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Hopelessness as a Predictor of Non-Response to Fluoxetine in Major Depressive Disorder

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Background. *The purpose of this study was to study hopelessness as a predictor of response to fluoxetine in outpatients with Major Depressive Disorder (MDD).*

Methods. *The degree of hopelessness was assessed during the baseline visit with the use of the Beck Hopelessness Scale (BHS) in 312 patients with MDD (56.1% women; 39.8 ± 10.3 years of age) who entered an 8-week, 20-mg, fixed-dose, open trial of fluoxetine. With the use of a logistic regression we tested whether BHS scores at baseline predicted clinical response, controlling for the severity of depression as reflected by the total score on the 17-item Hamilton Depression Rating Scale (HAM-D-17). With the use of a multiple regression we also tested whether BHS scores at baseline predicted HAM-D-17 scores at endpoint, controlling for HAM-D-17 scores at baseline.*

Results. *After controlling for depression severity at baseline, a greater degree of hopelessness was found to significantly increase the risk of non-response to fluoxetine (p = 0.0413), as well as the risk of greater endpoint depression severity (p = 0.0305).*

Conclusions. *Hopelessness appeared to be associated with poorer response to treatment with fluoxetine in MDD, and this was independent of depression severity. Similar studies involving treatment with higher doses of fluoxetine and for greater duration as well as a placebo comparator arm are needed to further explore the relationship between hopelessness, placebo response and drug response.*

Keywords Depression, Fluoxetine, Hopelessness, Predict, Response

INTRODUCTION

Although antidepressant medications have been widely prescribed for decades, predictions regarding which depressed patients will experience a clinical response are subject to uncertainty and error. Identifying strong predictors of clinical response could be useful in helping clinicians and patients select the appropriate intervention but also useful in furthering our understanding of what constitutes recovery from depression. Hopelessness is a factor that warrants further investigation as a potential predictor of improvement since hope and the expectation of improvement are features, which may be closely

related to placebo response (1). Indirect evidence supporting this argument comes by way of a study by Brown et al. (2) in which, among depressed patients who received placebo, those who experienced improvement were found to be significantly more likely to report a history of clinical response to an antidepressant. More direct evidence for a specific link between the placebo response and expectation of improvement comes by way of a study by Sotsky et al. (3), involving 293 depressed outpatients participating in a multi-center study who were randomized to receive interpersonal psychotherapy, cognitive behavioral therapy, imipramine or placebo for 16 weeks. In that study, the authors reported a higher degree of expectation of improvement at baseline predicted a lower level of depression severity at endpoint across all treatment groups, but within treatment groups this relationship was only consistent (present completer and intent-to-treat analyses) for patients who were randomized to placebo. However, despite the potential relationship

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between hopelessness and placebo response, studies that examine the role of hopelessness during the pharmacotherapy of depression are lacking.

Aims of the Study

The purpose of this study is to examine the potential impact of hopelessness on treatment with fluoxetine in outpatients with Major Depressive Disorder (MDD) who were enrolled in an 8-week, 20 mg, fixed-dose, open-trial of fluoxetine.

MATERIAL AND METHODS

A total of 384 outpatients, ages 18–65 years, who met criteria for a current major depressive episode according to the Structured Clinical Interview for DSM-III-R (4) were recruited through radio advertisements, newspaper advertisements or colleague referrals into an ongoing two-phase antidepressant trial conducted at the Massachusetts General Hospital Depression Clinical and Research Program (DCRP). All patients had a baseline 17-item Hamilton Depression Rating Scale (5) score ≥ 16 and were medication-free for at least two weeks prior to study entry.

