Symptom Clusters as Predictors of Late Response to Antidepressant Treatment

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Objective: While there is some indication from studies in the acute phase of antidepressant treatment that there are differences in the timing of improvement in symptoms, relatively little work has explored the patterns of change for specific symptom clusters and the predictability of these changes to signal eventual response during the acute phase of treatment. This article investigates the use of clusters of symptoms on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) to define the pattern of late response versus nonresponse to antidepressant medication.

Method: Using principal component analysis, the HAM-D-17 was divided into 4 symptom clusters (mood, sleep/psychic anxiety, appetite, and somatic anxiety/weight). Data for 996 patients with major depressive disorder (DSM-III-R criteria), who participated in a 12-week acute phase study with nefazodone, were subjected to a post hoc analysis of changes in symptom cluster scores. Patients were divided into 3 groups: early responders (< 4 weeks), late responders (4–12 weeks), and nonresponders (> 12 weeks) as defined by < 50% reduction in HAM-D-17 scores from baseline. The late-responder and nonresponder groups were subjected to the principal component analysis. Data were collected from October 1992 to November 1994.

Results: There were significant differences in the pattern of symptom change on the mood cluster (weeks 3–4) ($p < .0001$), the sleep/psychic anxiety cluster (weeks 3–4) ($p < .003$), and the somatic anxiety/weight cluster (weeks 3–4) ($p < .01$) for the late responders compared to the nonresponders. Using change scores, a discriminant function analysis correctly assigned 127 of the 182 late responders and 85 of the 133 nonresponders, or 70% of the late responders and 64% of the nonresponders, to their final response groups.

Conclusion: Monitoring changes in symptom clusters from the HAM-D-17 during this crucial early stage (first 4 weeks) can be used to distinguish late responders (after week 4) from nonresponders. Successful identification of nonresponders based on symptom cluster change in the first 4 weeks would facilitate a shortening of an ineffective treatment trial and allow for necessary changes in treatment strategy, helping physicians more closely follow treatment guidelines.

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Since the introduction of antidepressants, researchers have attempted to identify illness features (moderator variables) that would predict the rate and timing of response to antidepressant medications.[1–16] Numerous clinical features have been found to be associated with a positive response to antidepressant medications, including lower severity of depressive symptoms, certain depressive subtypes (e.g., atypical depression),[17,18] later age at onset, number of previous episodes, shorter length of illness, and higher levels of social support.[19] However, despite encouraging results, researchers have not identified a consistent set of pretreatment sociodemographic or illness characteristics that would predict patient response to a given antidepressant medication.[20–27] Attempts have also been made to predict outcome based on the trajectory and pattern of response during the acute phase of treatment (the first step in looking at these as possible mediator variables).[28,29] These efforts have generally focused on the speed with which the reduction in symptoms occurs (rapid or gradual onset of action), the timing of response (early or late in treatment), magnitude of the treatment response (response vs. remission), and persistence, i.e., the degree to which the reduction in symptoms is maintained across time (sustained or not). Several clinically significant patterns of response have been identified. Specifi-

cally, early pattern of response within the first several weeks of treatment is generally attributed to a nonspecific treatment response (placebo-type) and is typified by a rapid onset. However, this response is typically transient in nature. What is commonly referred to as a "true drug response" is believed to be observed only after the first several weeks of treatment and is characterized by a delayed onset with subsequent slow but enduring reduction in depressive symptoms, the so-called "delayed-persistent" response pattern.[28,30–34] Additionally, it has also been noted that patients treated with antidepressant medication often do not experience a clinically significant reduction in symptoms until weeks 4 to 6.[29,35,36]

While there is some uncertainty, researchers generally agree that patient nonresponse by weeks 4 to 6 should result in a medication change, and patients exhibiting a partial antidepressant response by weeks 4 to 6 may show increased benefit over an 8- to 12-week trial if maintained on the same medication with a change in dose of the medication.[17,19,37,38] Therefore, the nature of this early symptom change does provide some general guidance for the use of antidepressant medications.[19,39,40]

