Chronic Depression

Medication (Nefazodone) or Psychotherapy (CBASP) Is Effective When the Other Is Not

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Context: Although various strategies are available to manage nonresponders to an initial treatment for depression, no controlled trials address the utility of switching from an antidepressant medication to psychotherapy or vice versa.

Objective: To compare the responses of chronically depressed nonresponders to 12 weeks of treatment with either nefazodone or cognitive behavioral analysis system of psychotherapy (CBASP) who were crossed over to the alternate treatment (nefazodone, n=79; CBASP, n=61).

Design: Crossover trial.

Setting: Twelve academic outpatient psychiatric centers.

Patients: There were 140 outpatients with chronic major depressive disorder; 92 (65.7%) were female, 126 (90.0%) were white, and the mean age was 43.1 years. Thirty participants dropped out of the study prematurely, 22 in the nefazodone group and 8 in the CBASP group.

Interventions: Treatment lasted 12 weeks. The dosage of nefazodone was 100 to 600 mg/d; CBASP was provided twice weekly during weeks 1 through 4 and weekly thereafter.

Main Outcome Measures: The 24-item Hamilton Rating Scale for Depression, administered by raters blinded to treatment, the Clinician Global Impressions–Severity scale, and the 30-item Inventory for Depressive Symptomatology–Self-Report.

Results: Analysis of the intent-to-treat sample revealed that both the switch from nefazodone to CBASP and the switch from from CBASP to nefazodone resulted in clinically and statistically significant improvements in symptoms. Neither the rates of response nor the rates of remission were significantly different when the groups of completers were compared. However, the switch to CBASP following nefazodone therapy was associated with significantly less attrition due to adverse events, which may explain the higher intent-to-treat response rate among those crossed over to CBASP (57% vs 42%).

Conclusions: Among chronically depressed individuals, CBASP appears to be efficacious for nonresponders to nefazodone, and nefazodone appears to be effective for CBASP nonresponders. A switch from an antidepressant medication to psychotherapy or vice versa appears to be useful for nonresponders to the initial treatment.

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SUBSTANTIAL PROPORTION of patients treated for depression do not respond to the initial trial of either an antidepressant medication or depression-targeted psychotherapy.1 This so-called stage I antidepressant resistance2,3 is one of several degrees of resistance defined by prior treatment history. Numerous treatment options are available in such situations, including switching medication type or class, augmenting or combining medications, and switching to or augmenting with psychotherapy. There are few controlled data to guide clinicians as to the preferable next step.3,5 Importantly, many depressed patients initially receive psychotherapy alone. Surprisingly few studies5 have evaluated the role of medication following nonresponse to psychotherapy.7 None has evaluated the efficacy of psychotherapy following nonresponse to medication. Surprisingly few controlled switch studies are available even for medication-to-medication switches.7,8 This report provides the first prospective controlled trial evidence, using blinded rater methodology, to examine switching from nefazodone therapy to psychotherapy (specifically, cognitive behavioral analysis sys-
also excluded. Patients who had not responded previously to a

or to have significant, unstable general medical disorders were

cide, to have medical contraindications to antidepressant therapy,

year of intake. Patients considered to be at immediate risk of sui-

chotic disorders; obsessive-compulsive disorder; or schizotypal,

bipolar disorder or cyclothymia; schizophrenia or other psy-

HRS-D24 (both at screening and following a 2-week drug-free

sode recovery. Additionally, patients had to have a score of 20

current major depressive disorder with incomplete interepi-

double depression” (ie, a current major depressive

CURRENT MAJOR DEPRESSIVE DISORDERS

an abbreviated version of the Structured Clinical In-

This protocol was part of a multiphase collaborative research pro-

DSM-IV

Personality Disorders12 were used to estab-

Subjects

This protocol was part of a multiphase collaborative research pro-

EMETIC PSYCHOLOGY [CBASP]9 or switching from CBASP
to nefazodone therapy following completion with nonre-
sponse to a 12-week trial of the alternative treatment.

Methods

This protocol was part of a multiphase collaborative research pro-

program studying chronic depressive disorders (see Keller et al10 for

a full description of study design, rationale, and methods). The

institutional review boards at all 12 sites approved the study.

