Predictors of Response to Acute Treatment of Chronic and Double Depression With Sertraline or Imipramine

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Background: The literature on predictors of response to treatment of nonchronic major depression has identified shorter duration of illness, acute onset, and less severity of illness as positive predictors. Unfortunately, there are almost no data on predictors of response to treatment for chronic depression. This study examined predictors of response to pharmacotherapy (sertraline or imipramine) in the treatment of outpatients who had DSM-III-R-defined chronic major or double depression.

Method: The acute phase of the Chronic Major Depression and Double Depression Study is a double-blind, randomized, parallel-group 12-week comparison of sertraline and imipramine. Analyses are based on 623 patients who comprised the intent-to-treat sample, of whom 299 were nonresponders and 324 were responders, defined by a priori criteria as either remission or satisfactory therapeutic response. A stepwise logistic multiple regression analysis was performed on candidate clinical, psychosocial, and demographic variables previously identified as statistically significant in an attempt to develop a predictive model of positive antidepressant response.

Results: The sociodemographic variables that were predictive of positive response included living with spouse or partner or being at least a high school graduate. With regard to symptomatology and clinical history, responders had significantly lower baseline depression severity scores. In general, comorbid anxiety, substance abuse, and personality disorders did not influence rates of response. However, the presence of depressive personality traits was associated with a higher nonresponse rate. Among psychosocial variables, longer duration of personal relationships as well as higher baseline quality of life were associated with positive response. A stepwise logistic multiple regression identified 5 variables—living with spouse or partner, higher educational level, passive-aggressive personality, lower introverted-tense personality traits, and higher quality of life—that significantly and independently contributed to the predictive model. This model correctly classified 67% of patients.

Conclusion: A higher baseline quality of life, living with spouse or partner, and having more education were the strongest predictors of response to acute pharmacotherapy among chronically depressed patients. Clinical variables and comorbidity were not identified as independent predictors, although personality traits did appear to influence treatment response. Overall, the predictive value of these baseline measures was modest, and therefore of limited clinical utility.

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The clinical usefulness of clear and consistent predictors of response to treatment is obvious and compelling. Being able to select rationally the most effective treatment and being able to predict accurately the prognosis have great value to patients, their families, and clinicians.

A number of investigators have identified predictors of response to acute treatment of major depression.[1–5] Among the clinical predictors of positive response to antidepressant treatment are shorter duration of illness, acute onset, less severity of illness, psychomotor retardation, decreased interest, and emotional withdrawal. Other clinical predictors include melancholia, a lower neuroticism score, obsessive-compulsive personality, fewer comorbid psychiatric disorders, fewer comorbid general medical disorders, and various biological markers. Psychosocial variables that are predictors include fewer life events, better family functioning, and patient expectation of improvement. Unfortunately, none of these predictors are strong enough to be useful clinically.

Although chronicity has been associated with poor outcome, relatively few investigators have examined predictors of response to the pharmacotherapy of chronic depression. In one placebo-controlled, double-blind study of imipramine in chronically depressed patients, Kocsis et

al.[6] found that many variables predictive of response in nonchronic depression, such as age at onset, symptom profile, and severity and course of illness, were not predictive of response in this population. However, some variables on the Cattell 16-Personality Factor Scale that signified "neurotic" characteristics were associated with poor outcome. They concluded that although many chronically depressed patients can be expected to respond to imipramine treatment, "commonly available clinical and personality measures do not accurately forecast the response to treatment."[6(p260)]

This article examines predictors of response to pharmacotherapy of chronic depression, including double depression and chronic major depression. The data come from the acute treatment phase of the Chronic Major Depression and Double Depression Study,[7] a 12-site research project studying acute and longer term efficacy of sertraline and imipramine. Subsequent articles will examine predictors of relapse and recurrence during preventive therapy.

STUDY DESIGN AND METHOD

The acute phase study was a double-blind, randomized, parallel-group comparison in outpatients with DSM-III-R-defined[8] chronic major or double depression. Imipramine was selected as the comparator for sertraline because both drugs have demonstrated efficacy for the prevention of relapse or recurrence in major depressive disorder.[9,10]

Patients were randomly assigned to receive 12 weeks of treatment with sertraline or imipramine in a 2:1 ratio. Both medications were started at 50 mg/day, and dosage could be titrated to a maximum of 200 mg of sertraline or 300 mg of imipramine, according to clinical response and dose-limiting side effects. A detailed description of the rationale and design of the overall project, including continuation and maintenance phases, may be found in Rush et al.[11] and Keller et al.[7]

Patient Recruitment

Patients were recruited into the study when they sought treatment at the 12 collaborating centers or responded to newspaper, radio, or television advertisements. The study's rationale and procedures were explained to all study subjects, and all gave explicit written informed consent.