Many clinically significant questions remain. Although it may be helpful to distinguish early responders from late responders, the most important clinical dilemma persists for those patients who have not experienced a meaningful improvement in symptoms during the first 4 weeks. These patients present a significant challenge to practicing clinicians and make it difficult to implement treatment guidelines. The present analysis was undertaken to distinguish late-responding patients from nonresponding patients using early treatment information (pattern of symptom reduction in the first 4 weeks). Successful identification of nonresponding patients would allow the practicing clinician to shorten the duration of a potentially unsuccessful trial and move onto the next medication and/or psychotherapy in the treatment algorithm.[19,41]

One promising area of research involves the use of patterns of symptom change over time to predict treatment response.[42,43] Some of the research in this area has focused on how relative changes in the Hamilton Rating Scale for Depression (HAM-D)[44,45] factor structure may be helpful in predicting antidepressant treatment response.[46] Unfortunately, various studies with the HAM-D have extracted differing numbers of symptom factors in their analyses and have varied in their description of the factors. Yet the items defining these factors have been comparable and have typically been composed of 3 factors, the 2 primary factors (core symptoms of depression and anxiety-agitation) reported by Hamilton[44,45,47–49] and a third primary sleep factor.[50] The items defining core symptoms of depression in these studies have generally included depressed mood, decreased work and interests, nihilistic or suicidal thoughts, feelings of guilt, psychomotor retardation, decreased energy, and loss of libido. Mendels et al.[51] used subscales of the HAM-D to measure symptom change between 2 groups of patients. The authors included subfactors of cognitive disturbance, psychomotor retardation, sleep disturbance, anxiety/somatization, and melancholia. Analysis of the individual subfactors revealed significantly greater changes in the drug group relative to the placebo group with respect to cognitive disturbance, psychomotor retardation, sleep disturbance, and melancholia, but not the anxiety/somatization factor.

Taking the concept of distinctive patterns of response and the multidimensional construct of the 17-item HAM-D (HAM-D-17), our focus is to identify response patterns in the first 4 weeks that would differentiate late-responding and nonresponding patients. This study proposes to use the pattern of symptomatic change over this first initial phase, based upon the HAM-D-17 factor structure, to classify patients as late responders or nonresponders. We hypothesize that monitoring the patterns of change in symptom clusters provides a means of differentiating late-responding patients from their nonresponding cohorts. We asked the following questions:

1. Are there differences in the pattern of change during the first 4 weeks for treatment on the HAM-D-17 factors?
2. Can these differences be used to differentiate late responders from nonresponders?

METHOD

Subjects

Data for this post hoc analysis came from a multicenter study,[52] in which a total of 996 patients entered the study after meeting DSM III-R[53] criteria for nonpsychotic major depressive disorder (MDD). Data were collected from October 1992 to November 1994. Of the 996 subjects, 237 were determined to be late responders, and 342 were identified as nonresponders. The analysis for this study included the subset of the late responders (N = 182) and nonresponders (N = 133) with complete data at weeks 0, 1, 2, 3, and 4. Participants were 18 years of age or older with a current MDD episode of 6 months or longer in duration. Patients with a bipolar or a seasonal pattern to their MDD, those with any delusions or hallucinations during the current episode, and those with significant psychoactive substance abuse disorder within 6 months prior to baseline were excluded. Patients were also excluded if they were judged to be at serious risk of suicide or if there was a concurrent diagnosis of organic mental syndrome, schizophrenia, or any other psychotic disorder. All patients had a score of at least 20 on the HAM-D-17 at baseline. Demographics, clinical characteristics, and symptom severity scores for late responders and nonresponders are reported in Table 1.

