

What moderator characteristics are associated with better prognosis for depression?

Madhukar H Trivedi¹
David W Morris¹
Ji-Yang Pan²
Bruce D Grannemann¹
A John Rush¹

¹Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX, USA; ²Department of Psychiatry, Third Hospital of Sun Yat-Sen University of Medical Sciences, Shipai, Guangzhou, Peoples Republic of China

Abstract: A retrospective data analysis was conducted to evaluate the usefulness of baseline characteristics in predicting treatment response to antidepressant medication in 97 outpatients with nonpsychotic major depression treated for up to sixteen weeks with nefazodone. Baseline demographics (gender), illness features (symptom severity, length of illness, length of current episode, number of episodes, age of onset, longitudinal subtype, endogeneity, melancholia, family history of mood disorders), and social features (living status) were evaluated. Response to treatment was defined as a $\geq 50\%$ reduction in the 17-item Hamilton Rating Scale for Depression (HRSD₁₇) score. The results of a survival analysis indicated that patients with shorter histories of illness (< 4 years), a negative family history of depression, and those who were either married or were living with someone were more likely to have a positive outcome during the acute phase treatment of depression. The main findings are consistent with extensive previous literature indicating a better short-term outcome of depression where illness is shorter, where there is no family history, and where there is better social support.

Keywords: antidepressant, treatment predictor, social support, major depression

Introduction

Studies attempting to identify moderators and mediators of treatment (Baron and Kenny 1986; Kraemer et al 2002), such as baseline/pre-treatment predictors of response to antidepressants, have not yielded consistent findings (Bielski and Friedel 1976; Greenhouse et al 1987; Katz et al 1987; Croughan et al 1988; Hooley and Teasdale 1989; Joyce and Paykel 1989; Kocsis et al 1989, 1990; Brugha et al 1990; Danish University Antidepressant Group 1990; Vallejo et al 1991; Keller et al 1992; Goodwin 1993; Hoencamp et al 1994; Friedman et al 1995; Baldwin et al 1996; Cohn et al 1996; Aliapoulos and Zisook 1996; Nierenberg 2003). The identified clinical predictors have typically fallen into the following categories: (1) demographic characteristics (gender); (2) illness features (severity at baseline, length of illness, age of onset, length of current episode, number of episodes, longitudinal subtype, endogeneity, melancholia, family history of mood disorders); and (3) social factors (living status, social support).

Numerous illness characteristics have been found to be associated with a positive response to antidepressant medications, including severity of depressive symptoms, depressive subtypes, age at onset of illness, and past history of depressive episodes (AHCPR 1993). Several studies have shown that specific features of psychiatric history and of the current episode of depression influence treatment outcomes. Reimherr et al (1990) found that patients with only a single episode of depression responded slightly better to SSRI treatment than those with recurrent episodes (sertraline: 62% vs 52%; amitriptyline: 66% vs 62%). Additionally, patients with melancholic features

Correspondence: Madhukar H Trivedi
Mood Disorders Program & Clinic,
Department of Psychiatry, University of
Texas Southwestern Medical Center,
5323 Harry Hines Blvd, Dallas,
TX 75390-9119, USA
Tel +1 214 648 0188
Fax +1 214 648 0167
madhukar.trivedi@utsouthwestern.edu

responded slightly better than those without such features (sertraline: 56% vs 50%; amitriptyline: 63% vs 59%). Based on a sample of patients with recurrent depression, Greenhouse et al (1987) also found age, symptom severity, and number of previous episodes associated with time to sustained treatment response. The most extensively studied area of treatment predictors includes history of illness characteristics, such as number of previous episodes, length of illness, and the presence of either single episode or recurrent longitudinal subtypes. However, findings are not consistent across all studies. Hoencamp et al (1994) demonstrated that the baseline Hamilton Rating Scale for Depression (HRSD) score was of greater significance in predicting recovery than other variables, such as premorbid history, symptomatology, and endogenous features (Danish University Antidepressant Group 1986). Greenhouse et al (1987) found that patients with high HRSD scores tended to take longer to stabilize than patients with lower scores. However, Pande and Saylor (1993) were unable to replicate this finding. Conversely, patients with less severe depressive illness have been shown to be more likely to respond to amitriptyline or imipramine than those with severe depressive illness (Croughan et al 1988). Family history has also been found to be a prognostic indicator of outcomes. When comparing patients who experience full interepisodic recovery with partial and non-interepisodic recovery patients, Akiskal (1982) found that patients with a family history (first degree biological relative) of affective disorders were more likely to have an incomplete recovery when treated with tricyclic antidepressants.