Briefly, outpatients 18 to 75 years of age who were in a current

major depressive episode were eligible to enroll at one of 12 cen-
ters if they met the DSM-IV criteria for chronic major depressive

disorder (ie, current major depressive episode ≥ 2 years in
duration), “double depression” (ie, a current major depressive

episode superimposed on antecedent dysthymic disorder), or

 recurrent major depressive disorder with incomplete interepi-

sode recovery. Additionally, patients had to have a score of 20

or higher on the 24-item Hamilton Rating Scale for Depression

(HRS-D24) both at screening and following a 2-week drug-free

period at baseline prior to treatment initiation.

The Structured Clinical Interview for DSM-IV Axis I Disor-
ders11 and an abbreviated version of the Structured Clinical In-
terview for DSM-IV Personality Disorders12 were used to estab-

lish the intake diagnoses. Patients with organic mental syndromes;

bipolar disorder or cyclothymia; schizophrenia or other psy-

chotic disorders; obsessive-compulsive disorder; or schizotypal,

antisocial, or severe borderline personality disorder were ex-

cluded, as were those with principal current diagnoses of panic,
generalized anxiety, or posttraumatic stress disorders. Patients

were not eligible if they had abused alcohol or drugs within the last 6

months or suffered from bulimia or anorexia nervosa within 1

year of intake. Patients considered to be at immediate risk of sui-
cide, to have medical contraindications to antidepressant therapy,
or to have significant, unstable general medical disorders were

also excluded. Patients who had not responded previously to a

minimally adequate trial of nefazodone (ie, at least 4 weeks at ≥ 300
mg/d) were not eligible. Patients could not have been treated with

benzodiazepines within 2 weeks, fluoxetine or monoamine oxi-
dase inhibitors within 4 weeks, electroconvulsive therapy during

6 months, or depot neuroleptics within 6 months. No psycho-

therapy outside the study protocol was permitted.

Initial Acute-Phase Treatment Trial

Participants were recruited via advertisements in newspapers,

radio, and printed flyers as well as through physician refer-

rals. After providing written informed consent, subjects un-
derwent a complete medical history interview, physical exami-
nation, electrocardiogram, and laboratory screening test battery
to confirm medical eligibility. No nonprotocol psychotropic

medications were allowed during the study, including anxio-

lytics and sedative hypnotics. Patients agreed to randomization
to CBASP, nefazodone, or the combination for this 12-
week acute-phase trial (Figure 1).

Patients randomized to nefazodone monotherapy or com-
bined nefazodone therapy and CBASP received open-label treat-
mant with oral nefazodone. Those patients receiving nefaz-
odone, either with or without CBASP, received an initial daily
dose of 200 mg (100 mg twice a day), which was increased to

300 mg/d during the second week. Thereafter, when indi-
cated, the dose was increased in increments of 100 mg/d to a

maximum of 600 mg/d. To remain in the study, patients were

required to take a minimum of 300 mg/d by week 3. Patients

noncompliant with prescribed dosing were dropped from the

study. At the end of the initial acute-phase trial, the overall fi-
nal average daily dosage of nefazodone was 461.0 mg/d (SD,

143.3 mg/d). Psychopharmacology visits were conducted ac-

cording to a manual13 for clinical management (eg, review of

symptoms, adverse events, illnesses, and concomitant medi-
cations) and were limited to 15 to 20 minutes.

Cognitive-behavioral analysis system of psychotherapy, which

was developed to address the specific challenges of treating in-

dividuals with chronic depression, incorporates both cogni-
tive behavioral and interpersonal features.9 Treatment was con-
ducted according to a manual13 specifying sessions twice weekly
during weeks 1 through 4 and weekly thereafter until week 12.
Sessions could be held twice weekly during weeks 5 through 8
if the patient was having trouble mastering situational analy-
sis, the core procedure in CBASP.9 Patients who attended fewer

than 13 sessions or missed 3 consecutive sessions were dropped
from the study. The overall mean number of total CBASP

sessions for the intent-to-treat acute-phase sample was 16 (SD,

5.4).

Psychotherapists had either (1) an MD or PhD degree along

with at least 2 years of post-training experience or (2) an MSW

degree along with at least 5 years of post-degree experience.

All psychotherapists attended a 2-day training workshop and

met the criteria for mastery of CBASP treatment procedures on

2 pilot training cases, as assessed by videotape-based adher-
cence rating, before they were allowed to see study patients. Ad-
cherence monitoring to the CBASP protocol took place through-

tout the study. All study CBASP sessions were videotaped.