Procedure

Patients were treated with the antidepressant nefazodone, which was administered b.i.d., and the dose was titrated up to 400 mg/day by the end of the first or the second week. Patients who had not responded were titrated to 500 or 600 mg/day after week 2. Patients were restricted from concomitant use of other drugs except for lorazepam, temazepam, or oxazepam. Efficacy was assessed by HAM-D-17 scores at baseline and at weeks 1, 2, 3, 4, 6, 8, 10, 12, and 16, but data used in this study are from the first 12 weeks of initial acute phase of treatment, before the long-term continuation phase of the study began. This resulted in patient samples of 996 for week 0, 883 for week 1, 844 for week 2, 798 for week 3, 763 for week 4, 676 for week 6, 604 for week 8, 549 for week 10, and 493 for week 12. Of the 763 participants at week 4, the study sample evaluated the 315 partial and nonresponding patients who had complete data sets—no missed clinic visits from baseline to week 4.

Definition of Treatment Response

Response to treatment was defined as a 50% or more decrease in symptom severity from baseline[54] during the acute phase of treatment (first 12 weeks). Based on the intent-to-treat sample, 417 patients had a 50% reduction or greater in HAM-D-17 score on or before week 4 (early response), 237 had a 50% reduction or greater in HAM-D-17 score between weeks 4 to 12 (late response), and 342 did not have a 50% reduction in HAM-D-17 score over all observed visits (nonresponse).

Definition of Symptom Clusters

The symptom clusters were defined by using previous factor studies of the HAM-D[47,55] as well as the analyses of an independent sample.[50] A mood cluster, a sleep/psychic anxiety cluster, and a somatic anxiety/weight cluster (see Table 2 for specific items in each of these 3 clusters) were used. A fourth cluster has been defined and consists of 2 items, appetite (item no. 12) and loss of insight (item no. 16). However, both items have a low item-to-total correlation, and, since it is insufficient to define a factor with only 2 items,[56] this cluster was not used in the symptom cluster analyses presented in this article.

Analysis

The analyses were designed to explore the extent to which changes in HAM-D-17 symptom cluster scores at the first 4 treatment visits of the acute phase of treatment could be used to differentiate late responders and nonresponders. Only patients with HAM-D-17 scores at all of the first 5 visits (baseline [week 0] and weeks 1, 2, 3, and 4) were included in the analysis. Patients with complete data for the first 4 weeks of treatment resulted in samples of 182 late responders and 133 nonresponders. Symptom cluster scores during the first 4 treatment visits of the acute phase of treatment were used to conduct 2 sets of analyses. The first analysis included a t test using differences in scores to determine if symptoms changed over time during the first 4 weeks of treatment. A discriminant function analysis was then conducted to determine the effectiveness of symptom change scores in predicting final treatment outcome.

Table 1. Demographic and Clinical Characteristics of Patients at Baseline

Demographics	All Patients (N = 315)	Late Responders[a] (N = 182)	Nonresponders[b] (N = 133)
Age, mean (SD), y	41.8 (11.1)	42.3 (10.4)	41.3 (12.1)
Gender, %			
Female	60.3	64.3	54.9
Male	39.7	35.7	45.1
Race, %			
White	94.9	94.0	96.2
Other	5.1	6.0	3.8
Marital status, %			
Married	45.2	49.5	39.4
Not married	54.8	50.5	60.6
Illness features			
Age at onset, mean (SD), y	28.2 (13.2)	27.8 (12.9)	28.7 (13.6)
Single episode, %	35.6	34.1	37.6
Recurrent, %	64.4	65.9	62.4
Length of illness, mean (SD), y	13.7 (11.7)	14.5 (11.4)	12.6 (12.0)
No. of prior episodes, mean (SD)	2.7 (3.9)	3.0 (4.6)	2.2 (2.6)
Symptom severity			
HAM-D-17, mean (SD) score	24.7 (2.8)	24.6 (2.7)	24.8 (2.9)

[a]Patients requiring 4 to 12 weeks for treatment response.
[b]Patients with < 50% reduction in HAM-D-17 scores from baseline.
Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

