physiologic indicators of medication and placebo response using quantitative electroencephalography (QEEG). Thirty-one participants between the ages of 21 and 65 (mean age: 41.2) were enrolled in Study 1, a 9-week study using venlafaxine, with a 50% chance of assignment to a placebo condition. Of the participants from Study 1 who were randomized into the placebo or medication group (N=26), 12 or 54% were randomized into the placebo group. Fourteen participants between the ages of 22 and 60 (mean age: 38.1) were enrolled in Study 2, an 11-week protocol using sertraline, with a 75% chance of assignment to a placebo. Of the participants from Study 1, 9 or 82% were randomized into the placebo group.

For both studies, participants were recruited using advertisements in the community (flyers, newspapers, radio). Participants for both studies were enrolled if they met DSM-IV criteria for MDD as determined by the Structured Clinical Interview for DSM-IV (SCID), and had a score of 17 or higher on the Hamilton Depression Rating Scale (Ham-D). Individuals were excluded from either study if they had: a serious medical illness, a history of significant head trauma or abnormal EEG, substance-related disorder(s) during the past 6 months or a positive toxicology screen, Axis I disorders involving schizophrenia or other psychotic disorders, eating disorder, or delirium or dementia, Axis II cluster A or B personality disorder(s) severe enough to interfere with completion of study, or current suicidal intent or a history of serious suicide attempts. Enrolled female participants were asked to use an acceptable means of birth control. None of the participants were currently taking medications that had significant central nervous system effects. At this screening session, all participants were informed that they were enrolling in a treatment trial and to receive either an antidepressant or a placebo. Baseline ratings were taken between one to four days following the initial screening.

MEASURES

Outcome Variable: Participants' pre-treatment expectation of antidepressant medication was elicited at the beginning of the screening interview with the primary research nurse. Participants were asked, "How effective do you think the medication is going to be?" Their responses were rated as one of the following: (1) "not at all effective", (2) "somewhat effective", and (3) "very effective". In cases where the response was mixed, the nurse probed into the participants' feelings and thoughts about taking the medication until understanding was reached about the level of current expectation. Because none of the participants reported expecting the medication to be 'not at all effective', expectation was essentially a dichotomous variable.

Independent Variables: During the screening and baseline interview, information regarding participants' clinical history and clinical status was elicited, including age of onset of depression, duration of current depressive episode (months), number of past episodes of MDD, past history of taking antidepressants (yes/no), the presence of a external stress precipitating the index episode of depression, and socio-demographic information (gender, age, education, marital status, employment status).

(a) Illness severity: Data were collected during the screen session when the nurse and physician determined if the individual was eligible for the study. Depression severity was measured at baseline with the Hamilton Depression Rating Scale [Ham-D] (17 item version) ($_{32}$), and the Beck Depression Inventory [BDI] ($_{33}$). The Ham-D is a clinician-rated instrument capturing the severity of depression once a diagnosis has already been established and has a greater emphasis on somatic symptoms, relative to the BDI, which is a self-report scale with a greater emphasis on the cognitive symptoms associated with depression. These two instruments, while significantly correlated (r=.50, p<.001), are included for they provide unique information relevant to patients' clinical status.

(b) Clinical course characteristics:

i. Age of depression onset: participants' response to the question "How old were you when you first suffered from a depressive episode?"

ii. Number of previous MDD episodes: participants indication of how many times they experiences separate depressive episodes defined as clinically significant periods of depressive symptoms preceded by at least three months of feeling minimal or no symptoms of depression.

iii. Duration of current episode: participants' response to the question "how long have you been feeling depressed?'

iv. History of taking antidepressant(s): (yes/no)

v. Precipitating External Stress: based on information provided by participants in relation to 'what occurred around the time that you started to feel depressed'? The information was classified by the clinical nurse into three categories: 'absent', 'probably present', and 'definitely present'.