The CBASP supervisors at each site conducted weekly adher-
cence monitoring by videotape review using a standardized adher-
cence rating scale. Site supervisor adherence was similarly moni-
tored by a CBASP coordinator.

Assessment of Response

Vital signs and adverse events (volunteered or observed) were

assessed at each visit. The primary outcome measure was the

HRS-D24,15-17 which was completed on week by week

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4 and biweekly thereafter. Secondary outcomes included the Clinical Global Impressions–Severity scale (CGI-S),\textsuperscript{14} the 30-item Inventory for Depressive Symptomatology–Self-Report (IDS-SR\textsubscript{10}),\textsuperscript{19,20} and the Hamilton Rating Scale for Anxiety Psychiatric Anxiety factor score (HAM-A\textsubscript{9}). All clinical ratings were completed by an independent evaluator without knowledge of the treatment received.

A remission was defined as a final HRS-D\textsubscript{24} score of 8 or lower at both weeks 10 and 12. A response without remission was declared if there was a reduction of 50% or greater in the total HRS-D\textsubscript{24} score and there was a total score of 15 or lower at both weeks 10 and 12 but remission was not achieved. In addition, a single overall response/remission rate was calculated that combined those in the remission group with those who demonstrated response without remission. All other patients were considered nonresponders.

**ACUTE-PHASE OUTCOME**

A total of 454 patients were randomized either to CBASP monotherapy (n=228) or to nefazodone monotherapy (n=226). Of these, 173 in the CBASP group (75.9%) and 167 in the nefazodone group (73.9%) completed the 12-week acute-phase trial. Among completers, 33.3% (56/167) of those in the nefazodone group and 28.3% (49/173) of those in the CBASP group had response without remission. These response rates did not significantly differ from one another (\(\chi^2=1.08, P=.30\)). Remission rates for completers were 21.6% (36/167) for nefazodone and 23.7% (41/173) for CBASP; again, these remission rates were not significantly different (\(\chi^2=.22, P=.64\)).

Among the patients randomized at study baseline to either CBASP monotherapy or nefazodone monotherapy, 216 in the CBASP group and 220 in the nefazodone group constituted the intent-to-treat sample. For this sample, response and remission rates were determined based on the last available observation. The response rates without remission were 18.6% (41/220) in the nefazodone group and 14.4% (31/216) in the CBASP group. These response rates were not significantly different (\(\chi^2=1.45, P=.23\)). Remission rates were 29.1% (64/220) for nefazodone therapy and 33.3% (72/216) for CBASP; these remission rates were not significantly different (\(\chi^2=0.91, P=.34\)).

Altogether, 156 nonresponders randomized to nefazodone alone or CBASP alone completed the acute-phase trial (73 who started in the nefazodone group and 83 who started in the CBASP group). The 73 nonresponders in the nefazodone group received a mean final daily dosage of 491.1 mg/d (SD, 125.4 mg/d; range, 100-600 mg/d). Responders to nefazodone received a non-significantly higher final daily dosage (520.1 mg/d; \(F_{1,63}=2.73, P=.10\)). The 83 nonresponders in the CBASP group attended a total of 17.7 therapy sessions (SD, 1.9; range, 13-22). Responders to CBASP attended a slightly greater number of sessions than nonresponders (18.2; \(F_{1,171}=3.75, P=.054\)).

**SWITCH PROTOCOL**

There was no washout period for the switch (crossover) phase. Nonresponders to nefazodone simply stopped taking the medication and began CBASP treatment if they met the criteria to enter the crossover phase. Conversely, CBASP nonresponders stopped psychotherapy and began nefazodone treatment. All those who agreed to this crossover phase signed a new written informed consent. Visits, assessments, medication dosing, CBASP procedures, visit and session frequency, and outcome definitions during the new (crossover) treatment were identical to the methods used in the initial acute-phase trial.