RESULTS

A series of t tests was conducted to determine if changes in the symptom clusters over the first 4 weeks of treatment differed for the late responders and nonresponders. All the tests were conducted using the difference scores for weeks 0 to 1, 1 to 2, 2 to 3, and 3 to 4 for all 3 of the symptom clusters (mood, sleep/psychic anxiety, and somatic anxiety/weight). Mean change scores for the HAM-D-17 for weeks 0 through 4 are presented in Table 3. The analysis indicated a statistically significant difference in the reduction in depressive symptoms from weeks 3 to 4, as measured by the HAM-D-17, between the late-responding and nonresponding groups, with the late responders generally reporting a slight improvement on all 3 of the HAM-D-17 factors (mood, sleep/psychic anxiety, and somatic anxiety/weight) and the nonresponders reporting a slight worsening of depressive symptoms. The mean HAM-D-17 factor scores for weeks 0, 1, 2, 3, and 4 for the late responders and nonresponders are shown in Figures 1, 2, and 3 for the mood, sleep/psychic anxiety, and somatic

Table 2. Individual HAM-D-17 Items by Symptom Clusters

Mood (item no.)	Sleep/Psychic Anxiety (item no.)	Somatic Anxiety/Weight (item no.)
Depressed mood (1)	Initial insomnia (4)	Somatic anxiety (11)
Guilt feelings and delusions (2)	Middle insomnia (5)	Hypochondriasis (15)
Suicide (3)	Delayed insomnia (6)	Weight loss (17)
Work and interests (7)	Agitation (9)	
Psychomotor retardation (8)	Psychic anxiety (10)	
Somatic energy (13)		
Libido (14)		

Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Table 3. Early Symptom Change by Cluster and HAM-D-17 Total Score for Late Responders and Nonresponders[a]

HAM-D-17 Symptom Cluster	Late Responders (N = 182), Mean (SD)	Nonresponders (N = 133), Mean (SD)	p Value
Mood			
Weeks 0 to 1	–1.31 (2.03)	–0.94 (1.95)	
Weeks 1 to 2	–0.91 (2.09)	–0.77 (2.11)	
Weeks 2 to 3	–1.03 (2.26)	–0.73 (2.29)	
Weeks 3 to 4	–1.09 (2.47)*	0.14 (2.49)*	< .0001
Sleep/psychic anxiety			
Weeks 0 to 1	–1.28 (1.72)	–0.95 (1.67)	
Weeks 1 to 2	–0.78 (1.89)	–0.79 (1.71)	
Weeks 2 to 3	–0.70 (1.55)	–0.35 (1.55)	
Weeks 3 to 4	–0.16 (1.79)*	0.48 (1.85)*	< .003
Somatic anxiety/weight			
Weeks 0 to 1	–0.44 (1.04)	–0.20 (1.25)	
Weeks 1 to 2	–0.31 (1.11)	–0.23 (1.06)	
Weeks 2 to 3	–0.14 (1.05)	–0.22 (1.05)	
Weeks 3 to 4	–0.15 (0.94)*	0.13 (0.96)*	< .01
HAM-D-17 total score			
Weeks 0 to 1	–3.10 (3.11)*	–2.11 (3.28)*	< .007
Weeks 1 to 2	–2.08 (3.51)	–1.77 (3.25)	
Weeks 2 to 3	–1.78 (3.40)	–1.37 (3.40)	
Weeks 3 to 4	–1.48 (3.22)*	0.81 (3.71)*	< .0001

*t Test significance was set at $p < .05$.
[a]Negative numbers indicate a decrease in the factor score, whereas a positive value indicates an increase in the factor score.
Abbreviation: HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

anxiety/weight clusters, respectively. Mean HAM-D-17 total scores for late responders and nonresponders are shown in Figure 4.