(c) Temperament and Character Inventory($_{30}$): This self-report measure is comprised of measurement for four basic temperament dimensions: novelty seeking (NS), defined as inclination toward behavior initiation or exploratory behavior in response to novelty, impulsivity or active avoidance of frustration; harm avoidance (HA), or inclination toward inhibition of behavior due to worry, uncertainty or tendency toward fatigability; reward dependence (RD), indicating inclination toward social attachment and dependence on the approval of others, or persistence (P), involving an inclination toward perseverance in the face of frustration or fatigue. This scale also measures three character dimensions: self-directedness (SD), or the ability of an individual to adapt behavior in accordance with individually defined and chosen goals and values; cooperativeness (C), defined as identification with and acceptance of others and inclination to behavior in an agreeable manner; and self-transcendence (ST), or inclination toward spirituality with a strong awareness of everything being integral parts of a whole.

(d) The Multidimensional Health Locus of Control (MHLC) - Form B ($_{31}$): This 18-item self report scale is comprised of three subscales each made up of 6 items: internal-representing a belief that one's health is under one's own control; chance- a belief that health outcomes are determined by fate or chance; and powerful others- a belief that health outcomes are at the hand of others- namely doctors and family members. All items were rated on a 6 point scale, with the end points defined as 'strongly disagree' (=1) and 'strongly agree' (=6); higher scores reflect more agreement.

The MHLC can be obtained at http://www.vanderbilt.edu/nursing/kwallston/scoringmhlc.htm

(e) Socio-demographics: gender, age, education, marital status, and employment status. For marital status, the

possible categories included: "single or never married", "currently married", "divorced/separated/widowed" (since the widowed category included only three participants, it was combined with the divorced or separated category to enable inclusion in analyses). For employment status, the possible categories included: "full-time", "part-time", and "unemployed".

Statistical Analysis: Analyses were performed using the SPSS 11.5 statistical software package. To ensure comparability between the two groups comprising the sample, we compared their socio-demographic variables, illness characteristics, TCI, and MHLC scale scores, using the independent-samples t-test (for continuous variables) and Pearson chi-square (for categorical variables). Racial/ethnic variation was found to be significantly different across the two studies: study 2 enrolled more individuals of racialethnic minority status (8 of 14) than did study 1 (8 of 31) (chi squared $_{(1)}$= 4.1, p=.046). Consequently, race/ethnicity was controlled for in all bivariate and multivariate analyses. None of the other socio-demographic variables were significantly different across the two study groups, nor were there any group differences in clinical factors, pre-treatment expectations, and rating scale scores (BDI, TCI, MHLC).

Univariate statistics (descriptives, frequencies) were used to describe the characteristics of the study sample. Also, a series of independent logistic regression analyses were performed with each variable to determine the association of the socio-demographic variables, illness characteristics, TCI, and MHLC scales with participants' pre-treatment expectations of the antidepressant (controlling for ethnicity). Subsequently, variables that met a significance level of p <.10 were included in a series of multivariate logistic regression models that were analyzed in various ways in order to identify the set of factors most predictive of participants' pre-treatment expectation. For Model 1, all variables that met p<.10 in the individual bivariate analyses were entered simultaneously in the model. In Model 2, the analysis for Model 1 was repeated while also incorporating the baseline depression measures (Ham-D and BDI) in order to ensure that any variance due to severity of participants' depression in relation to pre-treatment expectations of outcome was accounted for. In Model 3, we utilized a forward stepwise regression procedure (Forward: Wald) in order to explore which of the variables was most predictive of participants' pre-treatment expectation, based on the likelihood-ratio. Finally, in Model 4, the same forward

stepwise regression procedure was conducted while entering the baseline depression measures. The adjusted odds ratio (OR) for each predictor variable was computed along with the 95% confidence intervals, and the log-likelihood ratio test was used to test the significance of the overall model of logistic relationships. Also, the Nagelkerke R2 was used to quantify the amount of variation in the outcome variable explained by the predictors.

