Predictors and Time Course of Response Among Panic Disorder Patients Treated With Cognitive-Behavioral Therapy

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Objective: Cognitive-behavioral therapy (CBT) is well documented as an efficacious treatment for panic disorder. We provided open CBT treatment to patients who subsequently participated in a maintenance treatment study. This article reports on predictors and trajectory of response in 381 participants who completed treatment at 4 sites.

Method: Participants who met criteria for panic disorder with or without agoraphobia (N = 381) completed assessment and entered treatment. Of these, 256 completed 11 sessions of CBT delivered by trained and supervised research therapists. Raters trained to reliability obtained demographic data and administered structured diagnostic interviews and the Hamilton Rating Scales for Depression and Anxiety and the Panic Disorder Severity Scale (PDSS) measures at baseline and posttreatment. We obtained self-report (SR) measures of anxiety sensitivity and adult separation anxiety at baseline and posttreatment and PDSS-SR ratings weekly. The study was conducted between November 1999 and July 2002.

Results: Treatment response rate was 65.6% for completers and 44.1% for the intent-to-treat sample. Greater severity of panic disorder and lower levels of adult separation anxiety predicted response. Beginning at week 4, responders showed greater mean decreases in PDSS scores than nonresponders and maintained the advantage throughout the treatment. By week 6, 76% of responders, compared to 36% of nonresponders, recorded PDSS scores at least 40% below baseline on 2 consecutive weeks (odds ratio = 5.42, 95% CI = 3.10 to 9.48).

Conclusion: These results suggest that CBT is just as effective for more severe panic disorder patients as it is for those with less severe panic disorder, regardless of other comorbid disorders, including agoraphobia. However, patients experiencing adult separation anxiety disorder are less likely to respond. Our results further inform clinicians that many people who will respond to 11 weeks of treatment will have done so by the middle of the treatment.

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Cognitive-behavioral therapy (CBT) and antidepressant medication are widely used efficacious treatments for panic disorder. We previously reported results of a 4-site study in which the relative efficacies of CBT, antidepressant medication (imipramine), and their combination were evaluated in a sample of patients having panic disorder with no or mild agoraphobia.[1] We found that CBT alone was as effective as imipramine alone, and CBT alone had a higher proportion of patients still classified as responders at follow-up than imipramine alone. There was little advantage to combination treatment. Based on these findings, and following a model of using the least invasive treatment first, we reasoned that it makes sense to treat panic disorder patients initially with CBT. Since our initial study excluded patients with moderate or severe agoraphobia and did not examine the value of a maintenance-treatment phase, we designed a study to examine these issues. The study was conducted between November 1999 and July 2002.

We recruited a heterogeneous group of panic disorder patients with a range of agoraphobia and other comorbidities and offered them CBT as an initial treatment approach. Responders were then randomly assigned to receive follow-up for 22 months with or without a 9-month maintenance treatment phase. Nonresponders were randomly assigned to receive continued CBT or to switch to medication. In this article, we report outcomes of the 11-week acute-phase CBT, and we examine which clinical or demographic characteristics predict response. Specifically, we provide effects of sex and minority status, depression, diagnostic comorbidity, and presence of interpersonal problems on acute treatment outcome. In addition, we describe the trajectory of response using Panic Disorder Severity Scale-Self Report (PDSS-SR) scores obtained throughout the treatment among patients who responded to CBT compared to those who did not.

METHOD

Participants

A total of 454 individuals referred by primary care physicians and psychiatric outpatient clinics and recruited through local media advertising underwent a preliminary telephone screening. Those who were eligible and interested provided signed informed consent and underwent a baseline assessment procedure. Those meeting diagnostic criteria for panic disorder completed a medical evaluation, including a physical examination and screening laboratory tests (blood count and chemistries, urinalysis, urine toxicology). Participants with no active medical illness or evidence of substance abuse or dependence, bipolar disorder, or psychosis then entered CBT based on the work of Barlow and Craske.[2] Individuals receiving antipanic medication at recruitment were eligible for study participation, with the agreement that they would discontinue these medications by the ninth week of the treatment.

