Treatment of Atypical Depression With Cognitive Therapy or Phenelzine

A Double-blind, Placebo-Controlled Trial

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Background: Patients with atypical depression are more likely to respond to monoamine oxidase inhibitors than to tricyclic antidepressants. They are frequently offered psychotherapy in the absence of controlled tests. There are no prospective, randomized, controlled trials, to our knowledge, of psychotherapy for atypical depression or of cognitive therapy compared with a monoamine oxidase inhibitor. Since there is only 1 placebo-controlled trial of cognitive therapy, this trial fills a gap in the literature on psychotherapy for depression.

Methods: Outpatients with DSM-III-R major depressive disorder and atypical features (N = 108) were treated in a 10-week, double-blind, randomized, controlled trial comparing acute-phase cognitive therapy or clinical management plus either phenelzine sulfate or placebo. Atypical features were defined as reactive mood plus at least 2 additional symptoms: hypersomnia, hyperphagia, leaden paralysis, or lifetime sensitivity to rejection.

Results: With the use of an intention-to-treat strategy, the response rates (21-item Hamilton Rating Scale for Depression score, ≤9) were significantly greater after cognitive therapy (58%) and phenelzine (58%) than after pill placebo (28%). Phenelzine and cognitive therapy also reduced symptoms significantly more than placebo according to contrasts after a repeated-measures analysis of covariance and random regression with the use of the blind evaluator’s final Hamilton Rating Scale for Depression score. The scores between cognitive therapy and phenelzine did not differ significantly. Supplemental analyses of other symptom severity measures confirm the finding.

Conclusions: Cognitive therapy may offer an effective alternative to standard acute-phase treatment with a monoamine oxidase inhibitor for outpatients with major depressive disorder and atypical features.

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PATIENTS AND METHODS

PATIENTS

The protocol was approved by the institutional review board. Subjects (recruited through media, printed announcements, and self or practitioner referrals) underwent triage by telephone. Outpatients (N = 366) with the complaint of depression participated in the Structured Clinical Interview for DSM-III-R (Outpatient Version),2,14 which uses the DSM-III-R23 criteria for MDD and other disorders. To assess MDD with atypical features, the Atypical Depression Diagnostic Scale (Jonathan W. Stewart, MD, written communication, October 20, 1988, and March 20, 1990) was administered for the initial episode. If the diagnosis was absent at the nadir, symptoms were reassessed at “any other time during the episode.” Criteria (according to the Atypical Depression Diagnostic Scale) for depression with atypical features included (1) maintains reactive mood and (2) shows 2 or more of the following: (a) increased appetite or weight gain; (b) oversleeping; (c) sensation of leaden paralysis or extreme heaviness of arms or legs, while depressed; and (d) lifetime sensitivity to interpersonal rejection.1,2

Diagnoses were confirmed by a faculty-level diagnostician at a follow-up interview. Entry criteria were (1) DSM-III-R MDD, (2) definite atypical depression, and (3) score of 14 or more on the 21-item Hamilton Rating Scale for Depression (HRSD-21)24 at the initial or follow-up interview. All patients provided a medical history and a physician reviewed laboratory screening. Patients were excluded if they (1) had a concurrent medical disorder or treatment that might cause depressive symptoms or required medication incompatible with MAOIs; (2) refused to be randomized or to maintain a tyramine-free diet; (3) had other current primary comorbid psychiatric disorders (eg, organic mental disorders, psychotic disorders, schizophrenia, schizoaffective disorders, alcoholism, or drug abuse or dependency in the last 6 months); (4) scored less than 14 on the HRSD-21 at diagnostic evaluation and follow-up, or before randomization (see description of nonspecific treatment below); (5) could not complete questionnaires; (6) represented an imminent suicide risk; or (7) had previously had an adequate trial of MAOIs or cognitive therapy that failed.

RESULTS

SAMPLE DESCRIPTION

One hundred forty-two outpatients with MDD and atypical features consented to participate in the trial. The subjects who were eligible and ineligible for randomization did not differ significantly on the variables in Table 1.

Attrition

Thirty-six patients were randomized to each cell. Attrition differed significantly among the treatment cells ($\chi^2 = 22.04; P = .001$). Five patients (14%) dropped out of cognitive therapy, 9 (25%) from phenelzine, and 23 (64%) from placebo. Attrition in the placebo group was significantly greater than in cognitive therapy ($\chi^2 = 18.94; P = .001$) and phenelzine ($\chi^2 = 11.03; P = .001$). The attrition between active treatments did not differ significantly ($\chi^2 = 1.42; P = .23$). Of patients in cognitive therapy, 1 dropped out before the first session, 2 moved, and 2 found the study procedures unacceptable.