Men and women between the ages of 21 to 65 years with a diagnosis of DSM-III-R-defined chronic major (current episode ≥ 24 months in duration) or double depression (current major depression superimposed on antecedent DSM-III-R dysthymia) were eligible for the study. All patients had to have scored at least 18 on the 24-item Hamilton Rating Scale for Depression (HAM-D)[12] at the end of the 1-week, single-blind, placebo-washout; women were required to ensure adequate contraception if they were able to become pregnant or to be postmenopausal or sterile as a result of a surgical procedure.

Patients excluded from the study included those with any of the following DSM-III-R-defined diagnoses: organic mental syndrome; current or lifetime diagnosis of bipolar illness, cyclothymia, schizophrenia or other psychotic disorder, or obsessive-compulsive disorder; antisocial, schizotypal, or severe borderline personality disorder; or anorexia nervosa or bulimia nervosa with vomiting or purging. Those with drug or alcohol abuse or dependence, or a principal DSM-III-R diagnosis of panic disorder, generalized anxiety disorder, or posttraumatic stress disorder within the past 6 months also were excluded. Patients deemed to represent a serious suicide risk and those with medical contraindications to study medications or evidence of significant unstable general medical disorders were also excluded. Further protocol criteria excluded patients requiring concomitant therapy with any psychotropic drug (except for chloral hydrate or temazepam) and patients who had failed a previous adequate trial of either study medication.

Definition of Treatment Response

Treatment response was defined a priori using the HAM-D[12] and the Clinical Global Impressions (CGI)[13] scale. Full remission was defined as a CGI-Improvement (CGI-I) score of 1 or 2 (very much or much improved) and a total final HAM-D (24-item) score of ≤ 7. Satisfactory therapeutic response was defined as a CGI-I of 1 or 2 *and* a total HAM-D (24-item) score reduced by 50% or more from baseline, with the HAM-D total score ≤ 15 and the CGI-Severity (CGI-S) score of ≤ 3. For the purpose of these analyses, responders included patients with full response or satisfactory therapeutic response.

Data Analysis

Analyses included all patients with sufficient information to classify response at endpoint, defined as the last available observation of the acute phase for each patient. We examined sociodemographic variables, clinical history, clinical aspects of the current episode, psychiatric comorbidity, and psychosocial variables. Patients with chronic major depression and patients with double depression were treated as a single sample for these analyses. Associations between treatment response and baseline predictors that were categorical were evaluated by a Cochran-Mantel-Haenszel chi-square test with pooled sites, depression type, and treatment as strata. Alternatively, a Fisher exact test was utilized in instances where sample sizes were small. Associations between treatment response and baseline predictors that were continuous were evaluated using an analysis of variance model including effects for pooled sites, depression type, and treatment. Baseline total scores for HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS),[14] Beck

Table 1. Sociodemographic Variables

Variable	Responders (N = 324)	Nonresponders (N = 299)	p Value
Age, mean ± SD y	41.3 ± 9.8	40.9 ± 10.3	.665
Sex, % female	64.2	61.9	.488
Education, % high school graduate or more	97.8	94.2	.012
Living situation			.010
Single/separated/ divorced/widowed, %	52.8	64.6	
With spouse or partner, %	47.2	35.4	

Depression Inventory (BDI),[15] Diagnostic Interview for Depressive Personality (DIDP),[16] and Quality of Life (Q-LES-Q)[17] were also classified into 2 severity groups based on the median score: scores less than the median and scores greater than or equal to the median. These groups were tested as categorical predictors as described above. The baseline MADRS score was further divided into 3 groups: scores in the lowest 25th percentile, scores in the middle 25th to 75th percentile, and scores in the upper 25th percentile. Association between treatment response and this group classification was tested using a Cochran-Mantel-Haenszel chi-square test for ordinal data using modified ridit scores with pooled sites, depression type, and treatment as strata.

The entire set of univariate analyses was repeated with a data set in which the satisfactory therapeutic responders (the middle group) were excluded. The purpose of these analyses was to see whether including only the extremes of response and nonresponse would improve the discriminating abilities of the predictors.

