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Anxious Depression and early changes in the HAMD-17 anxiety-somatization factor items and antidepressant treatment outcome

Amy H. Farabaugh, PhD^{1,*}, Stella Bitran, PhD¹, Janet Witte, MD, MPH¹, Jonathan Alpert, MD, PhD¹, Sarah Chuzi, BA¹, Alisabet J. Clain, MS¹, Lee Baer, PhD¹, Maurizio Fava, MD¹, Patrick J. McGrath, MD², Christina Dording, MD¹, David Mischoulon, MD, PhD¹, and George I Papakostas, MD¹

¹ Depression Clinical and Research Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA

² Columbia University College of Physicians and Surgeons Department of Psychiatry & the New York State Psychiatric Institute, New York, New York

Abstract

Objective—To assess the relationship between early changes in anxiety/somatization symptoms and treatment outcome among MDD subjects during a 12-week trial of fluoxetine. We also examined the relationship between anxious depression and treatment response.

Methods—510 MDD patients received 12 weeks of fluoxetine with flexible dosing (target dosages: 10 mg/day (week 1), 20 mg/day (weeks 2–4), 40 mg/day (weeks 4–8), and 60 mg/day (weeks 5–12)). We assessed the relationship between early changes in HAMD-17- anxiety/somatization factor items and depressive remission, as well as whether anxious depression at baseline predicted remission at study endpoint. . Baseline HAMD-17 scores were considered as covariates and the Bonferroni correction ($p \leq .008$) was used for multiple comparisons.

Results—Adjusting for baseline HAMD-17 scores, patients who experienced greater early improvement in somatic symptoms (gastrointestinal) were significantly more likely to attain remission ($\text{HAMD-17} < 8$) at endpoint than those without early improvement ($p = .006$). Early changes in the remaining items did not predict remission, nor did anxious depression at baseline.

Conclusions—Among the anxiety/somatization factor items, only early changes in somatic symptoms (gastrointestinal) predicted remission. Future studies are warranted to further investigate this relationship, as well as that between anxious depression and treatment outcome.

Keywords

Depression; Antidepressants; Anxious Depression; Anxiety; Predictors; Remission

Introduction

The Anxiety/Somatization factor of the 17-item Hamilton Rating Scale for Depression (HAMD-17) includes six items: anxiety (psychic), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), hypochondriasis, and insight. In a previous

*Address correspondence and requests for reprints to: Amy H Farabaugh, PhD, Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, 50 Staniford Street, Suite 401, Boston, MA 02114, Phone: 617-726-1629, afarabaugh@partners.org.

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study, we assessed whether early changes (defined as those observed between baseline and week 1) in the Anxiety/Somatization factor of the HAMD-17 predicted response to acute treatment with the SSRI fluoxetine, hypericum perforatum, or placebo (Farabaugh et al., 2005). Out of the six items, we found that a greater reduction in scores during the first week of therapy for the somatic symptoms (general) item, which is most commonly interpreted as a measure of fatigue, predicted superior outcome (greater remission rates) to active treatment but not placebo. However, given the post-hoc, exploratory nature of our analysis, it was not possible to conclude whether that finding represented a true or chance finding.

In an attempt to replicate and confirm our earlier findings, in the present work we assessed the relationship between early changes (defined as baseline to week 1) in HAMD-17 Anxiety/Somatization factor items and treatment outcome among major depressive disorder (MDD) patients participating in a 12-week study of fluoxetine monotherapy. Early change also provides clinical utility, as identifying potential responders early may help guide clinical decision making. In addition, in an attempt to replicate the STAR*D findings (Fava et al., 2008) we also sought to assess whether the presence of anxious depression (defined as having an Anxiety/Somatization factor score greater than or equal to 7 at baseline) predicted poorer chances of achieving remission. In order to accomplish these goals, we examined data from a previously published, 12-week, open-label, fixed-flexible dose trial of fluoxetine for MDD.

Methods

Data were derived from a previous study, designed to assess for predictors of MDD relapse in among fluoxetine responders. The study was conducted at two sites: the New York State Psychiatric Institute and the Depression Clinical & Research Program of the Massachusetts General Hospital (see McGrath et al., 2006, for a complete description). Institutional review boards at both sites approved the study, and all participants provided written informed consent.

At screening visit, outpatients between the ages of 18 and 65 were required to meet criteria for MDD diagnosed with the Structured Clinical Interview for DSM-IV -Patient Edition (SCID-I/P; First et al., 1996) in order to be eligible for the trial. No minimum depression severity score was required for inclusion. Out of the 510 subjects, 434 had a baseline HAMD-17 score greater than 13 (mean = 17.6, SD = 5.05). Medical screening included medical history, physical examination, electrocardiogram, complete blood count, urinalysis, blood chemistry screening, thyroid function tests, and a urine drug screen.