Three hundred eighty-one of the 454 patients who screened positive for panic disorder completed a baseline diagnostic interview and attended the first treatment session. The study was conducted at 4 sites, including the Center for Anxiety and Related Disorders at Boston University (N = 94), Hillside/Long Island Jewish Hospital in New York, N.Y. (N = 92), Western Psychiatric Institute and Clinic in Pittsburgh, Penn. (N = 104), and Yale University in New Haven, Conn. (N = 91). The institutional review board at each site approved the protocol for this study. One hundred twenty-five patients either dropped out or were removed from the treatment study for a variety of reasons (e.g., patient violated study protocol, patient improved and did not want to continue, or patient did not want to taper off medication): Boston, N = 21; New York, N = 33; Pittsburgh, N = 42; New Haven, N = 29. Among the 256 treatment completers there were 165 women and 91 men, with a mean age of 38.8 (SD = 11.7) years and a mean duration of illness of 11.6 (SD = 10.5) years (Table 1). Approximately equal numbers of participants were treated in Boston (N = 73), New York (N = 59), Pittsburgh (N = 62), and New Haven (N = 62).

Table 1. Demographic Characteristics of the Total Sample (N = 256)

Characteristic	Mean	SD
Age, y	38.7	11.7
Education, y	15.2	3.0
	N	%
Sex		
Male	91	35.5
Female	165	64.5
Marital status		
Married, remarried, separated	140	54.9
Never married	93	36.5
Divorced	22	8.6
Race/ethnicity		
White	224	87.5
Nonwhite	32	12.5
Income, $		
< 20,000	47	18.5
20,000–49,999	73	28.7
50,000–74,999	47	18.5
75,000–100,000	41	16.1
> 100,000	46	18.1
Work status		
Full-time	156	60.2
Part-time	48	18.8
Unemployed	23	9.0
Homemaker	23	9.0
Retired	8	3.1
Religion		
Catholic	143	55.9
Protestant	47	18.4
Jewish	25	9.8
Other	41	16.0
Diagnosis		
Panic disorder with agoraphobia	243	94.9
Panic disorder without agoraphobia	13	5.1
Previous panic disorder episodes		
None	187	73.0
1 or more	69	27.0
Comorbid MDD at baseline		
Negative	208	81.3
Positive	48	18.7

Abbreviation: MDD = major depressive disorder.

Treatment Procedures

Cognitive-behavioral therapy includes education about the nature of anxiety and panic, identification and correction of maladaptive thoughts about anxiety and its consequences, interoceptive exposure, and graded exposure to avoided situations and activities. Cognitive-behavioral therapy was administered in 11 sessions, 45 to 60 minutes in length, delivered over an 11-week period. (Due to missed visits, a maximum of 18 weeks may have occurred to complete the 11 sessions.) The session length was sometimes increased to a maximum of 90 minutes during the last 6 weeks to accommodate additional demands of the situational exposure component.

Therapists were experienced clinicians trained in the protocol at the Boston site under the direction of David A. Spiegel, M.D., and D.H.B. and monitored throughout the study. Training included didactic instruction, hour-for-hour supervision of at least 2 training cases, and group supervision meetings during which both specific application and general issues of the CBT treatment were discussed. Group supervision continued throughout the study period. Additionally, adherence monitoring was done on randomly selected tapes. Results were provided to the therapist and site supervisor and discussed as needed.

Assessment Instruments

The Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV)[3–4] was used to establish psychiatric diagnoses, including panic disorder and mood and anxiety disorder comorbidity. We modified the ADIS-IV in this study in order to shorten the time required for administration and included a 19-item agoraphobia scale that provides a score for agoraphobic severity. The Structured Interview Guide for the Hamilton Rating Scale for Anxiety (SIGH-A)[5,6] and the Hamilton Rating Scale for Depression (HAM-D)[7] are included in this assessment. An even shorter version of the ADIS-IV, containing only diagnostic symptomatology, was used at posttreatment assessment periods, with a time frame of 1 month rather than 3. These instruments are available from the second author (M.K.S.) upon request.

Raters across the 4 sites were trained to reliability, and 10% of all assessments were randomly selected for monitoring throughout the course of the study. The intraclass correlation coefficient (ICC) was calculated for the ADIS-generated diagnoses (N = 164). The ICC for panic disorder was 0.885, for agoraphobia was 0.658, for MDD was 0.99, for GAD was 0.999, for OCD was 0.747, for social phobia was 0.909, for specific phobia was 0.795, for dysthymia was 0.489, and for PTSD was 0.486. The ICC for the HAM-D (N = 181) was 0.997 and for the HAM-A (N = 193) was 0.990.