A multiple logistic regression model to predict response was developed from sets of predictors in each classification set (sociodemographic, depression severity indices, psychiatric comorbidity), which showed significant ($p \leq .05$) univariate association with endpoint response. The logistic regression model included adjustments for pooled sites, depression type, and treatment. A stepwise selection procedure evaluated the covariate set that included baseline classifications, total scores, total score classifications, and factor scores. Total scores and factor scores replaced item scores in the covariate sets for HAM-D, BDI, DIDP, and Q-LES-Q. The entry and stay decision levels for the stepwise selection procedure were $p < .10$ and $p < .15$, respectively. To minimize the loss of patients due to missing data for one predictor variable or more, a final logistic regression model was rerun including only the significant predictors, as well as pooled sites, depression type, and treatment.

RESULTS

Six hundred twenty-three patients comprised the intent-to-treat sample, of whom 324 (52%) were responders and 299 (48%) were nonresponders.

Table 2. Clinical Characteristics of Chronically Depressed Patients[a]

Variable	Responders	Nonresponders	p Value
Diagnosis at study entry			.113
Chronic major depression, %	48.8	44.2	
Double depression, %	51.2	55.8	
MADRS			
Total score, mean ± SD	25.1 ± 7.11	26.1 ± 7.39	.030
Patients with score ≥ 27, %[b]	41.2	47.5	.114
Total score < 20, %[c]	24.2	16.7	
Total score 20–29, %	52.9	53.2	
Total score > 29, %	22.9	30.1	.007
HAM-D			
Total score, mean ± SD	25.0 ± 4.75	25.2 ± 5.39	.499
Patients with score ≥ 25, %[b]	50.3	49.2	.995
CGI-Severity of Illness, mean ± SD	4.2 ± 0.55	4.2 ± 0.57	.475
Cornell Dysthymia Rating Scale total score, mean ± SD	40.5 ± 9.06	41.1 ± 9.75	.316
BDI			
Total score, mean ± SD	24.2 ± 8.62	25.1 ± 9.11	.119
Patients with score ≥ 25, %[b]	47.0	50.3	.231

[a]Abbreviations: BDI = Beck Depression Inventory, CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.
[b]Represents the median severity score for this scale.
[c]MADRS scores represent the lower quartile (MADRS total scores < 20), the middle two quartiles (MADRS total scores of 20–29), and the upper quartile (MADRS total scores > 29).

Among the sociodemographic variables (Table 1), age and sex were not predictive of response. However, responders were significantly more likely to be high school graduates (or more) and to be living with a spouse or partner.

Clinical Measures

Pretreatment severity of symptoms was minimally predictive of outcome (Table 2). The HAM-D, CGI-S, BDI, and Cornell Dysthymia Rating Scale[18] were not predictive of outcome. Only the MADRS was identified as a significant predictor, with responders having both a lower mean score, as well as having a higher proportion of patients (24% vs. 17%) in the lowest quartile of severity at baseline.

Item Analyses of Symptom Scales

Although the baseline HAM-D total score did not differ between responders and nonresponders, several specific items were predictive (Table 3). Responders scored lower on depressed mood and higher on the depersonalization/derealization item. The remaining items were nonpredictive.

On the baseline BDI, 5 items were predictive of response (Table 4). Patients were more likely to respond to treatment if they reported less sadness or discouragement,

Table 3. Hamilton Rating Scale for Depression Items (24-item)

	Responders		Nonresponders		
Item	Mean	SD	Mean	SD	p Value
Depressed mood	2.3	0.72	2.5	0.75	.006
Feelings of guilt	1.6	0.72	1.5	0.76	.568
Suicide	0.6	0.80	0.8	0.85	.083
Insomnia-early	0.9	0.89	0.8	0.92	.565
Insomnia-middle	1.2	0.84	1.1	0.86	.314
Insomnia-late	0.7	0.79	0.7	0.84	.796
Work and activities	2.5	0.81	2.5	0.81	.823
Retardation	0.6	0.67	0.7	0.70	.080
Agitation	0.5	0.72	0.5	0.69	.916
Anxiety-psychic	1.9	0.82	1.7	0.90	.147
Anxiety-somatic	1.5	0.94	1.4	0.98	.874
Somatic-gastrointestinal	0.5	0.64	0.4	0.63	.950
Somatic-general	1.6	0.58	1.6	0.60	.656
Genital symptoms	1.3	0.80	1.3	0.86	.690
Hypochondriasis	0.7	0.82	0.7	0.85	.710
Weight loss	0.3	0.63	0.3	0.62	.786
Insight	0.02	0.17	0.05	0.25	.172
Diurnal variation in mood	1.1	0.80	1.0	0.78	.237
Depersonalization and derealization	0.2	0.57	0.1	0.39	.016
Paranoid symptoms	0.1	0.29	0.1	0.35	.234
Obsessive-compulsive symptoms	0.1	0.25	0.1	0.30	.999
Helplessness	1.7	0.88	1.7	0.96	.683
Hopelessness	1.6	0.89	1.6	0.96	.352
Worthlessness	1.8	0.92	1.9	0.90	.161