**STATISTICAL ANALYSES**

The analyses performed included the analysis of baseline and demographic characteristics to assess comparability of the two crossover-phase treatment groups as well as comparisons of efficacy parameters and incidence of adverse events. Time to response and likelihood of response (\(\geq 50\%\) reduction in HRS-D\textsubscript{24} score) were tested with Kaplan-Meier survival analysis. The time to a reduction of 50% or greater in HRS-D\textsubscript{24} score was defined as the number of days from randomization to the crossover treatment until the first postrandomization observation of a decrease of 50% or greater in HRS-D\textsubscript{24} total score. If a decrease of 50% or greater was not observed, the time was right-censored using the visit date of the last usable postrandomization HRS-D\textsubscript{24} score from the entire 24-week period. Kaplan-Meier plots for the survival distribution for time to a reduction of 50% or greater in HRS-D\textsubscript{24} score were generated and comparisons were made using the log-rank test statistic (Figure 2).

To further explore response, we performed categorical analyses (eg, response and remission rates, attrition rates, and rates of adverse events) using the Fisher exact probability test, McNemar test (for within-subject comparisons), or Cochran-Mantel-Haenszel \(\chi^2\) test (stratified by study site) as appropriate. Changes in continuously distributed efficacy variables (HRS-D\textsubscript{24}, CGI-S, IDS-SR\textsubscript{10}, and HAM-A\textsubscript{9}) were analyzed using analysis of covariance at the endpoint visit with the crossover-phase baseline value as the covariate and fixed effects for treatment and site. These analyses were performed separately for the completer sample and the intent-to-treat sample. For the intent-to-treat sample, response status was determined based on the last available observation and the endpoint symptom severity used in the analyses on continuous variables. An exploratory analysis examined the correlation between the percentage change in HRS-D\textsubscript{24} score from entry to exit in the acute phase and the percentage change in HRS-D\textsubscript{24} score from entry to exit in the crossover phase (overall and by treatment group).

A piecewise mixed-effects random regression model was used to assess whether there were differences between nefazodone and CBASP in the rate (linear slope) of improvement in symptoms, with change in HRS-D\textsubscript{24} scores from baseline to week 4 as one variable and from week 4 to week 12 (or the last visit) as a second variable. The model included a random intercept and a random slope. We hypothesized that patients receiving nefazodone in the crossover phase (ie, patients who were switched from CBASP to nefazodone) would exhibit a more rapid rate of improvement in symptoms during the first 4 weeks than patients who were switched from nefazodone to CBASP, just as observed in the acute phase. This analysis examined the linear slopes between weeks 0 to 4 and weeks 4 to 12 in the crossover phase.

All statistical tests used 2-tailed probability values with unadjusted significance levels of \(P \leq .05\).

Of the 156 monotherapy nonresponders who completed the initial acute-phase trial, 140 (89.7%) consented to begin the alternate treatment. There were no significant differences in sociodemographic and clinical measures between those who agreed and those who declined to participate in the crossover trial. Twelve (16%) of the 73 patients initially treated with nefazodone declined the crossover treatment, while 4 (5%) of the 83 patients who initially received CBASP declined to proceed with crossover to nefazodone (\(\chi^2=5.7, P=.02\)).
A total of 61 patients were switched from nefazodone to CBASP, and 79 CBASP nonresponders were switched to nefazodone. With the exception of the percentage of patients with a lifetime history of anxiety disorders, baseline characteristics did not differ significantly between the two groups (Table 1). The mean dosage of nefazodone at the endpoint of the crossover phase was 419.0 mg/d (SD, 154.7 mg/d). The mean number of psychotherapy sessions attended during the crossover phase was 16.5 (SD, 4.4). Patients receiving nefazodone were scheduled to see a pharmacotherapist at each of 9 scheduled study visits during the crossover phase. The mean number of study visits attended during crossover for those in the nefazodone condition was 7.8 (SD, 1.8, n=61).

ATTRITION AND TOLERABILITY

During the crossover phase, 30 patients dropped out, 22 (28%) in the nefazodone group and 8 (13%) in the CBASP group ($\chi^2=4.61, P=.03$). This difference was probably caused by the fact that more patients receiving nefazodone dropped out because of adverse events (18% vs 3%; $\chi^2=6.79, P=.009$).

RESPONSE AND REMISSION

Response and remission rates are presented in Table 2 for both the intent-to-treat and completer samples. In the intent-to-treat sample, overall response rates were significantly higher for patients who crossed over to CBASP from nefazodone (57% [35/61]) than for patients who crossed over to nefazodone from CBASP (42% [33/79]; $\chi^2=5.03, P=.03$). There was no significant difference in rates of remission or response without remission between the two groups. In the completer sample, there were no significant between-group differences in the rates of response without remission, remission, or overall response.