A discriminant function analysis was conducted to determine the effectiveness of using symptom cluster change scores, during the first 4 weeks of treatment, in predicting final treatment outcome. This analysis used the change scores for the mood, sleep/psychic anxiety, and somatic anxiety/weight clusters to predict treatment response (late response or nonresponse). The best model, which included all symptom clusters from a stepwise selection procedure, used time periods as follows: for the mood cluster, the change scores from weeks 1 to 2, 2 to 3, and 3 to 4; for the sleep/psychic anxiety cluster, the change scores from weeks 2 to 3 and 3 to 4; and for the somatic anxiety/weight cluster, the change scores from weeks 0 to 1 and 3 to 4. This symptom cluster model correctly assigned 127 of the 182 late responders and 85 of the 133 nonresponders ($F = 9.73$, $df = 7,307$; $p < .0001$). Thus, using the pattern of changes in symptom clusters in the first 4 weeks of treatment resulted in a model that correctly identified 70% of the late responders and 64% of the nonresponders (67% overall). Next, this model was compared to a model that used changes in the HAM-D-17 total scores. The best model for the HAM-D-17 included the change scores for weeks 0 to 1 and weeks 3 to 4. This HAM-D-17 model correctly assigned 118 of the 182 late responders and 89 of the 133 nonresponders ($F = 24.47$, $df = 2,312$; $p < .0001$) or 65% of the late responders and 67% of the nonresponders (66% overall).

In order to more fully explore differences in the symptom clusters, a series of secondary analyses was conducted using a split-halves design with the sample divided by randomly assigning subjects. This resulted in 2 samples, with 158 subjects in sample 1 and 157 subjects in sample 2. The best model for sample 1 used time periods as follows: for the mood cluster, the change scores from weeks 1 to 2, 2 to 3, and 3 to 4; for the sleep/psychic anxiety cluster, the change scores from weeks 2 to 3 and 3 to 4; and for the somatic anxiety/weight cluster, the change scores from weeks 0 to 1 and 3 to 4. This discriminant model correctly assigned 68 (75%) of 91 late responders and 46 (69%) of 67 nonresponders ($F = 7.11$, $df = 7,150$; $p < .0001$). When this model was applied to sample 2, the discriminant model correctly assigned 62 (68%) of 91 late responders and 40 (60%) of 67 nonresponders ($F = 4.20$, $df = 7,149$; $p < .0003$). This analysis thus points out that discriminant function models maximize the correct assignment. However, when applied to a new sample, there can be a reduction in the number of correct assignments. It is also worth noting that the model applied to the second sample was also significant, i.e., a better than chance (50–50) assignment.

DISCUSSION

Most previous studies have focused on distinguishing early and late responders or responders and nonresponders to acute phase of treatment with antidepressant medications. Our study specifically focused only on the late responders versus the nonresponders. To the best of our knowledge, this is the first study evaluating the differences between late responders and nonresponders. After

Figure 1. Mood Symptom Cluster Mean Score During Acute Phase Treatment for Late Responders and Nonresponders

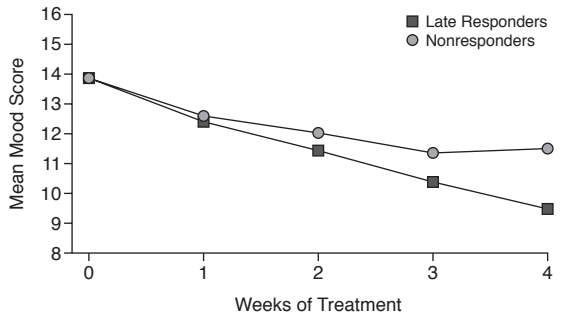


Figure 2. Sleep/Psychic Anxiety Symptom Cluster Mean Score During Acute Phase Treatment for Late Responders and Nonresponders

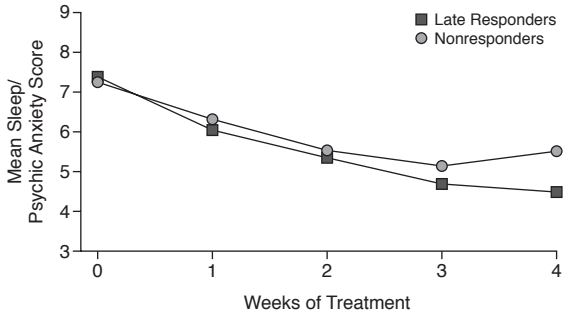


Figure 3. Somatic Anxiety/Weight Symptom Cluster Mean Score During Acute Phase Treatment for Late Responders and Nonresponders