RESULTS

Participants' socio-demographic and clinical characteristics are shown in Table 1. Over half of our sample had never before tried an antidepressant drug despite the fact that, on average, participants reported having experienced more than 2 previous episodes of major depression and only 4 of the participants (9%) reported that their current depression was their first episode. The majority (81%) indicated their depression was related to various psychosocial stresses; close to one-third of the sample described specific social or environmental stress factors that preceded or triggered their depression (e.g., death of loved one, divorce or separation, unemployment, relocation). In terms of their level of expectation of the medication prior to treatment, the outcome variable in this study, 58% of participants held expectations that medication treatment would be "somewhat effective" rather than "very effective". Not surprisingly in the context of a medication clinical trial, none of participants expected the medication to be ineffective.

Figure 1

Table 1: Sample Socio-Demographic and Clinical Characteristics

	N (%) or Mean ± SD
Age	40.2 ± 12.5
Gender (% males)	23 (51%)
Education (years)	14.9 ± 2.7
Race/Ethnicity: White	29 (64%)
Marital Status	
Single (never married)	26 (58%)
Currently Married	6 (13%)
Divorced, Separated, or Widowed	13 (29%)
Employment	
Full-time	17 (38%)
Part-time	10 (22%)
Unemployed	17 (38%)
Baseline Ham-17 (mean ± SD)	21.2 ± 3.6
Beck Depression Inventory (mean ± SD)	23.9 ± 8.9
Age of Onset of Depression (mean years ± SD)	21 ± 10.2
Number of Past Episodes of Depression	2.3 ± 2.1
Duration of Current Episode (mean months ± SD)	38 ± 65.2
Under 12 months	19 (43%)
Over 12 months	25 (57%)
History of Antidepressants (% yes)	22 (47%)
Precipitating External Stress	
Absent	8 (19%)
Probably Present	27 (62%)
Definitely Present	8 (19%)
Outcome Expectation	
Not Very Effective	---

The variables that were individually statistically correlated with pre-treatment expectations (while controlling for ethnicity) are shown in the second column of Table 2. The analysis suggest that participants of racial/ethnic minority status were more likely to hold higher expectations than were Caucasians, as were participants whose index depressive episode was reported to be shorter than one year in duration. Health attribution style, measured by the Multidimensional Health Locus of Control scales, was significantly associated with pre-treatment expectations: participants rated as holding a stronger belief in the impact of 'powerful others' (i.e. health care professionals) on their health well-being were more likely to hold high expectations of treatment. There were also trends approaching statistical

significance: females were less likely to hold high expectations of the psychotropic drug than were men (p=.09), and those who were unemployed at the time of entry into the study (either voluntarily or not) were more likely to anticipate that the treatment provided will be very effective (p=.08). Two TCI scales also demonstrated a trend in terms of significance: lower scores on Harm Avoidance (p=.05) and higher scores on Self Directedness (p=.06) were associated with higher treatment expectation. Finally, baseline depression severity, as measured by the Ham-D and BDI, was not related to higher or lower treatment expectation. Other clinical course factors, including age of onset of depression, number of past depression episodes, presence of precipitating external stress associated with the current depressive episode, and history of taking antidepressants, were not statistically significant correlates of participants' pre-treatment expectation.

Figure 2

Table 2 : Bivariate and Multivariate Logistic Regression Analyses of Pre-Treatment Expectation