Table 3 presents the observed values for HRS-D24, CGI-S, IDS-SR30, and HAM-APA at the baseline of the crossover phase and at the endpoint. The change from baseline to endpoint and the adjusted means of the change in each measure are also presented. The results of the analysis of covariance for all 4 parameters indicated that patients in both groups improved over time. In the intent-to-treat sample, the group switched from nefazodone to CBASP had a significantly greater improvement in HRS-D24 and HAM-APA scores than the group switched from CBASP to nefazodone. However, there were no significant differences in outcome on these 4 measures when completers were compared.

A piecewise random regression analysis comparing the rates of symptomatic improvement (linear slope) based on the HRS-D24 score (Figure 3) revealed no significant difference between the two groups during the first 4 weeks of the crossover phase ($F_{1,138}=0.16, P=.69$). However, a significantly greater rate of symptomatic improvement was evident for weeks 4 to 12 among the patients who were switched from nefazodone to CBASP ($F_{1,138}=10.38, P=.002$).

Results of this controlled, rater-blinded switch study indicate that a switch strategy for nonresponders provides...
substantial benefit for chronically depressed patients. Treatment with nefazodone following nonresponse to CBASP and treatment with CBASP following nonresponse to nefazodone were equally effective for patients who completed 12 weeks of treatment, with a response rate of approximately 50%. As in the initial trial, CBASP was associated with significantly less attrition due to adverse events than nefazodone, which is in keeping with the fact that patients were not blind to their treatment and the fact that psychotherapy has few adverse events.

Table 1. Demographic and Clinical Characteristics of the Crossover Phase Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 140)</th>
<th>Nefazodone → CBASP (n = 61)</th>
<th>CBASP → Nefazodone (n = 79)</th>
<th>Statistics*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, No. (%)</td>
<td>92 (65.7)</td>
<td>44 (72)</td>
<td>48 (61)</td>
<td>$\chi^2 = 2.70, P = .10$</td>
</tr>
<tr>
<td>Age, y†</td>
<td>43.1 ± 11</td>
<td>42.3 ± 12.0</td>
<td>43.7 ± 10.4</td>
<td>$F_{1,127} = 0.56, P = .46$</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>126 (90.0)</td>
<td>55 (90)</td>
<td>71 (90)</td>
<td>$\chi^2 = 0.03, P = .87$</td>
</tr>
<tr>
<td>Marital status, No. (%)‡</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2 = 2.12, P = .55$</td>
</tr>
<tr>
<td>Currently married or cohabiting</td>
<td>63 (45.0)</td>
<td>29 (48)</td>
<td>34 (43)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>40 (28.6)</td>
<td>14 (23)</td>
<td>26 (33)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>3 (2.1)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>34 (24.3)</td>
<td>16 (26)</td>
<td>18 (23)</td>
<td></td>
</tr>
<tr>
<td>Employment status, No. (%)‡</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2 = 2.15, P = .71$</td>
</tr>
<tr>
<td>Work for pay</td>
<td>96 (68.6)</td>
<td>42 (69)</td>
<td>54 (68)</td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>17 (12.1)</td>
<td>8 (13)</td>
<td>9 (11)</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>4 (2.9)</td>
<td>3 (5)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>4 (2.9)</td>
<td>1 (2)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>18 (12.9)</td>
<td>6 (10)</td>
<td>12 (15)</td>
<td></td>
</tr>
<tr>
<td>Data missing</td>
<td>1 (0.7)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Depression diagnosis, No. (%)‡</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2 = 2.19, P = .34$</td>
</tr>
<tr>
<td>Chronic major depression</td>
<td>56 (40.0)</td>
<td>27 (44)</td>
<td>29 (37)</td>
<td></td>
</tr>
<tr>
<td>Double depression</td>
<td>53 (37.9)</td>
<td>24 (39)</td>
<td>29 (37)</td>
<td></td>
</tr>
<tr>
<td>Recurrent depression, incomplete interepisode recovery</td>
<td>31 (22.1)</td>
<td>10 (16)</td>
<td>21 (27)</td>
<td></td>
</tr>
<tr>
<td>Age at onset of initial episode of MDD, y†</td>
<td>26.4 ± 12.4</td>
<td>25.7 ± 12.0</td>
<td>26.9 ± 12.8</td>
<td>$F_{1,114} = 2.32, P = .13$</td>
</tr>
<tr>
<td>Duration of current MDD, y†</td>
<td>8.0 ± 9.28</td>
<td>7.5 ± 9.1</td>
<td>8.3 ± 9.45</td>
<td></td>
</tr>
<tr>
<td>Age at onset of dysthymia, y†</td>
<td>21.6 ± 14.87</td>
<td>20.8 ± 13.1</td>
<td>22.3 ± 16.4</td>
<td></td>
</tr>
<tr>
<td>Duration of current dysthymia, y†</td>
<td>20.2 ± 15.59</td>
<td>20.6 ± 16.26</td>
<td>19.8 ± 15.3</td>
<td></td>
</tr>
<tr>
<td>History of alcohol abuse/dependence, No. (%)</td>
<td>43 (30.7)</td>
<td>17 (28)</td>
<td>27 (34)</td>
<td></td>
</tr>
<tr>
<td>Lifetime comorbid anxiety disorder, No. (%)</td>
<td>41 (29.3)</td>
<td>24 (39)</td>
<td>17 (22)</td>
<td></td>
</tr>
<tr>
<td>Previous treatment with psychotherapy, No. (%)</td>
<td>94 (67.1)</td>
<td>40 (66)</td>
<td>54 (68)</td>
<td></td>
</tr>
<tr>
<td>Previous treatment with antidepressant, No. (%)</td>
<td>95 (67.9)</td>
<td>41 (67)</td>
<td>54 (68)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CBASP, cognitive behavioral analysis system of psychotherapy; MDD, major depressive disorder.