Nine patients randomized to phenelzine did not complete the trial. Of these, the psychiatrist withdrew 3 whose depressive symptoms required alternative treatment. Six dropped out. One dropped out after the first session, 3 found the treatment unacceptable, and 2 found the study unacceptable.
Twenty-three patients randomized to placebo did not complete the trial. The psychiatrist withdrew 4 because their symptoms necessitated alternative treatment and 2 because they were noncompliant with study procedures. Of the 17 patients who withdrew their consent, 2 dropped out before the first session, 14 found the treatment unacceptable. Of the 17 patients who withdrew their consent, 2 dropped out before the first session, 14 found the treatment unacceptable. Of the 17 patients who withdrew their consent, 2 dropped out before the first session, 14 found the treatment unacceptable.

**Outcome Measures**

The 5 domains assessed were psychiatric diagnoses and symptom severity (reported herein), and cognitive, interpersonal, and personality functioning (to be reported separately). The blind evaluators collected the following symptom severity measures and scored DSM-III-R criteria for MDD at treatment weeks 4, 7, and 10 or at patient exit.

**Treatment Exposure**

Patients treated with cognitive therapy completed an average of 17.4 ± 0.9 sessions (range, 0-20) during an average of 8.8 ± 0.5 weeks (range, 0-11.1). Patients treated with phenelzine completed an average of 9.8 ± 0.4 sessions (range, 1-11) during an average of 8.8 ± 0.5 weeks (range, 0-10.6). Patients treated with placebo completed an average of 6.9 ± 0.6 sessions (range, 0-11) during an average of 5.9 ± 0.6 weeks (range, 0-10.3).

**Primary Outcome Measures and Analyses**

The raw data collected for each group at baseline and at blind evaluations (weeks 4, 7, and 10) were reduced to unadjusted means and SEs for the HRSD-21, Clinical Global Impression Scale, and Beck Depression Inventory (Table 2).

**Covariate Selection**

Randomization did not achieve complete pretreatment equivalence among cells. Length of illness, Research Diagnostic Criteria primary depression, age at onset, and...
Table 1. Demographic and Severity Characteristics of Randomized Depressed Outpatients With Atypical Features