Table 4. Beck Depression Inventory

	Responders		Nonresponders		
Item	Mean	SD	Mean	SD	p Value
Sadness	1.4	0.78	1.5	0.79	.008
Discouraged about future	1.3	0.79	1.4	0.86	.037
Failure	1.3	0.83	1.4	0.86	.269
Satisfaction	1.7	0.74	1.8	0.79	.442
Guilty	1.1	0.88	1.2	0.89	.491
Punished	0.8	1.07	0.8	1.12	.643
Disappointed	1.3	0.64	1.4	0.76	.143
Self-critical	1.4	0.71	1.4	0.76	.466
Suicidal thoughts	0.5	0.56	0.6	0.62	.213
Crying	1.0	1.06	1.0	1.04	.815
Irritated	1.1	0.74	1.1	0.72	.335
Interested in other people	1.3	0.77	1.4	0.84	.488
Making decisions	1.4	0.87	1.4	0.89	.957
Looking worse	1.2	1.02	1.4	1.06	.010
Working	1.4	0.71	1.5	0.73	.033
Sleeping	1.2	0.93	1.2	0.93	.818
Tired	1.4	0.85	1.6	0.88	.002
Appetite	0.6	0.82	0.6	0.78	.829
Weight loss	0.2	0.62	0.1	0.48	.087
Eating less	0.7	0.47	0.6	0.48	.565
Worried about health	0.5	0.57	0.5	0.61	.648
Interested in sex	1.3	1.11	1.2	1.15	.804

less sense of looking worse, and less tiredness or difficulty working.

Comorbid Axis I and Axis II Disorders

Overall, the existence of any comorbid anxiety disorder was not predictive of response or nonresponse (Table 5).

Table 5. Comorbid Anxiety Disorders and Substance Abuse History[a]

Disorder	% Responders	% Nonresponders	p Value
Anxiety			
Panic disorder	9.0	5.4	.097
Social phobia	9.3	15.1	.112
Simple phobia	7.7	4.4	.110
Obsessive-compulsive disorder	0	0	n/a
Generalized anxiety disorder	5.0	5.7	.792
Any anxiety disorder	21.7	22.1	.785
Substance abuse history			
Alcohol abuse (lifetime)	27.2	31.4	.709
Any illicit substance abuse (lifetime)	32.2	37.5	.827

[a]Individuals are considered positive for a given disorder if they satisfy DSM-III-R criteria currently or in the past based on the Structured Clinical Interview for DSM-III-R (SCID).[19]

Table 6. Comorbid Personality Disorders[a]

Item	% Responders	% Nonresponders	p Value
Avoidant	23.0	27.9	.117
Dependent	12.7	9.1	.268
Obsessive-compulsive	19.8	16.1	.402
Passive-aggressive	8.1	4.0	.036
Self-defeating	16.4	16.1	.431
Paranoid	7.7	7.4	.945
Schizotypal	0.6	0.3	.999
Histrionic	4.0	2.0	.246
Narcissistic	5.3	3.0	.149
Borderline	11.2	6.4	.067
Antisocial	0.6	0.7	.999
Any personality disorder	47.1	51.3	.233

[a]Individuals are considered positive for a given disorder if they satisfy DSM-III-R criteria currently or in the past based on the SCID-II.[20]

A past history of substance abuse was not predictive of response. The presence of at least 1 concurrent personality disorder also was not predictive of response to medication (Table 6). An Axis II passive-aggressive personality disorder diagnosis was predictive of a favorable response to acute treatment.