In addition to illness features that predict treatment response, researchers have attempted to examine the effects of social or situational factors on treatment outcome. Direct measures of social support and functioning, ie, Social Adjustment Scale, Social and Occupational Functioning Assessment Scale (Weissman and Bothwell 1976; APA 1994), and indirect measures such as living status have been found to be positively related to response. Vallejo and colleagues (1991) directly tested the effects of social support on response after 6 weeks of medication treatment. They found that patients treated with imipramine, with higher levels of social support showed a greater percent decrease in HRSD scores than patients with lower levels of social support. Tomaszewska and colleagues (1996) obtained similar results in a population of patients with non-melancholic depression, and found higher levels of social support in those patients who responded favorably to treatment.

The vast majority of research evaluating the relationship between social support and major depressive disorder (MDD) has largely focused on the role played by social support in improving clinical outcomes in general. Research has not focused as much on patients being treated specifically with antidepressant medications or psychotherapy. The relationship between social support and psychological wellbeing has long been documented (Myers et al 1975; Dean and Lin 1977; Andrews et al 1978; Cohen and Wills 1985). Studies have suggested that social support plays a significant role in mediating the development of depressive symptoms by buffering the effects of negative life events (Aneshensel and Stone 1982; Brown 1988; George et al 1989; Zlotnick et al 1996). Brugha et al (1997) found that patients with a longer course of illness, as manifested by multiple recurrent episodes, reported significantly lower levels of social support than patients with a shorter course of illness. Ezquiaga et al (1998) found that the psychological support provided by a spouse was significant, with high levels of support being associated with positive treatment outcomes. In a sample of 552 women aged 18–65, Costello (1982) found that lack of intimacy with a spouse or cohabitant and lack of a confidant were associated with clinically significant levels of depression. Hooley and Teasdale (1989) found, in a 9-month post-hospitalization follow-up of patients with unipolar depression, that patients with higher levels of marital discord had significantly higher relapse rates. Coyne and colleagues (2002) found higher levels of marital distress in depressed females than in community controls. Interestingly, there appear to be gender differences in the reporting of marital distress, with depressed females reporting higher levels of marital distress than their partners (Ensel 1982; Crowther 1985). In their 1992 study, Goering et al found that in a population of women with MDD, few demographic or clinical factors were related to the course of symptoms over the 6-month study period. Recovery was predicted based on the patients' ratings of their current marital relationship and by the spousal rating of their premorbid relationship.

The purpose of this study was to identify baseline demographic, illness, and social features that predict response to an antidepressant medication, nefazodone, in patients with MDD. The demographic, illness, and social feature predictors evaluated were: gender, age of onset, severity at baseline, length of illness, length of current episode, number of episodes, longitudinal subtype, endogeneity, melancholia, family history of mood disorders, and living status.

Methods

Subjects

Participants in this study were 97 outpatients with MDD: 59 females and 38 males, age 38.5 ± 10.0 (mean $\pm$ SD). They were treated for up to sixteen weeks with nefazodone in the Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas, USA. This sample has been reported as part of a larger multicenter trial (Trivedi et al 2001). Prior to interview, all patients provided written informed consent. All participants met the Structured Clinical Interview for DSM-III-R (SCID) (Spitzer et al 1992) criteria for MDD and were 18 years of age or older. The duration of the current major depressive episode was ≥ 6 months. Patients with bipolar disorder, seasonal affective disorder, substance abuse or dependence disorders, as well as those with delusions or hallucinations during the current episode, were excluded. Patients judged to be at serious risk of suicide and those with a concurrent diagnosis of organic mental syndrome, schizophrenia, or any other psychotic disorder, were not included in the sample. All patients had a 17-item Hamilton Rating Scale for Depression (HRSD₁₇) (Hamilton 1960, 1967) score ≥ 20 at the baseline evaluation. See Table 1.