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cognitive Therapy (n = 36)</th>
<th>Phenelzine Sulfate (n = 36)</th>
<th>Placebo Pill (n = 36)</th>
<th>Test Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%): F</td>
<td>26 (72)</td>
<td>25 (69)</td>
<td>22 (61)</td>
<td>FET</td>
<td>.66</td>
</tr>
<tr>
<td>Race, No. (%): W</td>
<td>32 (89)</td>
<td>34 (94)</td>
<td>34 (94)</td>
<td></td>
<td>.73</td>
</tr>
<tr>
<td>Age, mean ± SE, y</td>
<td>39.8 ± 1.48</td>
<td>38.7 ± 1.63</td>
<td>40.3 ± 1.68</td>
<td>F = 2.54†</td>
<td>.08</td>
</tr>
<tr>
<td>Marital status, No. (%)</td>
<td>Single</td>
<td>9 (25)</td>
<td>6 (17)</td>
<td>7 (19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Married or living together</td>
<td>19 (53)</td>
<td>21 (58)</td>
<td>19 (53)</td>
<td>FET</td>
</tr>
<tr>
<td></td>
<td>Widowed</td>
<td>8 (22)</td>
<td>9 (25)</td>
<td>10 (28)</td>
<td></td>
</tr>
<tr>
<td>Education, mean ± SE, y</td>
<td>14.1 ± 0.40</td>
<td>14.3 ± 0.28</td>
<td>14.4 ± 0.37</td>
<td>FET</td>
<td>.80</td>
</tr>
<tr>
<td>Employment, No. (%):</td>
<td>Employed at least part-time</td>
<td>23 (64)</td>
<td>26 (72)</td>
<td>23 (64)</td>
<td>FET</td>
</tr>
<tr>
<td></td>
<td>Homemaker</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unemployed</td>
<td>12 (33)</td>
<td>8 (22)</td>
<td>13 (36)</td>
<td></td>
</tr>
<tr>
<td>HRSD-21 at randomization, mean ± SE‡</td>
<td>18.4 ± 0.60</td>
<td>16.8 ± 0.48</td>
<td>17.4 ± 0.50</td>
<td>F = 2.34†</td>
<td>.10</td>
</tr>
<tr>
<td>Length of current episode, mean ± SE, mo</td>
<td>72.7 ± 17.97</td>
<td>49.6 ± 9.02</td>
<td>52.7 ± 13.40</td>
<td>F = 0.81†</td>
<td>.45</td>
</tr>
<tr>
<td>Age at onset, mean ± SE, y</td>
<td>22.9 ± 1.87</td>
<td>28.9 ± 1.98</td>
<td>26.8 ± 1.93</td>
<td>F = 2.54†</td>
<td>.08</td>
</tr>
<tr>
<td>Length of illness, mean ± SE, y‡</td>
<td>17.0 ± 1.97</td>
<td>9.9 ± 1.52</td>
<td>13.4 ± 2.18</td>
<td>F = 3.45†</td>
<td>.04</td>
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<tr>
<td>No. of episodes, mean ± SE§</td>
<td>2.2 ± 0.20</td>
<td>1.9 ± 0.25</td>
<td>2.1 ± 0.20</td>
<td>F = 1.05</td>
<td>.65</td>
</tr>
<tr>
<td>Depressive subtype, No. (%)</td>
<td>Recurrent depression</td>
<td>25 (69)</td>
<td>17 (47)</td>
<td>24 (67)</td>
<td>FET</td>
</tr>
<tr>
<td></td>
<td>RDC primary depression‡</td>
<td>27 (75)</td>
<td>17 (47)</td>
<td>18 (50)</td>
<td>FET</td>
</tr>
<tr>
<td></td>
<td>RDC definite endogenous</td>
<td>4 (11)</td>
<td>0 (0)</td>
<td>4 (11)</td>
<td>FET</td>
</tr>
<tr>
<td></td>
<td>DSM-III melancholia26</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>FET</td>
</tr>
<tr>
<td>Family history, No. (%):</td>
<td>Familial depressive disease</td>
<td>5 (14)</td>
<td>2 (6)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Depressive spectrum disease</td>
<td>22 (61)</td>
<td>16 (44)</td>
<td>17 (47)</td>
<td>FET</td>
</tr>
<tr>
<td></td>
<td>Sporadic depressive disease</td>
<td>3 (8)</td>
<td>8 (22)</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>6 (17)</td>
<td>10 (28)</td>
<td>12 (33)</td>
<td></td>
</tr>
<tr>
<td>Lifetime comorbid DSM-III-R diagnoses, No. (%)§</td>
<td>27 (75)</td>
<td>28 (78)</td>
<td>31 (86)</td>
<td>FET</td>
<td>.57</td>
</tr>
<tr>
<td>Current double depression, No. (%)**</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>FET</td>
<td>.70</td>
</tr>
</tbody>
</table>

*FET indicates Fisher exact test; HRSD-21, 21-item Hamilton Rating Scale for Depression; and RDC, Research Diagnostic Criteria.25
†Analysis of variance with df = 2,105.
‡Tested as a covariate for analysis of covariance, and P = .10.
§Five subjects are omitted from the mean because they had too many depressive episodes to count or the number was indistinguishable. These subjects are included in percentages.
¶See Winokur and colleagues27 and Winokur.28
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HRSD-21 score at randomization were identified as possible covariates.

The mean duration of illness (years) for the cognitive therapy cell was significantly greater than for phenelzine, but did not differ from that of the placebo cell. The mean duration of illness for the placebo cell did not differ from that of the phenelzine cell. A rate of Research Diagnostic Criteria primary depression of 75% in the cognitive therapy cell was significantly greater than that in the phenelzine cell, but not greater than that in the placebo cell. There was no difference in primary depression between the phenelzine and placebo cells. The phenelzine cell had the greatest age at onset, while the cognitive therapy cell had the lowest age at onset, and the placebo cell fell in the middle. These cells did not differ significantly. Finally, post hoc comparisons on the HRSD-21 at randomization disclosed no significant differences. All other comparisons among treatments on the variables in Table 1 did not differ significantly.

Because of intercorrelations among the 4 potential covariates, backward elimination was used to select statistically important covariates. Variables that remained significant (P<.10) were age at onset and HRSD-21 score, which were included as covariates in tests of the primary hypothesis.