	Bivariate OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 4 OR (95% CI)
Socio-Demographics					
Race/Ethnicity					
Non-White	3.7 (1.03, 13.3)*	1.2 (0.1, 15.3)	1.4 (0.11, 19.2)		
White	1.0	1.0	1.0		
Gender					
Female	0.32 (0.1, 1.2)‡	0.11 (0.01, 1.2)‡	0.1 (0.01, 1.3)‡		
Male	1.0	1.0	1.0		
Employment					
Unemployed	4.0 (0.8, 19.5)‡	3.8 (0.5, 26.3)	3.9 (0.5, 28.5)		
Employed part-time	3.9 (0.7, 23.5)	2.6 (0.3, 21.0)	3.0 (0.3, 27.5)		
Employed full-time	1.0	1.0	1.0		
Clinical Course factors:					
Duration of episode					
Under 12 months	7.5 (1.4, 40.8)*	24.5 (1.1, 533.0)*	18.3 (0.7, 505.7)‡	5.9 (1.1, 31.4)*	4.4 (0.7, 26.7)
Over 12 months	1.0	1.0	1.0	1.0	1.0
Multidimensional Health LOC					
Belief in Powerful Others	1.2 (1.03, 1.4)*	1.1 (0.95, 1.4)	1.1 (0.9, 1.4)	1.2 (0.99, 1.4)‡	1.2 (0.99, 1.4)‡
Temperament & Character Inventory					
TCI: Harm Avoidant	0.9 (0.7, 1.0)‡	0.85 (0.7, 1.1)	0.84 (0.7, 1.1)	0.8 (0.7, 0.97)*	0.81 (0.7, 1.0)*
TCI: Self Directedness	1.2 (0.99, 1.4)‡	1.1 (0.9, 1.4)	1.1 (0.9, 1.5)		
Depression Severity					
Hamilton Depression Scale	0.99 (0.8, 1.2)		1.0 (0.9, 1.2)		1.1 (0.8, 1.4)
Beck Depression Inventory	0.98 (0.9, 1.1)		1.1 (0.8, 1.5)		0.97 (0.9, 1.1)

*p<.05; ‡ p<.10

Model 1: All significant bivariate variables (column 1) analyzed simultaneously:
-2 Log Likelihood=36.3; Nagelkereke R2 =.55; Model p=.002
Model 2: All significant bivariate variables and depression severity variables analyzed simultaneously:
-2 Log Likelihood=35.7; Nagelkereke R2 =.54; Model p=.01
Model 3: Forward stepwise analysis (Forward: Wald) of all significant bivariates (from Model 1):
-2 Log Likelihood=42.5; Nagelkereke R2 =.43; Model p=.001
Model 4: Forward stepwise analysis (Forward: Wald) of all

significant bivariates (from Model 1) while incorporating depression severity variables:

-2 Log Likelihood=41.5; Nagelkereke R2 =.42; Model p=.007

Table 2 also displays the results of a series of logistic regression models with participants' outcome expectation ('somewhat' versus 'very effective') as the outcome variable. In the first two models, pre-treatment expectation was regressed on all of the independent variables that met a p?.10 level of significance when analyzed separately. When these were entered simultaneously, this yielded few results, likely because of lack of sufficient statistical power due to the small sample size per the number of variables analyzed. The one variable that was significantly associated with the outcome was the duration of depressive episode (p=.04). Participants reporting a shorter episode of depression (under 12 months), were 24 times more likely to report high expectation in comparison with participants reporting a longer episode lasting more than one year. The introduction of the baseline depression scores attenuated the significance of this latter variable, likely because of loss of statistical power. Gender approached statistical significance in both Models 1 and 2, with females less likely to hold high pre-treatment expectations, however this variable was not retained as significant in the forward stepwise regression models.

Stepwise logistic regression, which identifies the variables that statistically contribute most to the prediction of the outcome after partialing out the effects of all of the other variables, is a useful procedure for studies that are exploratory in nature. Model 3 shows the results of the forward stepwise regression analysis of all variables that were individually associated with the pre-treatment outcome expectation at p ? .10. The analysis suggested that the duration of participants' current episode of depression and their scores on the temperament dimension of Harm Avoidance (HA) are the most statistically meaningful factors associated with level of expectation of the treatment prior to initiation of a drug/placebo trial. For each unit increase in HA, participants' odds of being in the high expectation category decreased by 20%. Alos, participants whose depressive episode was shorter than one year were six times more likely to have expectations that treatment would be 'very effective'. The inclination of participants to attribute more power and control over one's health status to doctors and other "powerful others" was also a meaningful contributor to accounting for the variance on the outcome

variable, but this factor was short of meeting statistical significance (p=.06). This three predictors model accounted for 43% of the variance of the outcome variable and was helpful in distinguishing between participants reporting expectations that treatment would be 'very effective' (79% cases correctly predicted) and those reporting expecting treatment to be 'somewhat effective' (83% cases correctly predicted). Overall, this model correctly classified 81% of the cases and is statistically significant (-2 Log Likelihood=42.5; p=.001).