The following criteria were defined as exclusionary: significant suicidal risk, pregnancy, breastfeeding or absence of effective contraception for women, unstable physical disorders, neurological disorders significantly affecting CNS function, including a history of seizures, a lifetime history of any organic mental disorder, psychotic disorder, or mania, substance abuse or dependence active in the previous six months, except for nicotine dependence, concurrent use of medications suspected to cause or exacerbate depression, clinical or laboratory evidence of hypothyroidism without adequate and stable replacement, and a history of non-response to an adequate trial of a selective serotonin reuptake inhibitor (defined as a four-week trial of ≥ 40 mg of fluoxetine or its equivalent daily).

After a one-week medication-free wash out period, patients who continued to meet inclusion criteria at the baseline visit began open-label fluoxetine for 12 weeks. Target dosing of fluoxetine was: 10 mg daily for week 1; 20 mg daily for weeks 2–4; 40 mg daily for weeks 4–8; 60 mg daily for weeks 5–12. Medication management visits were weekly for the first 6 weeks, biweekly for weeks 7–10, and weekly for weeks 11 and 12.

The primary efficacy measure was the 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton, 1960). The Anxiety/Somatization factor of the HAMD-17 includes six items: anxiety (psychic), anxiety (somatic), somatic symptoms (gastrointestinal), somatic symptoms (general), hypochondriasis, and insight. Early change in these items of the HAMD-17 was defined as the change in score between baseline and week 1 (baseline minus week 1). The HAMD-17 instrument was administered at each visit by clinical study investigators. The baseline total Anxiety/Somatization factor score of great than or equal to 7 was used to define anxious depression (Fava et al., 2008).

Data Analysis

Logistic regressions were performed to investigate whether early changes (from baseline to week 1) in the 17-item Hamilton Depression Rating Scale (HAMD-17; Hamilton 1960) Anxiety/Somatization factor items were associated with meeting criteria for remission (HAMD-17 < 8) at endpoint of the acute phase (week 12 or early discontinuation visit). These regressions were adjusted for multiple comparisons using the Bonferroni correction with $p < 0.008$ considered statistically significant at the 95% level for each of the 6 comparisons. For all of the regressions, meeting criteria for remission at endpoint (by last observation carried forward) was the dependent variable, and initial severity of MDD at baseline was an independent variable as well as the change in score from baseline to week 1 of the HAMD-17 anxiety/somatization items. We did not control for chronicity of depression, as it was not a significant predictor of poorer outcome in either the parent study or another study conducted by Fava and colleagues (1997). We also used logistic regression to investigate whether anxious depression predicted remission at endpoint, after controlling for severity of depression. All analyses were conducted on the intent to treat (ITT) sample, with the additional criterion that a subject had to have a HAMD-17 score at baseline and at week 1 to be entered into the sample. As a post hoc analysis, to address that there was no HAMD-17 cutoff at baseline for inclusion, the analyses were run with only those participants who had a HAMD-17 score at baseline of > 13 ($n = 434$). Results were similar and produced no additional significant results; therefore, only the results from the initial sample of participants ($n=510$) are reported in this paper. Using G*Power, (Erdfeider et al., 1996) we computed the power needed to detect an effect with a sample size of approximately 500 subjects ($p < .05$; two tailed). The power was computed as > 0.99 .

Results

Five hundred and ten subjects (mean age = 37.56 ± 11.23 ; 270 women) were eligible for the intent to treat analysis, based on having HAMD-17 scores available for both baseline and week 1. The demographic and clinical characteristics of this sample are summarized in Table 1.

Patients who eventually achieved remission demonstrated a significantly greater reduction in the somatic symptoms (GI) item score from baseline to week 1 compared to non-remitters ((OR = 1.77; CI = 1.18–2.65) $p = .006$). This relationship remained statistically significant even after the Bonferroni correction (Table 2 & Table 3). Specifically, remitters demonstrated a mean reduction of $.14 \pm .64$ from baseline to visit 1, compared to nonremitters who demonstrated a mean reduction of $-.03 \pm .51$ from baseline to visit 1. Early changes (baseline to week 1) in scores for the remaining anxiety somatization subscale items were not significantly different between remitters and non-remitters, after applying the Bonferroni correction for multiple comparisons (Table 3). Additionally, anxious depression status at baseline did not predict remission at endpoint (OR = .989; $p = .97$).

Discussion

Anxious depression at baseline did not predict remission at endpoint of acute treatment, which is not consistent with the findings from STAR*D, which suggested that anxious depression significantly predicted response to level one treatment (Fava et al., 2008). In terms of individual items and early change after one week of antidepressant treatment, only changes in somatic symptoms (gastrointestinal) were predictive of remission. Early change suggests a return of appetite in patients with the depressive symptom of anorexia. The odds of being a remitter compared to a nonremitter increased by 76% for each additional point of improvement on this item.