Revised-Measures ANCOVA of HRSD-21

With ANCOVA, the main effects for time and treatment were significant (F2,103 = 27.5; P<.001 and F2,103 = 6.83; P<.01, respectively). The interaction between treatment and time was not significant (F2,103 = 1.12; P=.35). The contrasts for the main effects indicate significant differences when comparing phenelzine with placebo (F1,103 = 11.90; P<.001) and cognitive therapy with placebo (F1,103 = 7.73; P<.01). There was no significant difference between phenelzine and cognitive therapy (F1,103 = 0.37; P = .54). Post hoc pairwise contrasts of the treatment cells showed that at week 4, phenelzine reduced the adjusted mean HRSD-21 scores (13.36 ± 1.06) more than placebo (17.20 ± 1.05) (F1,103 = 6.66; P = .01). At weeks 7 and 10, both cognitive therapy and phenelzine reduced the adjusted mean HRSD-21 score over that of placebo (week 7: F1,103 = 7.29; P<.01 [cognitive therapy vs placebo]; F1,103 = 12.60; P<.001 [phenelzine vs placebo]; week 10: F1,103 = 8.94; P<.01 [cognitive therapy vs placebo]).
SECONDARY OUTCOME MEASURES AND ANALYSES

Response Rates

Most definitions of positive response rates for the active treatments (which used end points from each measure and were unadjusted for the influence of the covariates) were greater than 50% (Table 3). Analyses by χ² showed significant differences in response rates when positive response was defined at blind evaluation as follows: HRSD-21 score of 9 or less (χ² = 8.98; P = .01), Clinical Global Impression Scale score of 2 or less (χ² = 10.67; P < .01), and no MDD with an HRSD-21 score of 9 or less (χ² = 7.45; P = .02). Post hoc comparisons on these definitions of response showed that cognitive therapy and phenelzine produced higher response rates than placebo, and that cognitive therapy and phenelzine did not differ. With the use of traditional α levels, response rates did not differ between the 3 groups when a positive response was defined at blind evaluation as follows:

**Random Regression Modeling**

In the RCR analysis, only the HRSD-21 score at randomization was retained through the backward elimination steps. To linearize change in HRSD-21 scores over the 10 weeks, the time scale was transformed by using the natural logarithm of day of randomization +1; thus, slope estimates approximate change in HRSD-21 score per unit change in the log of day after baseline. Significantly different slopes over...
time were found among the 3 treatments (treatment × time interaction, $F_{2,161} = 4.25$; $P < .02$). There is a significantly larger negative slope for the phenelzine cell ($F_{1,161} = 7.56$; $P < .01$) compared with placebo, and for the larger cognitive therapy slope compared with placebo ($F_{1,161} = 5.29$; $P < .03$). The slopes for the 2 active treatments did not differ significantly ($F_{1,161} = 0.23$; $P = .63$). Slopes estimates (per natural logarithm of day in treatment) for the 3 treatments (with SEs) are $-0.78 \pm 0.33$ for placebo, $-1.83 \pm 0.31$ for cognitive therapy, and $-2.03 \pm 0.31$ for phenelzine. The estimated time course of HRSD-21 scores for each of the 3 cells across the 10 weeks of acute-phase treatment was based on a subject with an average baseline HRSD-21 score of 17.5 (Figure 2).

Adverse Effects

There were no serious or persistent adverse events. From 38 potential side effects, 23 symptoms were reported by 3 or more patients and rated by the psychiatrist as “due to the study” and “moderate.” Incidence density ratios (ie, [frequency of symptoms with phenelzine/treatment weeks]/[frequency of symptoms with placebo/ treatment weeks]) were computed. Weakness or fatigue, drowsiness or sedation, insomnia, dry mouth, dizziness, and increased appetite were significantly more likely to be reported by patients treated with phenelzine than those treated with placebo ($\chi^2$ test; $P < .01$, Bonferroni correction). More patients treated with phenelzine reported marked side effects (33/36 [92%]) than did patients treated with placebo (19/36 [53%]).

The results of this placebo-controlled, randomized trial indicate that both cognitive therapy and phenelzine are effective treatments for patients with MDD and atypical features. Effects of cognitive therapy and phenelzine were comparable on all outcome measures.

The implication is that cognitive therapy is an effective acute-phase alternative to MAOIs for patients with MDD and atypical depression. This trial has design features relevant to evaluating the efficacy of cognitive therapy and phenelzine for depression. It is only the second randomized trial of cognitive therapy, to our knowledge, to include a pill placebo plus clinical management. The first was the National Institute of Mental Health Treatment of Depression Collaborative Research Program. Both studies used an evaluator blind to treatment assignment to assess efficacy, which is infrequent in studies of cognitive therapy.

In conclusion, the results of this randomized controlled clinical trial suggest that cognitive therapy, when
provided twice weekly by experienced and competent therapists, reduces symptoms more than placebo and as much as phenelzine in outpatients diagnosed as having MDD and atypical features. Acute-phase cognitive therapy appears to be a safe and effective alternative to standard acute-phase treatment with MAOIs for outpatients with atypical depression.

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