Exclusion criteria included pregnant women and women of child bearing potential who were not using a medically accepted means of contraception, women of child bearing potential taking a birth control pill, lactating women, patients with serious suicidal risk or serious, unstable medical illness, patients with a history of seizure disorder, patients with the DSM-III-R diagnoses of organic mental disorders, substance use disorders, including alcohol, active within the last year, schizophrenia, delusional disorder, psychotic disorders not elsewhere classified, bipolar disorder, or antisocial personality disorder, patients with a history of multiple adverse drug reactions or allergy to the study drugs, patients with mood congruent or mood incongruent psychotic features, current use of other psychotropic drugs, patients with clinical or laboratory evidence of hypothyroidism, patients whose depression had failed to respond in the past to a trial of either higher doses of fluoxetine (60–80 mg/day), or to the combination of fluoxetine and desipramine, or the combination of fluoxetine and lithium, patients who had failed to respond during the course of their current major depressive episode to at least one adequate antidepressant trial, defined as six weeks or more of treatment with either > 150 mg of imipramine (or its tricyclic equivalent) or > 60 of phenelzine (or its monoamine oxidase inhibitor equivalent). SSRI (other than fluoxetine) treatment failure was not a basis for exclusion from the study.

During the screen visit, an IRB-approved written informed consent was obtained from all patients. A medical and psychiatric history, physical examination, serum chemistries, hematological measures, electrocardiogram (EKG), and urine pregnancy test were then performed. The 31-item of the Hamilton Rating Scale for Depression (HAM-D-31) was also adminis-

tered during the screen visit. The screen visit was conducted by experienced psychologists or psychiatrists. In our group, training in the use of instruments such as the HAM-D-31 and SCID-P is done by peer review of videotaped interviews. Patients were asked to return one week later for the baseline visit. All patients returned for their baseline visit (n = 384) and were started on a 20mg, fixed-dose regimen of fluoxetine. The HAM-D-31 was administered during the baseline visit. Of the 384 patients enrolled, 312 also completed the Beck Hopelessness Scale (6) at baseline. The BHS is a self-rated scale containing 20 statements, each of which the patient responds to either being true or false. We scored answers consistent with hopelessness as 1 while those not consistent with hopelessness as 0. Subsequent visits took place every other week for a total 8 weeks. The HAM-D-31 was administered during all study visits.

Statistical Analyses

Chi-square tests and unpaired t-tests were used to compare patients from the present sample (n = 312) with the remaining sample (n = 72) on a number of demographic and clinical variables. A responder was defined as having a 50% or greater reduction in HAM-D-17 score from baseline to endpoint. An intent-to-treat (ITT) analysis was used to define the severity of depression at endpoint, in which the last recorded HAM-D-17 score substituted the score at week 8 for patients who prematurely discontinued the study. A t-test was used to compare BHS scores at baseline between responders and non-responders. A logistic regression was performed to test whether BHS scores at baseline predicted clinical response, controlling for HAM-D-17 scores at baseline. With the use of a multiple regression we then tested whether BHS scores at baseline predicted HAM-D-17 scores at endpoint, controlling for HAM-D-17 scores at baseline.

RESULTS

There were no statistically significant differences between patients that did (n = 312) and did not (n = 72) complete the BHS scale at baseline in terms of age (39.8 ± 10.3 versus 40.3 ± 11.1 years, respectively), gender (175/312 or 56.1% women versus 35/72 or 48.6% women, respectively), duration of the current Major Depressive Episode (MDE) (3.3 ± 5.6 versus 4.5 ± 13.2 years, respectively), number of MDEs (4.2 ± 9.4 versus 4.6 ± 9.4, respectively), age of first onset of MDD (25.6 ± 13.1 versus 26.9 ± 13.6 years, respectively), or baseline HAM-D-17 score (19.5 ± 3.3 versus 20.2 ± 3.9, respectively) (p > 0.05 for all analyses). Of the 312 patients, 181 (58.0%) responded. 45 patients prematurely discontinued treatment (14.4%). The mean BHS score for the entire sample was 11.6 ± 5.1. The mean BHS scores at baseline in responders and non-responders were 10.9 ± 4.9 versus 12.5 ± 5.1 respectively (p = 0.0083, DF = 310). A logistic regression with clinical response entered

as the dependent variable, BHS scores during the baseline visit as the independent variable and controlling for HAM-D-17 scores during the baseline visit. Higher BHS scores predicted a greater likelihood of non-response ($p = 0.0413$; chi-square = 6.391; Coef/SE = 2.041; 95% C.I. = 1.021–1.176). A multiple regression with endpoint HAM-D-17 scores entered as the dependant variable with BHS scores during the baseline visit as the independent variable and controlling for HAM-D-17 scores during the baseline visit. Greater BHS scores predicted greater HAM-D-17 endpoint scores ($p = 0.0305$; coefficient = 0.162; standard error = 0.074).