These results do not duplicate an earlier finding from our group, which suggested that the presence of early improvement on the HAMD-17 items concerning fatigue and general somatic symptoms was significantly predictive of achieving remission with active treatment. Recently, early clinical worsening, based on the HAMD-17, has been shown to be predictive of outcome (Cusin et al., 2007), and structural MRI data has recently suggested that faster rates of symptom improvement were associated with greater grey matter volume in the anterior cingulate cortex, insula, and right temporo-parietal cortex (Chen et al., 2007). Change in appetite may prove valuable as a predictor of subsequent remission on active treatment, especially if replicated in other studies. Trivedi and others (2005), in a 12 week treatment study of nefazodone for depression, found that early changes (first 4 weeks) on the mood cluster, the sleep/psychic anxiety cluster, and the somatic anxiety/weight cluster of the HAMD-17 discriminated between late responders and nonresponders.

These findings suggest that early improvement on the HAMD-17 item concerning appetite was significantly predictive of achieving remission with active treatment. This finding is in contrast to others (Bech et al, 2009) who have not found that change in appetite, as measured by the HAMD-17, is sensitive to response. Despite the possibility that this is a chance finding, it is also possible that early changes in somatic symptoms (gastrointestinal) may be linked to antidepressant treatment outcome, which is consistent with studies suggesting a relationship between somatic symptoms and depression (Henriques et al., 2009; Mussell, et al., 2008; Trivedi, 2004). Additionally, there is evidence that change in appetite is suggestive of relapse and improvement in treatment (Kanai et al., 2003; Trivedi, 2004).

Limitations of this study include the lack of a control arm, which prevents us from ruling out placebo effects. Our findings may only be applicable to antidepressant treatment with fluoxetine, and may not be generalizable to other antidepressants, especially those with a different mechanism of action. In addition, patients were started on 10 mg, rather than 20 mg fluoxetine, for one week in order to improve tolerability. While this may have influenced the main findings, there is data to suggest that doses lower than 20 mg of fluoxetine may be therapeutic (Wernicke et al., 1988). To replicate the previous study (Farabaugh et al., 2005), we controlled for severity of depression (at baseline) by using the HAMD-17 as a covariate; however, we recognize that the HAMD is also a measure of anxiety and this may have biased our results. Thus, we may have overcorrected by controlling a measure that also rates anxiety.

Given the myriad implications of early identification of possible benefits of medications (Farabaugh et al., 2005), studies have not only examined patterns of response, but also several other possible predictors of outcome. Future studies are needed to replicate findings, and to determine whether predictors are the same or different, depending on the mechanism of action of the antidepressant agent, as well as to further determine predictors of psychotherapy.

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Table 1
Demographic and clinical factors for the intent-to-treat sample

	Sample (n=510)	
	n	%
<i>Ethnicity:</i>		
Hispanic	42	8.2
Black	45	8.8
Caucasian	400	78.4
Asian	13	2.5
Native American	1	.2
Other	9	1.8
<i>Gender:</i>		
Female	270	52.9
<i>Marital Status:</i>		
Single	299	58.6
Married	94	18.4
Separated	25	4.9
Divorced	88	17.3
Widowed	4	.8
<i>Employment:</i>		
Employed	330	64.7
<i>Remission:</i>		
Remitters (n = 342)	201	39.4
<i>Anxious Depression</i>	156	30.6

Table 2
Early Changes in Anxiety/Somatization factor score at baseline

(Anxiety/Somatization factor score ≥ 7 at baseline)

	Mean	SD
Age (years)	37.56	11.23
Education (years)	14.73	2.542
HAMD-17 Baseline	17.56	5.048
HAMD-17 at Endpoint	7.36	5.597
Nonremitters' HAMD-17 at baseline	17.58	5.275
Remitters' HAMD-17 at baseline	16.79	4.766

Table 3
Early Changes in HAM-D-17 Anxiety/Somatization Factor Items in Relationship to Treatment Outcome, intent-to-treat sample

	Remitters mean change baseline– week 1		Non-remitters mean change baseline– week 1		SD	p	Wald	OR	95% CI
Anxiety (psychic)	.3433 +/-	.96258	.2340 +/-	.97569	.312	1.024	1.129	.892	1.429
Anxiety (somatic)	.1741 +/-	1.07449	.1277 +/-	1.04095	.828	.047	1.025	.823	1.275
Somatic symptoms(gastrointestinal)	.1443 +/-	.64349	-.0284 +/-	.50629	.006	7.563	1.765	1.177	2.645
Somatic symptoms(general)	.2338 +/-	.74165	.0426 +/-	.75472	.055	3.676	1.349	.993	1.833
Hypochondriasis	.0796 +/-	.60302	.0851 +/-	.89034	.954	.003	.991	.731	1.343
Insight	.0050 +/-	.07053	.0071 +/-	.08422	.842	.039	.751	.044	12.679

Bonferroni correction for 6 comparisons:

* Significant at 5% significance level if $p \leq .008$