In Model 4, the baseline depression severity scores were held constant in the model while conducting forward stepwise regression analysis. This analysis eliminated the significance of the episode duration variable, suggesting there may be collinearity between depression scores at baseline and episode duration. However, further analysis suggested this is not likely to be the case. When pre-treatment expectation was separately regressed on episode duration, the association remained significant (p=.03) when either or both of the baseline depression scores were incorporated into the analysis. Most likely, the lack of statistical significance for episode duration in Model 4 merely reflects a loss of statistical power when the depression scores are entered in the model. At any rate, this latter model is statistically significant (p=.007) and accounts for 41.5% of the variance of pre-treatment expectations.

DISCUSSION

This is the first study to explore the association between various individual and clinical factors, including health locus of control and temperament/character, and individuals' expectation of medication in the context of a randomized clinical trial for depression. The premise of this study is that patients' anticipation of treatment benefit is a critical factor in their decision to seek out treatment and to remain invested in the treatment, as well as an important factor in promoting symptomatic changes ([3]). We found several factors that helped to distinguish between individuals expecting treatment to be "very effective" and those expecting it to be "somewhat effective". One of the most important of these was the duration of depressive episode. Individuals with higher expectations tended to report a shorter duration of current episode (less than 12 months). This suggests that a shorter episode of illness may make recovery seem more tangible or viable. Or, perhaps, the neurobiological and psychological changes accompanying depression (e.g., distorted judgment about prospects for future life satisfaction) have not become quite as fixed in the minds of

participants. There is no previous research to refer to on this question, as the empirical relationship between duration of illness and pre-treatment expectation among psychiatric patients has been reported in only one previous study ([20]), which found no significant association. To try to better understand why participants entering treatment with a shorter depressive episode held higher treatment expectations, we examined whether participants' previous experience with antidepressant treatment, the severity of depression at baseline, or the extent to which the depression was precipitated by external stress affected this association and found that these factors did not change the association between a higher outcome expectation and a shorter episode of depression. If this finding is replicated in future studies, it would be critical to gain better understanding of how the duration of depressive illness interacts with patients' expectations and the extent to which this interaction impacts treatment outcome.

Participants' score on the Harm Avoidance (HA) scale of the TCI was another important correlate of patients' pre-treatment expectation in this study. Based on Cloninger's unified biosocial theory of personality ([30]), higher scores on HA signify a tendency to react with pessimism, worry, shyness, lethargy and general inhibition to danger or uncertainty. Conversely, lower scores on HA suggest temperament characterized as relaxed, outgoing, self-confident and energetic. In our study, higher HA scorers tended to have lower treatment expectation, a finding that is in keeping with the cautious or defensive posture that defines HA. This finding would be easier to interpret were it shown that the temperament dimension of HA is independent of depressive symptoms. However, various studies utilizing the TCI have found that HA scores tend to be negatively correlated with depression ([34,35,36,37]), with lower HA scores predicting better antidepressant treatment outcomes ([38]), and antidepressant treatment response is associated with a decrease (though not normalization) in HA scores ([39,40,41,42]). This evidence, suggesting that HA may be a trait marker for depression, raises a question about whether an association between HA scores and treatment expectations is really an association between expectation and level of depression. Our data, however, suggest that higher HA is correlated with lower treatment expectations independently of depression severity. Testing whether the association between HA and treatment expectation attenuates or disappears when baseline symptom scores (Ham-D and BDI) are added to the regression equation, we found that HA regression coefficients did not change

meaningfully. The association between treatment expectation and temperament and character dimensions deserves further study, ideally using longitudinal designs that allow assessments over a period of time, as the symptoms of depression change in the natural course of the illness.