Procedures

Patients were evaluated at baseline using a SCID to obtain demographic (age and gender), social (living status), and illness features (length of episode, depressive subtype, age at onset, recurrence, length of illness, number of episodes, family history of depression). Melancholia was characterized based on the SCID (Spitzer et al 1992), and endogeneity was defined using the Research Diagnostic Criteria (Spitzer et al 1977). Symptom severity was assessed at baseline using the HRSD₁₇ and the thirty-item Inventory of Depressive Symptomatology – Clinician Rated (IDS-C₃₀) (Rush et al 1986, 1996) and again with the HRSD₁₇ at weeks 1, 2, 3, 4, 6, 8, 10, 12, and 16. Nefazodone was administered twice daily for 12 weeks. Dosages were titrated up to 400 mg/day by the end of the second week. Patients not responding to the initial titration schedule were titrated to 500 or 600 mg/day after week 3. Patients were restricted from concomitant use of other drugs except lorazepam, temazepam, or oxazepam.

Statistical analysis

Cox's proportional hazard models (Cox 1972) were used to test for differences in treatment response for a series of

Table 1 Predictors of response to antidepressants: baseline

Predictors of response	n	Mean	SD	%
Age	97	38.5	10.0	
Females/Males	97			60.8/39.2
Marital status	97			
Single				19.6
Engaged				1.0
Married				37.1
Cohabiting				8.2
Divorced				32.0
Widowed				2.1
HRSD at baseline	97	23.9	2.1	
Age at onset	96	25.1	11.0	
Length of illness ^a	96	13.2	9.7	
Length of current episode	97	67.0	75.8	
Number of episodes	95	2.3	1.9	
Single/Recurrent	95			40.0/60.0
Endogenous/Nonendogenous	81			42.0/58.0
Melancholic/Nonmelancholic	97			43.3/56.7
Family history of affective disorder (Positive/Negative)	94			36.2/63.8

^a Months.

Abbreviation: HRSD, Hamilton Rating Scale for Depression.

demographic, social support, and illness features. The demographic characteristic and social support predictors evaluated were gender and living status, respectively. Illness features included length and severity of current episode, length of illness, number of episodes, age at onset, longitudinal subtype, endogeneity (Spitzer et al 1977), melancholia (Spitzer et al 1992), and family history of mood disorders. For these analyses response to treatment was defined as a $>50\%$ reduction in the baseline HRSD total score.

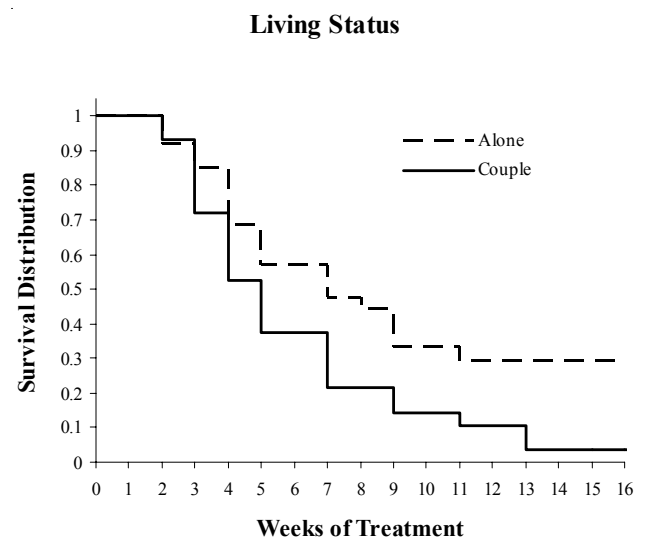


Figure 1 Estimated likelihood of response based on Cox's regression analyses for living status.

Results

Demographic and social features

The analysis of living status indicated better response to treatment for the married patients (married or cohabiting) than those patients living alone (single, engaged, divorced, widowed): 84% and 51%, respectively ($\chi^2=6.9$, $df=1$, $p<0.009$). While the response rates were similar in the first few weeks of treatment, after week 4, married patients show clearly higher rates of response than the unmarried patients (see Figure 1). This result is qualified by differences in the dropout rates (single, 34%; married, 14%). There was no statistically significant effect for gender. See Table 2.

Illness features

Four predictors were used to create a test for differences in response based on characteristics of the current depressive episode: severity (HRSD score 20–23 vs HRSD score ≥ 24);

length of the current episode (0–48 months vs >49 months (this median split provided sample size for the two groups to make a reasonable comparison)); endogenous vs nonendogenous; and melancholic vs nonmelancholic. Length of the current episode revealed that patients whose current episode was less than 4 years were more likely to respond (70%) than those with longer current episodes (62%). This effect was marginally significant ($\chi^2=3.2$, $df=1$, $p<0.08$). Dropout rates were about the same for these two groups (28% and 26%, respectively). Since chronic depression has been defined as episodes lasting 2 years or more, a secondary analysis was conducted using a 24-month threshold to distinguish short vs longer current episodes. No statistically significant differences were found. Baseline severity, endogeneity, and the presence of melancholia were not significantly related to treatment response.