Measures of Depressive Personality

None of the 7 Schneiderian traits comprising depressive temperament,[21] nor the overall measure of depressive temperament, was predictive of drug response (Table 7). By contrast, previously identified[5] characteristics of depressive personality (low self-esteem, introversion, and quietness) were found to be predictive of nonresponse to pharmacotherapy.

Social Adjustment

Among psychosocial variables (Table 8), those who responded were more likely to have a higher sense of overall life satisfaction, more frequent sexual activity, and a longer duration of a relationship. Again, living alone was associated with a poorer response.

Table 7. Diagnostic Interview for Depressive Personality (DIDP)

	Responders		Nonresponders		
Characteristic	Mean	SD	Mean	SD	p Value
Gloomy	0.9	0.88	1.0	0.89	.285
Pessimistic	1.0	0.87	1.1	0.85	.227
Negative reactivity	1.0	0.88	1.0	0.86	.842
Bitter	0.7	0.74	0.8	0.75	.173
Remorseful	1.1	0.88	1.2	0.82	.049
Low self-esteem	1.3	0.85	1.4	0.81	.027
Given to worry	1.2	0.88	1.2	0.88	.913
Burdened	1.0	0.91	1.1	0.90	.919
Critical of others	1.1	0.85	1.0	0.87	.202
Introverted	1.2	0.84	1.3	0.80	.021
Quiet	1.0	0.89	1.2	0.86	.003
Serious	1.2	0.80	1.3	0.81	.035
Constricted	0.7	0.84	0.8	0.88	.287
Tense	0.9	0.81	0.9	0.84	.469
Limited capacity for fun	1.0	0.90	1.0	0.90	.203
Unassertive	1.0	0.89	1.1	0.89	.189
Passive	1.0	0.89	1.1	0.87	.215
Overly dependent	0.7	0.78	0.7	0.77	.782
Difficulty criticizing others	1.0	0.78	1.0	0.81	.912
Hypersensitive to rejection	1.3	0.85	1.3	0.81	.270
Oral	0.2	0.50	0.3	0.55	.072
Counterdependent	1.6	0.65	1.6	0.68	.991
Moralistic	1.0	0.84	1.0	0.87	.598
Self-critical	1.7	0.61	1.8	0.52	.293
Self-denying	1.2	0.84	1.2	0.84	.482
Underachiever	0.9	0.81	0.9	0.82	.347
Negativistic score	9.3	4.98	9.9	4.74	.266
Introvert/tense score	5.9	3.26	6.5	3.35	.009
Passive/unassertive score	5.2	3.07	5.5	2.92	.183
Self-denying score	6.4	2.16	6.5	2.03	.496
Total DIDP score	26.7	10.70	28.3	10.28	.061

Table 8. Psychosocial Variables

Item	Responders	Nonresponders	p Value
Occupational status			
Employed, %	79.5	80.4	.946
With irregular/rotating duties, %	30.1	37.8	.122
Job level appropriate to level of education, % about right	61.7	54.6	.607
Longest uninterrupted years of employment, mean ± SD	9.8 ± 8.27	9.6 ± 8.32	.762
Other			
Global assessment of satisfaction, mean ± SD score	3.7 ± 0.75	3.9 ± 0.74	.016
Sexual satisfaction, % not satisfied	27.1	29.6	.967
Frequency of sexual activity, mean ± SD score[a]	3.7 ± 1.44	3.9 ± 1.42	.031
Duration of longest relationship, mean ± SD y	13.7 ± 10.47	11.7 ± 9.10	.030
Number of children, mean ± SD	1.7 ± 1.51	1.5 ± 1.49	.168

[a]Lower score indicates higher frequency of sexual activity.

Table 9. Quality of Life Variables

	Responders		Nonresponders		
Item	Mean	SD	Mean	SD	p Value
Physical health	3.4	0.94	3.3	1.03	.123
Mood	2.1	0.76	1.9	0.73	.002
Work	2.5	1.03	2.3	1.00	.080
Household activities	2.3	0.90	2.2	0.90	.107
Social relationships	2.4	0.98	2.2	0.93	.021
Family relationships	2.7	1.02	2.8	0.99	.449
Leisure time activities	2.2	0.93	2.2	0.93	.657
Function in daily life	2.6	0.84	2.5	0.85	.050
Sexual drive and interest	2.2	1.16	2.1	1.18	.734
Economic status	2.3	1.13	2.3	1.06	.652
Living situation	3.1	1.05	2.9	1.08	.045
Physical ability without dizziness	4.2	0.82	4.1	0.91	.492
Vision for work or hobbies	3.6	1.10	3.5	1.15	.210
Sense of well-being	2.4	0.82	2.2	0.78	.005
Medication	3.3	0.88	3.1	0.81	.017
Life satisfaction during past week	2.3	0.78	2.1	0.74	.004
Total score	54.3	9.82	52.3	10.03	.009