We also sought to identify any relationships between participants' health LOC and pre-treatment expectations. Various studies have established the association between higher 'internal' LOC, also known as 'self-efficacy', or the perception of one's own ability to take care of one's health, and successful response to treatment for depression ([43,44,45]), but the association between LOC and treatment expectancy has not previously been studied. Our data suggest that 'external' health locus of control is likely a meaningful correlate of treatment expectation (demonstrated a statistical trend): participants with higher scores on external health LOC, indicating a propensity to attribute more control over one's health to "powerful others" (e.g., doctors, family members), were more likely to come into treatment with higher treatment expectations. It is possible that the relative weight of external versus internal LOC depends on the specific outcome or treatment context studied. In relation to the associations others have found between internal LOC and treatment outcome, our finding may also support the idea proposed by Reynaert et al. ([44]) that LOC operates via two different mechanisms to influence symptom reduction. According to these authors, inclination toward internal LOC may be a demonstration of "auto-suggestion", or an ability to mobilize positive emotions and cognitions that directly support symptomatic improvement. On the other hand, having more of an external LOC (e.g., belief in 'powerful others') may be a reflection of "hetero-suggestion", described as an inclination toward belief in the power of others or external events to heal oneself. Consistent with our finding, it may be that external LOC influences symptom-based outcomes indirectly through its positive association with treatment expectations. This interesting possibility should be investigated in prospective studies that measure both LOC and treatment expectations over time.

Contrary to the findings of several studies ([7, 11, 22, 24]), we did not find participants' pre-treatment expectations to be related to the severity of their depressive symptoms. Participants who were more symptomatic had neither higher nor lower expectation of the medication relative to their less symptomatic counterparts. Limited research findings regarding this relationship have been mixed. In the context

of psychotherapy, Gibbons et al. ([6]) also found no significant correlations between patients' pre-treatment expectations and scores on either the BDI or Ham-D. However, Joyce & Piper ([7]) and Hansson & Berglund ([11]), found that higher level of severity of symptoms was associated with lower pre-treatment outcome expectations. Still others have found that patients expected to gain more from drug treatment and psychosocial treatment if they had more severe symptomatology at treatment initiation ([22], [24]). The majority of these studies examine expectation in the context of psychotherapy rather than pharmacology treatment, and so it is difficult to know the extent to which expectations are comparable in terms of their dynamics with patients' characteristics. Nevertheless, because of the conceptual relevance of symptom severity to treatment expectation, baseline depression scores were incorporated into some of the analytic models (Models 2 and 4) to examine their effect on the associations between expectation and other correlates. We found that depression severity scores tended to attenuate the associations between expectation and other variables. For instance, the inclusion of BDI and Ham-D scores eliminated the significance of depressive episode duration (Model 4). The additional analyses that we conducted suggested that the likely cause of this is loss of statistical power rather than a substantive relationship (i.e. spurious) between outcome expectation and episode duration. At any rate, the relationship between severity of illness and treatment expectation in the context of pharmacologic as well as psychotherapeutic treatment deserves more research attention.

Clinical course factors aside from duration of episode, including the number of past episodes, history of treatment with antidepressants, age of depression onset, and the presence of identifiable external stress leading up to the index episode of depression, were not significantly correlated with baseline treatment expectations. This finding was somewhat surprising since these factors are implicated in the individuals' past experiences with their illness and with recovery. As such, we might have expected that they would shape individuals' attitudinal stance when initiating treatment in a medication clinical trial ([46]). Unfortunately, we did not have information about participants' history of professional mental health treatment besides anti-depressants. History of psychotherapy/counseling may be an important factor to consider when exploring treatment expectations in drug as well as non-drug treatment studies. Further examination of the extent to which the course of illness and history with prior treatments predict outcome

expectations is warranted in future studies to ascertain which factors are relevant for understanding who is more likely to anticipate benefit from treatment.

Of the socio-demographic characteristics, racial/ethnic minority status was a significant bivariate correlate of treatment expectation in our antidepressant clinical trials. Participants of racial/ethnic minority status were more likely than whites to expect medication to be 'highly effective' at the onset of the drug trial. While this variable was not retained in the multivariate analysis, given the inconsistency of this finding with other related studies, this warrants some attention. Researchers have generally found racial/ethnic minorities to hold less favorable attitudes toward drug treatment than whites ([47,48]) and another study of psychiatric inpatients found that racial/ethnic minorities held lower treatment expectations than whites ([20]). The departure of our finding from these studies may be explained by the distinctiveness of our sample, for instance the individuals' level of acculturation and inter-cultural trust ([49]), about which we have no information. It is also quite possible that expectations among volunteers for a randomized clinical trial are different from treatment expectations held by individuals receiving psychiatric treatment in other contexts.