*For categorical variables, the $\chi^2$ values were determined using the Cochran-Mantel-Haenszel test stratified by site. Analysis of variance $F$-test values were determined for continuous variables.

†Values are mean ± SD.

‡Percentages may not add to 100% because of rounding.

Table 2. Response* and Remission† Rates at the End of the Crossover Phase

<table>
<thead>
<tr>
<th>No. (%)‡</th>
<th>Nefazodone → CBASP</th>
<th>CBASP → Nefazodone†</th>
<th>$\chi^2$§</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completers (n = 110)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>53</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response without remission</td>
<td>21 (40)</td>
<td>14 (25)</td>
<td>2.73</td>
<td>.10</td>
</tr>
<tr>
<td>Remission</td>
<td>13 (25)</td>
<td>16 (28)</td>
<td>0.01</td>
<td>.92</td>
</tr>
<tr>
<td>Overall response/ remission</td>
<td>34 (64)</td>
<td>30 (53)</td>
<td>2.86</td>
<td>.09</td>
</tr>
</tbody>
</table>

| Intent-to-Treat Sample (n = 140) |
| No. of subjects | 61 | 79 | | |
| Response without remission | 13 (21) | 12 (15) | 0.95 | .33 |
| Remission | 22 (36) | 21 (27) | 2.63 | .11 |
| Overall response/ remission | 35 (55) | 33 (42) | 5.03 | .03 |

Abbreviations: CBASP, cognitive behavioral analysis system of psychotherapy; HRS-D24, 24-item Hamilton Rating Scale for Depression.

*Response was defined as a reduction of 50% or greater in the HRS-D24 score and a total score of 15 or lower.
†Remission was defined as a final HRS-D24 score of 8 or lower.
‡Percentages may not add to overall values because of rounding.
§The $\chi^2$ values were determined using the Cochran-Mantel-Haenszel test; df = 1 for all $\chi^2$ values.
The finding of differential attrition was unexpected. Although there was a significant difference in the overall response rate between the two crossover groups in the intent-to-treat sample (57% response for those who crossed over to CBASP vs 42% for those who crossed over to nefazodone), this was likely due to the higher overall attrition rate among those receiving nefazodone than among those receiving CBASP. Slower titration of nefazodone might have resulted in a lower number of patients dropping out of the crossover trial because of adverse events, potentially increasing the response and remission rates.