The most consistent predictors of medication response were in the area of quality of life (Table 9). Those who responded reported a significantly higher quality of life at baseline. Among the variables predictive of response were better mood, better social relationships, better living situation, greater satisfaction with medication, higher satisfaction during the past week, better overall sense of well-being, and better success in daily functioning.

Table 10 lists the 28 statistically significant univariate predictors of response to pharmacotherapy. These include 2 sociodemographic, 8 clinical, 1 comorbidity, 6 depressive personality, 3 psychosocial, and 8 quality of life measures.

A stepwise logistic multiple regression analysis was performed to reduce the number of predictor variables summarized in Table 10 to those that significantly and independently contributed to a prediction model. A second regression analysis was then performed that was limited to variables identified as significant in the first analysis. The procedure selected 5 variables (Table 11) that were predictive of response: 3 that were psychosocial (living with spouse or partner, more education, and higher baseline quality of life) and 2 that were related to personality (presence of passive-aggressive personality and lower levels of tense/introversion). Taken together, the model correctly classified 67% of patients into the appropriate responder and nonresponder groups.

Predictors of Nonresponse Versus Full Response (Excluding Satisfactory Therapeutic Responders)

A second analysis was then performed in which the predictor variables were compared between the full responder group (N = 202) and the nonresponder group (N = 299), excluding the satisfactory therapeutic responder group (N = 122) from the analysis. Very similar predictors of response emerged using this excluded-

Table 10. Univariate Predictors of Response[a]

Items Significantly Different Between the 2 Responder Groups	Responders		Nonresponders		p Value
	%		%		
Sociodemographic variables					
Living with spouse or partner	47.2		35.4		.010
High school graduate or beyond	97.8		94.2		.012
Axis I and Axis II comorbidity					
Passive-aggressive personality	8.1		4.0		.036
	Mean	SD	Mean	SD	
Psychosocial variables					
Frequency of sexual activity score	3.7	1.44	3.9	1.42	.031
Duration of longest relationship, y	13.7	10.47	11.7	9.10	.030
Global assessment of satisfaction score	3.7	0.75	3.9	0.74	.016
Clinical ratings					
MADRS total score	25.1	7.11	26.1	7.39	.030
HAM-D					
Depressed mood	2.3	0.72	2.5	0.75	.006
Depersonalization/derealization	0.2	0.57	0.1	0.39	.016
BDI					
Sadness	1.4	0.78	1.5	0.79	.008
Discouraged about future	1.3	0.79	1.4	0.86	.037
Looking worse	1.2	1.02	1.4	1.06	.010
Working	1.4	0.71	1.5	0.73	.033
Tired	1.4	0.85	1.6	0.88	.002
DIDP					
Remorsefulness	1.1	0.88	1.2	0.82	.049
Low self-esteem	1.3	0.85	1.4	0.81	.027
Introverted	1.2	0.84	1.3	0.80	.021
Quiet	1.0	0.89	1.2	0.86	.003
Serious	1.2	0.80	1.3	0.81	.035
Introverted/tense	5.9	3.26	6.5	3.35	.009
Q-LES-Q					
Overall quality of life (total score)	54.3	9.82	52.3	10.03	.009
Mood	2.11	0.76	1.93	0.73	.002
Social relationships	2.39	0.98	2.21	0.93	.021
Function in daily life	2.61	0.84	2.46	0.85	.050
Living situation	3.07	1.05	2.88	1.08	.045
Sense of well-being	2.43	0.82	2.24	0.78	.005
Satisfaction with medication	3.27	0.88	3.06	0.81	.017
Life satisfaction during past week	2.29	0.78	2.10	0.74	.004

[a]Abbreviation: Q-LES-Q = Quality of Life, Enjoyment, and Satisfaction Questionnaire.