Four measures were used to define strata based on history of illness (single vs recurrent; age at onset: 1–19 vs 20 or older; length of illness: 0–9 years vs >10 years; and number of episodes: 1 vs 2 vs 3 or more). Length of illness was significantly related ($\chi^2=5.2$, $df=1$, $p<0.03$) to outcome. Patients with shorter illnesses were more likely to respond than those with longer illnesses (see Figure 2). Single versus recurrent depression, age of onset, and number of episodes were not significantly related to treatment response.

Strata were created based on a positive versus negative family history of major mood disorders in first-degree relatives. There was a significant difference based on family history ($\chi^2=4.6$, $df=1$, $p<0.04$). Patients with a negative family history were more likely to respond (77%) than those with a positive family history (62%) (see Figure 2). Dropout rates before completing 16 weeks of treatment were similar (21% and 30%, respectively).

Analyses of combined predictors

To explore the relationships between individual baseline features that predicted response, survival analysis was conducted and included all three individual predictors: marital status, length of illness, and family history. Once living status entered the model, no other predictors significantly improved the model. Thus, there was substantial overlap between these individual predictors, as might be expected in this relatively small sample. The parallel analyses conducted using an HRSD score ≥ 10 criteria produced the same results for living status ($\chi^2=7.7$, $df=1$, $p<0.006$) and length of illness ($\chi^2=4.3$, $df=1$,

Table 2 Predictors of response to antidepressants and baseline HRSD

Predictors of response	n	Baseline HRSD	
		Mean	SD
Gender			
Female	59	23.9	2.2
Male	38	23.8	2.1
Marital status ^a			
Unmarried	53	23.9	1.9
Married	44	23.8	2.4
Age at onset			
0–19	40	23.8	2.1
20+	56	23.9	2.2
Length of illness ^a			
0–9	42	24.1	2.4
10+	54	23.7	1.9
Length of current episode			
0–48	50	24.0	2.2
49+	47	23.7	2.1
Number of episodes			
1	40	23.9	2.1
2	26	23.9	2.6
3+	30	23.8	1.9
Single	38	23.9	2.1
Recurrent	57	23.8	2.2
Endogenous	34	23.3	1.4
Nonendogenous	47	24.4	2.7
Melancholic	42	24.5	2.5
Nonmelancholic	55	23.4	1.7
Family history of affective disorder			
Positive	34	23.8	2.4
Negative	60	23.9	2.0

^a $p<0.05$ comparing 2 subgroups (survival analysis).

Abbreviation: HRSD, Hamilton Rating Scale for Depression.