The finding of differential attrition was unexpected. In the acute-phase trial, although the reasons for premature termination were different in the CBASP and nefazodone groups, overall dropout rates were almost identical. Specifically, greater attrition due to adverse events in the nefazodone group was essentially matched by attrition due to dissatisfaction with treatment in the CBASP group. Across the sequential trials, attrition was comparable in the nefazodone groups whether it was the first or second treatment received, whereas a significantly smaller proportion of patients dropped out while receiving CBASP when it was the second treatment in the sequence. It appears that the experience of an unsuccessful initial trial of pharmacotherapy may have strengthened the motivation of patients to participate in an adequate trial of psychotherapy, whereas nonresponse to CBASP did not improve patients’ ability to tolerate unpleasant adverse effects of medication.

Interestingly, the overall response and remission rates observed in the intent-to-treat crossover sample were similar to those observed in the acute phase of this study¹⁰ as well as to those observed by our collaborative research group⁹ in another sample of chronically depressed patients who were crossed over to sertraline or imipramine following nonresponse to one of these two antidepressant medications. These results underscore how important it is that clinicians not be discouraged—though their chronically depressed patients may be—by initial treatment resistance.

Few data are available to guide the clinician about the best way to treat depressed patients who have not responded to an initial adequate course of treatment. The present study provides support for a switch from medication to psychotherapy and vice versa. Other strategies include switching within treatment (eg, switch to another antidepressant medication) or augmentation either with another treatment of the same modality or with a treatment of a different modality (ie, combined treatments). Compared with medication augmentation strategies for nonresponders to an antidepressant medication, switching antidepressant classes has the advantages of simplicity and parsimony (eg, lower cost and lower risk of drug-drug interactions). However, further studies are required to test the relative short- and long-term effectiveness of the different strategies as well as their relative acceptability. In the present study, a larger propor-

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### Table 3. Mean Scores for Continuous Efficacy Outcomes During the Crossover Phase

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Nefazodone → CBASP</th>
<th>CBASP → Nefazodone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td><strong>Endpoint</strong></td>
<td><strong>Change</strong>†</td>
</tr>
<tr>
<td>HRS-D₂₄</td>
<td>24.1 (6.5)</td>
<td>13.4 (8.4)</td>
</tr>
<tr>
<td>CGI-S</td>
<td>4.2 (0.8)</td>
<td>3.1 (1.1)</td>
</tr>
<tr>
<td>IDS-SR₃₀</td>
<td>33.9 (10.2)</td>
<td>20.4 (12.3)</td>
</tr>
<tr>
<td>HAM-A₉₀</td>
<td>1.5 (0.6)</td>
<td>0.8 (0.6)</td>
</tr>
</tbody>
</table>

**Intention-to-Treat Sample**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Statistics‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRS-D₂₄</td>
<td>F₁,₉₆ = 2.26, P = .14</td>
</tr>
<tr>
<td>CGI-S</td>
<td>F₁,₇₀ = 1.25, P = .27</td>
</tr>
<tr>
<td>IDS-SR₃₀</td>
<td>F₁,₁₂₅ = 4.21, P = .04</td>
</tr>
<tr>
<td>HAM-A₉₀</td>
<td>F₁,₉₆ = 2.26, P = .14</td>
</tr>
</tbody>
</table>

**Completers**

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Statistics‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRS-D₂₄</td>
<td>F₁,₉₆ = 2.26, P = .14</td>
</tr>
<tr>
<td>CGI-S</td>
<td>F₁,₇₀ = 1.25, P = .27</td>
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</tr>
<tr>
<td>HAM-A₉₀</td>
<td>F₁,₉₆ = 2.26, P = .14</td>
</tr>
</tbody>
</table>

Abbreviations: CBASP, cognitive behavioral analysis system of psychotherapy; CGI-S, Clinical Global Impressions–Severity scale; HAM-A₉₀, Hamilton Rating Scale for Anxiety Psychic Anxiety factor subscale; HRS-D₂₄, 24-item Hamilton Rating Scale for Depression; IDS-SR₃₀, 30-item Inventory for Depressive Symptomatology–Self-Report. *Values are mean (SD). †Least squares adjusted means. ‡P values are comparing adjusted mean change from baseline to end point.

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Figure 3. Mean HRS-D₂₄ (24-item Hamilton Rating Scale for Depression) scores in the crossover phase. CBASP indicates cognitive behavioral analysis system of psychotherapy.

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tion of participants were willing to cross over to medication after nonresponse to psychotherapy than the reverse.