The PDSS,[8] a 7-item scale developed for our previous study,[1] was used as the main outcome measure for the present study. This scale provides ratings of panic frequency, distress during panic, anticipatory anxiety, panic-related avoidance of situations and sensations, and the degree of work and social impairment/interference due to panic disorder. It has good interrater reliability and good concurrent validity.[8] The Clinical Global Impressions-Improvement scale[9] consists of a 7-point scale rating overall improvement in illness, distress, and impairment. Both scales were administered by an independent evaluator (IE) monthly during treatment and at the post-acute assessment. Additionally, a self-report version of the PDSS, the PDSS-SR,[10] was developed and tested for this study and administered at each treatment session. Response was defined as at least a 40% reduction from the baseline level in IE-rated PDSS score and a CGI score of *much* or *very much* improved. The ICC for the PDSS (N = 434) was 0.993.

We administered the Anxiety Sensitivity Index,[11,12] a measure of fear of bodily sensations, and the Albany Panic and Phobia Questionnaire (PPQ),[13] in which we used subscales that assess fear of agoraphobic situations, social situations, and situations and activities that produce bodily sensations.

Participants completed the 15-item form of the Inventory of Interpersonal Problems (IIP).[14,15] We used subscales of interpersonal sensitivity, ambivalence, and aggression. We further administered a measure of adult separation anxiety, the Adult Separation Anxiety Checklist (ASA-CL).[16] Adult separation anxiety disorder is a recently identified condition that occurred frequently in a group of outpatients with mood and anxiety disorders.[17] Data from the National Comorbidity Study Replication revealed a high prevalence of adult separation anxiety disorder with high levels of panic disorder.[18]

Data Analysis

Preliminary examination of frequency distributions and identification of outliers was performed. Categorical cross-tabulations were examined for responder/nonresponder, sex, and site using the χ^2 statistic. Preliminary examination of the demographic measures was performed using analysis of variance (ANOVA), first examining for responder/nonresponder and sex effects and their interaction and second for responder/nonresponder and site effects and their interaction. Next, we examined outcome predictors by performing 2 (responder status) by 2 (sex) analyses of covariance (ANCOVAs) including measures found to be relevant during the preliminary analyses as covariates. We planned an integrative analysis to follow these, namely, a logistic regression analysis with responder/nonresponder as the outcome measure, including several demographic measures at the first step, followed by the various instrument scales and total scores at a second step, to discern the salience of these measures in predicting responder outcome.

We then examined the pattern of change in PDSS scores separately for responders and nonresponders. We conducted these analyses in 2 ways. First, we compared the trajectory of change in PDSS-SR total scores for the 2 groups across all treatment sessions using repeated measures (RM)-ANCOVA. In this analysis, we characterized within-treatment changes by performing a 2 (responder status) by 2 (sex) RM-ANCOVA examining the weekly PDSS total scores across the treatment period, including age, duration of illness, education level, and treatment week when medication was stopped. Next, we used odds ratios (ORs) to compare the groups during treatment on frequency of meeting responder criteria, i.e., a 40% or

Table 2. Analysis of Covariance Results for Baseline Instrument Scales and Totals by Response Outcome and Sex[a,b]