Table 11. Prediction of Treatment Response: Results of the Multiple Logistic Regression Analysis

Predictor Variable	Odds Ratio	p Value
Lives with partner	1.7	.002
At least high school graduate	3.1	.019
Quality of life total	1.0	.009
Passive-aggressive personality	2.7	.013
DIDP introverted-tense composite score	0.9	.037

middle approach. No longer significant as a predictor was the psychosocial variable "duration of longest relationship," as well as passive-aggressive personality, and several personality traits on the DIDP (introverted, quiet, serious). Variables that achieved significance as predictors of response were lower scores on the HAM-D items suicidality and retardation, lower BDI total score, and lower scores on DIDP traits of bitterness and being passive-unassertive. Simple phobia and borderline personality were also significant predictors of response.

DISCUSSION

This article reports on predictors of response to pharmacotherapy for acute treatment of chronic and double depression in a random assignment clinical trial. The strongest predictors of response reflected a more positive quality of life at baseline, including better overall mood, daily functioning, and sense of well-being. Moreover, those who were married and living with their spouse or partner, or who were more educated (high school graduate or above), were more likely to respond.

Clinical variables were generally less predictive than we had expected. When significant relationships were found, indicators of symptom severity were associated with poorer outcomes. Surprisingly, most types of comorbid psychiatric illnesses did not adversely affect the response to treatment. However, since the entrance criteria for the study excluded those with the most severe personality disorders, primary anxiety disorders, obsessive-compulsive disorder, or recent alcohol and active substance abuse, we must be cautious about the generalizability of these findings. Nonetheless, the study included substantial comorbid psychiatric illness, and its presence had little if any effect on outcome. That persons with severe borderline personality disorder were excluded from the study may help to explain the finding that milder forms of this Axis II disorder were predictive of positive response. Nevertheless, some of the features of borderline personality disorder such as affective lability and irritability may be responsive to antidepressant pharmacotherapy.

The most plausible explanation for these findings is that the presence of depression over years and even decades may have deleterious effects sufficient to "overpower" most other clinical variables. Our patients had been chronically depressed for a mean of nearly 9 years, and those with double depression had a median duration of dysthymia for over 23 years. Importantly, more than half of this sample had never received any antidepressant medication, and less than one third had previously received an adequate trial of pharmacotherapy.

Consistent with this hypothesis, indicators of psychosocial function were the most powerful predictors of response, followed by measures of personality. Those pa-

tients whose outlook was poorest, whose sense of well-being and daily function were lowest, and who had the least life satisfaction were less likely to respond, even though their symptomatology was not worse. Thus, it was the patient's perception of quality of life and actual psychosocial status that were more predictive of response to pharmacotherapy than clinical history or status.

A significant limitation of this study is the lack of a parallel placebo-control group. This group, if included, would have permitted more global correlates of favorable outcome to be disaggregated from more specific predictors of response to active pharmacotherapy. Rush et al.[11] have described the overall aims and design of this research program, but to summarize briefly, the investigators decided not to use a placebo-control group (despite its obvious advantages) because of ethical concerns. Also, an acute phase placebo-control group was not necessary to test the primary aims of our research program, namely to determine the relative efficacy of sertraline against a standard comparator, imipramine, and to provide the preliminary lead-in to the planned maintenance study. As it stands, there are some parallels between the predictors of response in this study and the predictors of placebo response in prior studies of patients with shorter duration of depression.

We were surprised that the exclusion of the middle group, the satisfactory responders, did not increase the number of predictors. The only difference between the 2 analyses was that quite a few of the predictors identified as significant in the univariate analysis became more significant when the middle group was excluded and full responders were compared to nonresponders. On the other hand, some of the predictors identified in the univariate analysis stayed the same or lost some significance.

A key finding is that a majority of these patients responded to a vigorous trial of standard antidepressant medications, including patients with significant comorbidity. This is particularly important clinically because many clinicians still consider such patients to be better candidates for psychotherapy than pharmacotherapy.

Despite finding a number of variables that were statistically significantly related to outcome, we uncovered no relationships that can improve prediction of response with sufficient precision to be applied clinically. The search for this elusive information must continue. Our results, and those of earlier investigators, suggest that clinical and demographic descriptors will not provide the key. Perhaps more sensitive assessments of brain activity, both before treatment and in response to specific medications, will allow more useful and specific predictors to be uncovered.

Drug names: chloral hydrate (Noctec), imipramine (Tofranil and others), sertraline (Zoloft), temazepam (Restoril and others).

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