Although significant improvement was observed in approximately 50% of patients who completed the crossover treatment, only about 1 in 4 patients (28% [16/57] for nefazodone and 25% [13/53] for CBASP) achieved full remission; that is, about half of the responders still had significant residual symptoms at the end of the crossover phase. Responders without remission have less robust social recoveries than those who achieve full remission21,22 and are at higher risk for subsequent relapse.23 Chronically depressed patients might benefit from the combination of both CBASP and nefazodone or from longer courses of treatment. Consistent with this, roughly 40% of chronically depressed patients who had a response but not a remission after 12 weeks of acute-phase treatment with either imipramine or sertraline converted to full remission during continuation therapy with the same agent.24

Several methodological limitations affect interpretation of these results. First, in the absence of a placebo condition, it is difficult to determine whether the effects that are observed are due to treatment. We did not use a placebo-controlled design in the crossover phase because of concerns about withholding active treatment from chronically depressed patients who had already not responded to initial treatment with nefazodone or CBASP. Absence of a placebo control group is less critical in the study of populations in which low placebo response rates have been documented. Such populations include those with treatment-resistant depression (placebo response rates of 10%-20%)25-27 and those with a chronic depressive illness (double depression; placebo response rate, 13%).28

Second, switching treatments only for nonresponders who were able to complete the acute trial limits the generalizability of findings to such acute study completers. If we had switched treatments at the point where nonresponse was evident rather than at a specific predetermined time point, we might have observed higher (or lower) response or remission rates during the crossover trial. Similarly, we cannot determine how well the switch strategy would have worked for those who decided to drop out prior to completing the acute phase of treatment. Third, although patients with a number of comorbid conditions were allowed to participate in this study, the exclusion of patients with greater levels of comorbidity further limits generalizability of our findings. We do not know whether such excluded patients would have responded preferentially to one or the other crossover treatment.

Fourth, nonresponders in the two groups who entered the crossover phase may not have been comparable since they were not rerandomized at initiation of the switch. However, our confidence in the validity of comparing these groups is strengthened by the absence of significant differences in sociodemographic and clinical characteristics in the main trial10 and in the crossover trial. In fact, minimal improvement during the initial treatment trial was predictive of success (albeit weakly) with both crossover strategies. Nevertheless, without randomization of nonresponders to alternate treatments, interpretation of these comparative results remains tentative. On the other hand, these results have high applicability to routine practice, where treatment would never be chosen by randomization.

This is the first prospective, comparative randomized study of switching depressed outpatients from medication to psychotherapy and vice versa in the context of nonresponse to but completion of the first treatment. Given the magnitude of the problem of nonresponse to antidepressant medication, randomized controlled studies of switch strategies as well as augmentation strategies are desperately needed. The only other large controlled crossover trial found that roughly 50% of imipramine nonresponders responded to sertraline and vice versa; this study was conducted among chronically depressed outpatients who completed 12 weeks of acute treatment with either of these two medications.9

It is essential to know more about the range of efficacy of other second-step treatments. For example, we do not know whether nonresponders to either nefazodone or CBASP, given a different medication as a switch strategy, would have achieved equivalent or even greater success. The recently initiated Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (www.star-d.org) randomized controlled trial is comparing 4 different switch treatments (sustained-release bupropion, cognitive therapy, sertraline, or extended-release venlafaxine) in outpatients who do not respond to a selective serotonin reuptake inhibitor (citalopram) as the first treatment. The STAR*D trial will determine whether a switch within the class of selective serotonin reuptake inhibitors, an out-of-class switch, a switch to a dual-action agent, or a switch to cognitive therapy is most effective.

The findings of the present study provide the first evidence from a controlled trial of the value of switching to an antidepressant medication or to psychotherapy after the failure of the alternative treatment in an initial trial. The evidence specifically pertains to nefazodone and CBASP. The general principle may hold for other antidepressant medications, as suggested by the findings of Thase et al8 with imipramine and sertraline. It remains to be determined whether other forms of depressed-focused psychotherapies would yield similar benefits to CBASP. It would be of interest, for example, to determine whether therapies with a more interpersonal or psychodynamic focus are useful when a cognitive behavioral strategy is not.

For patients with chronic depression, the present results provide a strong basis for switching to CBASP after a medication does not produce a response and, conversely, for switching to medication after patients do not respond to an adequate trial of psychotherapy.

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REFERENCES