	Nonresponders		Responders		Response Outcome		Sex		Response/Sex Interaction	
Assessment	Male (N = 34)	Female (N = 54)	Male (N = 57)	Female (N = 109)	F	p	F	p	F	p
HAM-A	16.2 (9.4)	18.5 (10.0)	19.9 (10.6)	18.4 (9.3)	0.73	.39	0.54	.46	3.42	.07
HAM-D	10.4 (6.7)	11.3 (6.9)	12.8 (7.7)	11.5 (7.4)	0.68	.41	0.06	.81	2.56	.11
PDSS[c]	13.1 (4.3)	12.8 (5.1)	14.4 (3.9)	14.3 (4.3)	4.87	.03	0.31	.58	0.07	.79
PPQ	60.2 (31.0)	76.0 (32.4)	58.8 (30.4)	68.3 (34.7)	0.89	.35	6.87	.01	0.47	.49
ASI	32.1 (10.9)	35.6 (12.3)	33.9 (11.1)	34.6 (12.8)	0.01	.95	1.07	.30	1.83	.18
ASA-CL	15.4 (9.0)	20.9 (11.1)	15.0 (8.8)	16.0 (10.0)	4.63	.03	5.73	.02	3.89	.05
IIP										
Interpersonal sensitivity	7.6 (4.6)	9.6 (4.3)	7.8 (4.3)	8.1 (4.8)	0.70	.40	2.31	.13	2.03	.16
Ambivalence	4.4 (4.7)	4.7 (4.4)	4.5 (4.2)	3.8 (4.5)	0.38	.54	0.12	.73	0.31	.58
Aggression	4.4 (3.0)	5.5 (4.2)	5.3 (3.9)	4.5 (4.2)	0.01	.93	0.01	.92	4.51	.04
Agoraphobia										
Current	15.9 (10.9)	19.5 (13.1)	13.9 (12.5)	19.1 (13.8)	0.55	.46	6.01	.02	0.13	.72
Worst	23.5 (17.5)	29.2 (20.0)	26.1 (17.9)	29.6 (19.9)	0.25	.62	2.49	.12	0.01	.92

[a]Analysis of covariance results presented as mean (SD).
[b]Duration of illness, household income, and site were included as covariates.
[c]Response criteria partially based on the change in PDSS score from baseline to the end of the acute treatment period at 12 weeks.
Abbreviations: ASA-CL = Adult Separation Anxiety Checklist, ASI = Anxiety Sensitivity Index, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, IIP = Inventory of Interpersonal Problems, PDSS = Panic Disorder Severity Scale, PPQ = Albany Phobia and Panic Questionnaire.

greater decrease from baseline PDSS score at 2 consecutive sessions.

RESULTS

Raters judged 168 (65.6%) participants to be responders and 88 participants to be nonresponders at the end of acute treatment. Conservatively concluding that the 125 individuals who did not complete the treatment were also nonresponders, the intent-to-treat response rate was 44.1% (168/381). A detailed examination of study attrition is in preparation. The current article focuses on outcome patterns and predictors among study completers. At study entrance, 116 patients were taking medication, including benzodiazepines only (N = 52), antidepressants only (N = 37), or both (N = 27). Baseline medication use was not associated with outcome.

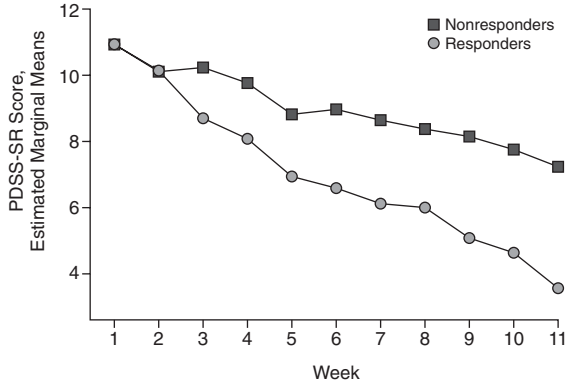
Predictors of Response Among Treatment Completers

Initially, we compared responders and nonresponders across demographic measures. Response rates did not differ across sex, race, marital status, or diagnosis of panic disorder with versus without agoraphobia. (See Table 1.) We next performed an ANCOVA to examine predictors of response. (See Table 2.) Results indicated that responders had higher baseline PDSS scores and lower baseline scores on the ASA-CL than nonresponders. There was a statistically significant interaction between responder status and sex for the ASA-CL, in which female nonresponders exhibited higher scores than nonresponders, while male responders and nonresponders exhibited scores similar to female responders (p = .05). There was a statistically significant interaction between responder status and sex for the aggression subscale of the IIP, in which scores for nonresponding women were higher than those for the nonresponding men, while the converse was true of the responder groups (p = .04). Women scored statistically significantly higher on the PPQ total and the current agoraphobia total than men (p = .01).