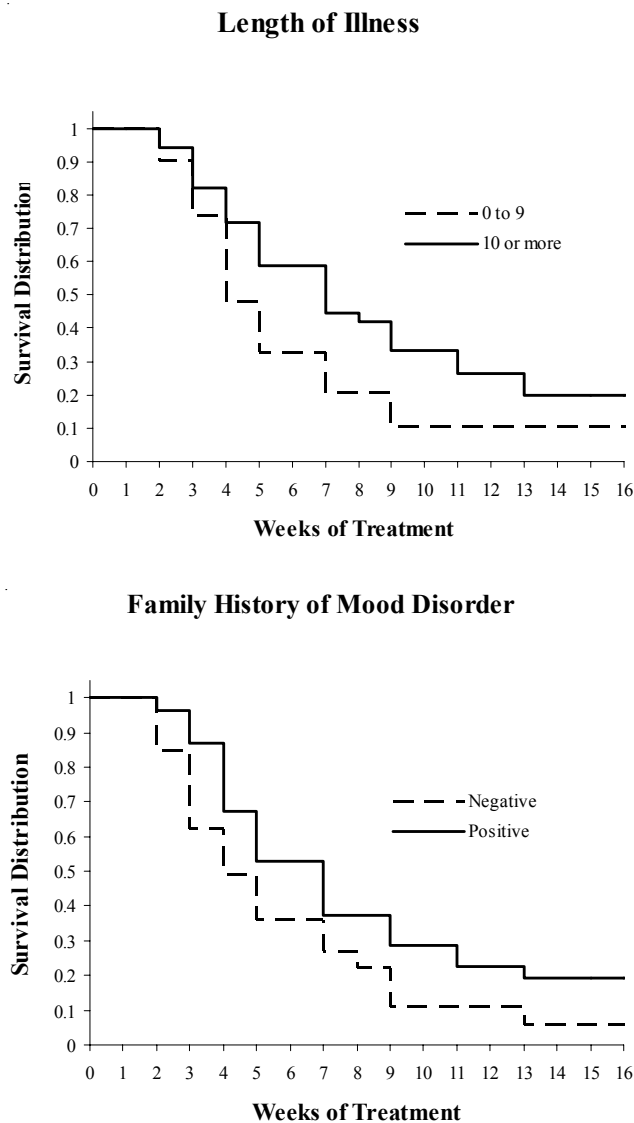


Figure 2 Estimated likelihood of response based on Cox's regression analyses for length of illness and family history of depression.

$p < 0.04$). A significant difference, as opposed to a marginal difference, was found for length of episode ($\chi^2 = 4.3$, $df = 1$, $p < 0.04$). Only one major difference was found for the single vs recurrent depression groups. A significant difference was found using this response criterion ($\chi^2 = 4.6$, $df = 1$, $p < 0.04$). Patients with a recurrent history responded better than those in their first episode.

Discussion

The results of this study suggest that three easily discernable patient characteristics can help predict a patient's response to antidepressant medication, in this case, nefazodone. The characteristics found to be most useful were, living status, total length of illness, and family history of depression. The

findings associated with illness features are consistent with previous studies reporting longer current episodes associated with a lower likelihood of response to antidepressants (Bielski and Friedel 1976; Rush et al 1983; Keller et al 1984, 1992).

Although more elaborate methods of outcome prediction such as receptor analysis or neuroimaging (Espisito and Goodnick 2003) may be useful, they have not yet led to consistent findings and are very likely not to be practical in routine clinical practice. The results of this study suggest, simple, easy to obtain data, such as marital status, show great promise in the prediction of response to antidepressant treatment. Interestingly, in our sample, being married or living together appeared to have a profound positive effect on the overall response rates, with married or cohabiting patients meeting criteria for treatment response with greater frequency than their single cohorts. Living status also had an impact on the patients' willingness to stay in treatment. The married/cohabiting group remained in treatment longer even in the absence of response, a finding consistent with Hagerty and Williams (1999) who found patients living alone were more likely to drop out of treatment. Numerous drug utilization studies have shown that over 45%–50% of patients who start an antidepressant are not in treatment by 3 months, suggesting a strong need to be able to preemptively identify predictors of not only response but also dropouts. While not all studies have found social support to be a significant predictor of treatment outcome (Hirshfeld et al 1986; George et al 1989), the majority of the studies have suggested social support and even more specifically marital status as positive predictors of response. The quality of the marital relationship also provides a significant aid in predicting treatment response. Moreover, recent data from a number of studies (Hunkeler et al 2000; Unutzer et al 2002; Trivedi et al 2004) suggest there is a clear benefit for a disease management approach in the treatment of depression. These studies have emphasized more frequent patient contact as well as more robust psychosocial and educational support for patients to enhance adherence, improve the patient's ability to self-monitor their symptoms, and increase patients' understanding of the chronic medical illness nature of their depressive disorders. These data thus provide another dimension of evidence that optimal outcome can be enhanced if pharmacotherapy is augmented with social support.

The current study is limited by several factors including a moderate sample size, the use of only one antidepressant

medication, and the lack of a placebo control group. It is also possible that factors indicating a chronic and or severe disorder like length of illness may predict poorer outcome irrespective of the treatment(s) used. Moreover, it is also likely that social support, life stressors, and family history of psychiatric comorbidity are indicators of positive outcome for MDD across various treatment modalities and may also increase the chances of spontaneous response. Therefore, in the absence of a placebo or an active control, the demographic and clinical features identified may be thought of as good prognostic predictors of outcome independent of treatment modality. Despite these limitations, the current study does provide additional support for the hypothesis that easy to identify patient factors may be able to significantly improve the quality of patient care by increasing physician efficiency when prescribing antidepressant medications. These clinical predictors, although not prescriptive, can assist in treatment planning and aid with patient education regarding potential outcomes. Of the three clinical predictors identified (living status, total length of illness, and family history of depression), living status appears to be the most promising mediator of treatment outcome. Future study of clinical predictors of treatment response for emerging antidepressant medications should include social features, such as living status and an assessment of the quality of relationships, in addition to the commonly used demographic and illness features in predictor analyses.

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