DISCUSSION

The results of the present study reveal a significant relationship between the degree of hopelessness present in MDD patients immediately before the onset of pharmacotherapy with fluoxetine and the likelihood of responding by 8 weeks. Specifically, a greater degree of hopelessness was found to decrease the likelihood of achieving clinical response, and this relationship was independent of the severity of depression at baseline. In addition, a greater degree of hopelessness at baseline was also related to a greater severity of depression by the end of treatment, also controlling for the severity of depression at baseline. To our knowledge, this is the first study examining hopelessness as a predictor of clinical response to pharmacotherapy in MDD. To date, only one other study has examined the relationship between hopelessness and acute treatment for depression. In a study of 107 depressed adolescents who underwent a brief trial of psychotherapy, Brent et al. (7) found that higher levels of hopelessness before treatment predicted the persistence of depression after treatment.

The present study adds to a growing literature suggesting that hopelessness may complicate the treatment of depression in a variety of ways. In addition to decreasing one's risk of responding to treatment, a high degree of hopelessness has also been found to persist in elderly patients with remitted depression who had a history of suicide attempt (8, 9). Furthermore, patients with a high degree of hopelessness may also be at risk of receiving sub-optimal treatment for their depression, since the results of one study indicate that hopeless patients overestimate the risks and underestimate the benefits of potentially life-saving treatments (10). This finding is particularly important for patients with treatment-resistant depression, who have not responded to prior antidepressant treatments and typically require higher doses of medication and/or more aggressive treatment in order to respond. As a result, after protracted treatment courses treatment-resistant patients may experience an even greater tendency to under-estimate the benefits of the next treatment.

In addition to adversely affecting the treatment of depression, hopelessness has also been linked to an increased risk of suicide across psychiatric diagnoses (11), which currently ranks as the third leading cause of death in adolescents (12). In parallel, hopelessness has been shown to predict a variety of other adverse health outcomes in large epidemiologic studies ranging from incident myocardial infarctions, hypertension and cancer as well as an increase in all-cause mortality (13,14,15,16,17). In fact, this relationship between hopelessness and these adverse outcomes remains significant even after adjusting for other biological, socioeconomic or behavioral risk factors such as depression, smoking, perceived health or social support.

Limitations

One limitation of the present study is the absence of placebo, which would help further clarify to what extent the effect of hopelessness on clinical response is mediated through the placebo effect. A further limitation is that of sampling bias. Clinical trials have a number of inclusion and exclusion criteria and, as a result, patients in clinical trials do not directly reflect the typical outpatient population of MDD patients. This may be particularly true of the present study since patients at serious risk for suicide, who presumably would also have a greater degree of hopelessness than non-suicidal patients, were excluded. In addition, the present trial involved treatment with 20 mg of fluoxetine daily for 8 weeks. As a result, it is unclear whether or not treatment with higher doses of fluoxetine given for a longer duration would have yielded different results. Finally, our assessment of hopelessness during the baseline visit provides a cross-sectional measure of severity and is not informative about possible heterogeneous patterns of hopelessness during the course of illness. There may be patients whose level of hopelessness is static, for example, and others whose level of hopelessness fluctuates frequently according to life events. Our results do not address the relative likelihood of clinical response for patients in these two hypothetical groups. Future studies addressing these limitations are necessary to shed light on the relationship between hopelessness and clinical response to pharmacotherapy in patients with MDD.

CONCLUSION

In the present work, hopelessness appears to be associated with poorer response to treatment with fluoxetine in outpatients with MDD, and this was independent of depression severity. Similar studies involving treatment with higher doses of fluoxetine and for a greater duration as well as a placebo comparator arm are needed to further explore the relationship between hopelessness, placebo response, and drug response.

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