As an integrative analytic procedure, we performed a logistic regression using a backward-stepping procedure predicting responder/nonresponder outcome. The PDSS total score was the strongest predictor of the response outcome (B = .187, Wald statistic = 15.99, df = 1, p < .001), followed by the ASA-CL total score (B = –.059, Wald statistic = 11.81, df = 1, p < .001). Higher score on the PDSS and lower score on the ASA-CL were associated with higher rates of response to CBT. A score greater than 21 on the ASA-CL is thought to identify a categorical diagnosis of adult separation anxiety disorder.[19] When we repeated the above procedure using a dichotomized ASA-CL (≤ 21 vs. > 21), ASA-CL continued to predict worse outcome. The estimated OR indicated that patients with adult separation anxiety disorder were 3.74 (95% CI =1.80 to 7.80) times more likely to be nonresponders.

We further examined other baseline comorbid diagnoses to evaluate their possible role as predictors of response. Of the 117 (45.7%) participants who had at least 1 comorbid condition, 58 (49.5%) had 1 additional diagnosis, 38 (32.5%) had 2 additional diagnoses, 14 (12%) had 3 additional diagnoses, and 7 (6%) had 4 or more additional diagnoses. Generalized anxiety disorder (N = 65, 55.6%) was the most common comorbid diagnosis present, followed by major depressive disorder (MDD) or dysthymia (N = 48, 41%), specific phobia (N = 30, 25.6%), and social phobia (N = 28, 23.9%). There were no differences in treatment response between patients with comorbidity (68.4%) and without comorbidity

Figure 1. Weekly Ratings of Estimated Marginal Means of PDSS-SR Scores by Group[a,b]



[a]First significant difference occurs at week 4.
[b]t = 2.89, df = 253, p = .0004.
Abbreviation: PDSS-SR = Panic Disorder Severity Scale-Self Report.

Table 3. Odds of Becoming a Responder at the End of Acute Treatment as Predicted by 40% Decrease in PDSS-SR for 2 Consecutive Sessions by Range of Weeks Considered

	Consecutive 40% PDSS-SR Decrease					
Range of Weeks (sessions)	Responders, N = 168		Nonresponders, N = 88		Odds Ratio	CI
	Yes	No	Yes	No		
1–2	33	135	8	80	2.44	1.08 to 5.55
1–3	57	111	13	75	2.96	1.52 to 5.79
1–4	96	72	20	68	4.53	2.53 to 8.14
1–5	109	59	24	64	4.93	2.80 to 8.68
1–6	127	41	32	56	5.42	3.10 to 9.48
1–7	136	32	37	51	5.86	3.31 to 10.38
1–8	142	26	41	47	6.26	3.46 to 11.31
1–9	145	23	42	46	6.90	3.76 to 12.67
1–10	151	17	46	42	8.11	4.22 to 15.58
1–11	155	13	50	38	9.06	4.47 to 18.35

Abbreviation: PDSS-SR = Panic Disorder Severity Scale-Self Report.

(63.3%). With the exception of adult separation anxiety disorder, no comorbid diagnosis was associated with response outcome. A currently unpublished report focuses on comorbidity as a moderator and outcome measure in this population (L.B.A., K.S.W., D.H.B., et al., unpublished data, 2007).

Pattern of Within-Treatment Change in PDSS Scores Among Completers

Participants completed the PDSS-SR at each study visit. We used RM-ANCOVA to examine weekly scores across the treatment period (time) separately for responders and nonresponders. (See Figure 1.) There was a statistically significant time-by-group interaction (Greenhouse-Geisser F = 9.31, df = 8,1772; p = .001), indicating that responders showed a significantly greater decline in PDSS-SR scores throughout the treatment than nonresponders. A statistically significant difference in mean PDSS-SR score in responders as compared to nonresponders was first observed at session 4 and was maintained for all sessions thereafter (p = .036).

Next, we compared final responders and nonresponders on the frequency of achieving a 40% reduction in PDSS-SR score for 2 consecutive weeks during treatment. By week 6, the OR that a responder met this criterion, compared to a nonresponder, was 5.42 (95% CI = 3.10 to 9.48). Seventy-six percent of responders had experienced a 40% reduction in PDSS score for 2 consecutive weeks compared to 36% of nonresponders. Table 3 shows the OR for each of the 11 weeks.

DISCUSSION

We examined predictors of response and patterns of response among panic disorder patients with or without agoraphobia who completed a course of treatment with CBT. The response rates in this study are similar to those reported by Schmidt et al.[20] and to those found in our prior study of panic disorder without agoraphobia using medication or CBT.[1] In the current study, CBT was more, not less, effective for patients with more severe symptoms.