In terms of other socio-demographic characteristics, gender and employment status both demonstrated a statistical trend toward significance in some of the analyses. Unemployed participants held higher expectations than those who were fully employed (part-time employment was not a significant correlate). This association between employment status and treatment expectations has been noted before ([20]), but contrary to our findings, working full-time was associated with a more positive outlook related to treatment. In terms of gender differences, in our study there was a (non-significant) trend indicating that women held lower expectations of the treatment than men. These demographic characteristics may or may not prove significant in future studies. Finally, we did not find participants' age, education, and marital status to be significant correlates of treatment expectations. Previous studies suggest that these characteristics are inconsistently associated with treatment expectations, although older, married and less educated individuals seem to be more inclined toward higher expectations ([20], [22]).

While these results offer new insights, the limitations of this study should temper any generalizations based upon these data. We studied medication related expectations in the context of placebo-controlled, double-blinded randomized

clinical trials. Considering that the potential of receiving a placebo rather than active medication, which was quite high in one of the two studies utilized (75%), may have impacted the nature and dynamics of participants' treatment expectations, we must be cautious and suggest that these findings may not apply to a regular clinical setting. Further, our sample size was fairly small, yielding low statistical power that may have increased the likelihood of both Type I and Type II errors. The lack of statistical power tempers our confidence that the simultaneous analysis of all potential factors associated with participants' outcome expectation to identify their relative contribution yields accurate findings in this study. Moreover, while we may refer to the various independent variables as 'shaping' expectation, because many are either immutable characteristics or factors that logically predate individuals' treatment expectations, given the correlational nature of this study we cannot infer causality. Finally, our method of assessing expectation was rather limited as we ended up with a dichotomous variable that did not capture the full range of potential expectation (none of our patients reported low expectation of the medication). Moreover, our measure also did not capture several aspects of treatment expectation, such as the strength of expectancy versus the magnitude of the expected response ($_{50}$), expectations of the process versus outcome of treatment ($_3$), or the distinction between affective aspects of expectancy and more cognitive based judgments about treatment credibility ($_{51}$). Future studies should develop and utilize more sensitive and comprehensive measures of treatment expectation.

Nevertheless, by exploring the association between personal characteristics and pre- treatment expectation in the context of a randomized placebo controlled antidepressant trial, we have begun to identify several potential predictors of treatment expectation among individuals seeking drug treatment for MDD. We recommend that more sensitive measures of treatment expectation be developed and used in research that follows the natural progression of depression over time. Longitudinal designs would allow us to understand the interaction between personal or contextual factors and treatment expectation over time and also allow us to differentiate between those factors that impact treatment outcomes directly and those that impact treatment outcomes indirectly by way of their association with treatment expectations. Ideally, if conducting cross-sectional analyses of factors relating to treatment outcome expectation, future studies would rely on larger sample sizes in order to conduct multivariate analyses with sufficient statistical power.

In summary, this study sought to explore various individual and illness characteristics that are associated with pre-treatment outcome expectation among depressed patients entering randomized placebo controlled drug trials. We found that a slight majority of participants expected treatment to be "somewhat effective" (58%) rather than "very effective" (42%). Of the socio-demographic characteristics, clinical factors, health locus of control and temperament/character dimensions that were examined, we found the duration of the index depressive episode and the propensity toward temperament characterized by "harm avoidance" (Cloninger's TCI) to be two of the most significant correlates of pre-treatment expectations. Contrary to previous work regarding treatment expectations in various contexts, we did not find pre-treatment expectation to be associated with the severity of (depressive) symptoms. Suggestions are made for further research to better understand the nature and development of individuals' treatment expectations.

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