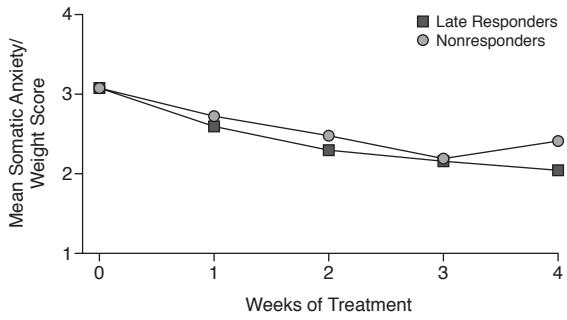
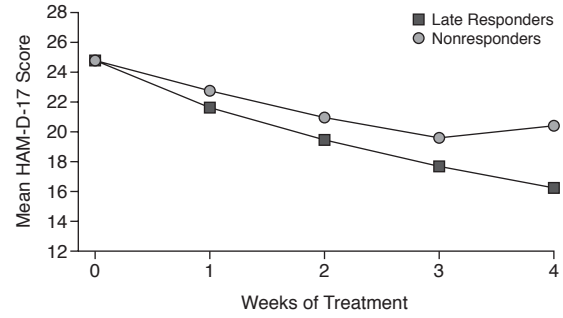


Figure 4. HAM-D-17 Total Mean Score During Acute Phase Treatment for Late Responders and Nonresponders



examining the data from this 12-week antidepressant trial, we were able to identify changes in HAM-D-17 symptom clusters scores, occurring within the first 4 weeks of treatment, that distinguished between late responders and nonresponders. Specifically, all 3 HAM-D-17 symptom clusters, mood, sleep/psychic anxiety, and somatic anxiety/weight, showed significant differences between late responders and nonresponders. Distinctions of this nature become clinically relevant for physicians initiating treatment with antidepressant medications, aiding in the decision to maintain a patient on a medication with the expectancy that there may be a later response and gain of additional benefit or to switch medication due to nonresponse. The results of this study suggest that late responders can be distinguished from nonresponders within the first 4 weeks of treatment and that these changes are more salient if HAM-D-17 responses are examined at a symptom cluster level.

Research predicting response to treatment has been almost exclusively focused on total symptom severity scores from measures such the HAM-D. Changes in total symptom severity scores typically do not allow for insight into the changes in individual symptoms that make up the total score. This study, in contrast, used the factor structure of the HAM-D-17 to define 3 clusters of symptoms (mood, sleep/psychic anxiety, and somatic anxiety/weight), evaluated how these symptom clusters changed for the 2 groups of depressed patients (late responders and nonresponders) during the first 4 weeks of treatment with an antidepressant, and determined how well the changes in symptom clusters predicted eventual outcomes. We found a general decreasing trend in the scores on the mood cluster over the first 3 weeks of treatment for both groups. However, between weeks 3 and 4, the late responders continued to improve, while the nonresponders stopped improving. A similar pattern was found for the somatic anxiety/weight cluster, with decreasing scores in the first 3 weeks among late responders as well as nonresponders, with these decreases continuing for the late responders but not for the nonresponders. The most interesting patterns of change were seen in the sleep/psychic anxiety cluster, where, again, both groups decreased during the first 3 weeks of treatment, whereas, between weeks 3 and 4, the late responders' scores continued to decrease, while the nonre-

sponders' scores increased. These results suggest that the pattern of change is not the same for mood, sleep/psychic anxiety, and somatic anxiety/weight symptom clusters for patients who will respond later in acute treatment when compared to patients who will not respond in the 12 weeks of acute treatment.