Responders did not differ from nonresponders with respect to sex, age, race, duration of illness, or baseline medication use. Additionally, baseline DSM-IV comorbidity, including comorbid MDD, did not predict worse outcome in our study than in those without comorbidity. Although panic disorder consistently predicts poor outcome in major depression, the reverse is not consistently observed. In particular, our results and those of others suggest that panic disorder patients with co-occurring MDD need not be treated differently than those without depression.

Higher baseline agoraphobia scores did not predict a poorer response in our study than lower baseline agoraphobia scores. High levels of agoraphobia sometimes predict worse outcome than low levels; however, the treatment we administered specifically targeted both panic and agoraphobic symptoms, and this fact may explain our results. Nor did low income predict worse treatment response in this sample than high income. This finding is similar to that observed by Roy-Byrne et al.[21] and underscores the importance of ensuring availability of this simple treatment in public mental health clinics. Our finding that lower baseline PDSS score predicts a lower response rate may be a floor effect, since the criterion for responder requires a 40% decrease in PDSS score.

The finding that the presence of adult separation anxiety disorder predicted worse outcome deserves some comment. Agoraphobia resembles separation anxiety in that individuals with agoraphobia may have fear and avoid-

ance of being alone. However, the focus of fear for agoraphobics is panic, while the focus of fear in separation anxiety is danger to a significant other. Our treatment did not target separation anxiety. In fact, little attention has been paid to this syndrome, in spite of the fact that there is now substantial evidence for its existence and frequent occurrence in clinical and nonclinical populations with other DSM-IV conditions. Adult separation anxiety occurs de novo in adulthood and is the most common pathological outcome of childhood separation anxiety.[18,22] We did not assess childhood separation anxiety in the current project. Our finding suggests that there is a need to develop treatments targeting separation anxiety disorder symptoms separately from agoraphobia.

Both responders and nonresponders showed overall improvement in our study. However, the trajectory of change was very different for the 2 groups. Panic disorder severity showed statistically significantly greater reductions for responders beginning as early as the fourth week of treatment ($p = .036$). Moreover, patients who reported 2 consecutive weeks of PDSS-SR scores at least 40% lower than baseline by the sixth week of treatment were 5 times more likely than those who did not to meet response criteria by the end of 12 weeks (OR = 5.42, 95% CI = 3.10 to 9.48). These findings are potentially important in alerting clinicians to consider alternative treatment strategies and/or augmentation beginning early in the treatment course. We advocate regular assessment of PDSS-SR scores, consistent with the important notion of measurement-based care, promulgated by investigators in the Sequenced Treatment Alternatives to Relieve Depression study.[23]

This study has several limitations. Our dropout rate was relatively high. We recruited individuals who were taking medication only if they were willing to commit to discontinuing pharmacotherapy. This is not ordinarily a requirement for CBT for panic disorder. Instead, these decisions are usually made by patients and therapists based on a range of considerations. Also, completers were defined conservatively as those attending a predetermined number of sessions within a predetermined time period. Given that our results showed that early improvement was common among responders, some dropouts may have simply felt they did not require more treatment.

An important limitation is the fact that we had no control condition, so we have no way of knowing the extent to which treatment effects are specifically related to CBT or to the passage of time. However, we would point out that our results are very similar to those obtained by our previous study,[1] which did include a control, making the possibility less likely that passage of time was responsible for the main effect here. The fact that there were relatively few predictors of outcome might result from the fact that responders included individuals who may have improved with time and/or therapist attention and regular monitoring as well as those who responded to specific techniques used in CBT. The lengthy mean duration of illness (11 years) also suggests that time alone was not likely to be explanatory for most patients.

The strengths of these findings are the large sample size, the use of 4 sites, rigorous adherence to the treatment protocol, and multivariate analyses in a trial of CBT alone for panic disorder. Most studies of psychosocial treatment have employed only univariate data with smaller sample sizes. More research is needed to clarify how the presence of adult separation anxiety moderates poorer outcome in CBT treatment.

While many individuals responded well to this first-stage treatment, greater attention should be accorded to second-stage strategies for those who do not respond adequately. Forthcoming results from a subsequent randomized study with our population of nonresponders speaks to this issue, as does an additional study examining optimal strategies for maintaining response among responders.

Drug name: imipramine (Tofranil).

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