A second set of analysis was designed to evaluate whether these change scores in the first 4 weeks of treatment could be used to predict late response versus nonresponse. A model including the changes in the mood cluster scores for weeks 1 to 2, 2 to 3, and 3 to 4; the changes in the sleep/psychic anxiety cluster scores for weeks 2 to 3 and 3 to 4; and the change scores for the somatic anxiety cluster for weeks 0 to 1 and 3 to 4 correctly classified 70% of the late responders and 64% of the nonresponders. This result suggests that, while these differences were significant only for the changes seen from weeks 3 to 4, there may still be meaningful information in the symptom scores and their changes from week to week for all the symptom clusters.

In general, there are 3 important findings from this study. First, for patents who have not achieved a full response during the first 4 weeks of treatment, there are differences observed in the patterns of change in the mood, sleep/psychic anxiety, and somatic anxiety/weight symptom clusters when late responders are compared to nonresponders. Second, these symptom clusters and their differential pattern of changes do provide information that is not available from the general measure of symptom severity. It is also worth noting that there are meaningful changes week to week and that to know which patients will benefit from continued treatment and which patients will not requires close monitoring during the first few weeks of treatment. Third, these changes for both the symptom clusters and the HAM-D-17 total scores occur between weeks 3 and 4, when the scores for the late responders continue to decrease, while the scores for the nonresponders start to increase, suggesting that simple changes from baseline to week 4 may not be effective in identifying those who will respond and differentiating them from those who will not.

We are not aware of studies that have examined changes in symptom clusters during the first 4 weeks of antidepressant pharmacotherapy in order to differentiate late responders from nonresponders. Studies have generally shown that a true antidepressant medication response is typically characterized by delayed onset (beyond the first several weeks) and long-term enduring improvement, differing from placebo response, which in turn typically manifests rapidly, within the first 2 weeks of treatment, and is short-lived. Clinicians generally agree that treatment nonresponse at weeks 4 to 6 should result in a medication change or an augmentation of the antidepressant medication, and, moreover, patients exhibiting a partial antidepressant response by weeks 4 to 6 may show increased benefit for 8 to 12 weeks if maintained on the same medication, albeit with a dose escalation. However, there are very few studies that have addressed this question. The results of this study suggest that an even finer line may be drawn, with the pattern of change in symptom clusters between weeks 3 and 4 providing enough information to differentiate between late responders and nonresponders. While these differences are observed with all 3 symptom clusters, they are most dramatic with the sleep/psychic anxiety and the mood factors.

There are limitations to the current study. First, the HAM-D is limited in its ability to measure the breadth of these symptom clusters (i.e., the somatic anxiety/weight cluster is made up of only 3 items). Second, treatment interventions did not include placebo or other comparator treatments. Hence, replication of these findings with other treatment interventions and with other symptom rating scales would be warranted. Third, the findings are based upon treatment response to a single antidepressant medication, nefazodone, with further trials using additional antidepressant medications indicated in order to evaluate generalizability. Additionally, the sample utilized in the analysis was limited to those patients who were adherent to the treatment protocol. Specifically, only those patients who were seen for all the early acute phase clinical visits (weeks 0, 1, 2, 3, and 4) were included in this analysis. This may limit, to some degree, the generalizability of the sample to those patients who are adherent with treatment and attend regularly scheduled treatment visits.

CONCLUSION

It is very important to continue to identify mediators of treatment response and provide clinical guidance to clinicians during the most crucial, acute phase of treatment for patients with MDD. This study provides a critical first step in identifying the covariation between these symptom clusters and factors that mediate treatment response. Monitoring changes in symptom clusters may provide a way to differentiate late responders from nonresponders early in treatment (i.e., the first 4 weeks) and shorten a potentially ineffective trial, as well as ensure that clinicians do not abort a potentially successful trial prematurely and label the antidepressant trial ineffective prior to the appropriate exposure.

Drug names: lorazepam (Ativan and others), nefazodone (Serzone and others), oxazepam (Serax and others), temazepam (Restoril and other).

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