Efficacy and Tolerability of Tranylcypromine Versus Phenelzine: A Double-Blind Study in Antidepressant-Refractory Depressed Inpatients

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Background: The aim of this study was to examine whether phenelzine is a suitable alternative to tranylcypromine in antidepressant-resistant depression.

Method: A total of 77 severely depressed inpatients, meeting the DSM-IV criteria for major depressive disorder, who failed to respond to fixed plasma level treatment with either tricyclic antidepressants or fluvoxamine were withdrawn from psychotropic medication and included in a double-blind flexible-dose 5-week comparison of tranylcypromine and phenelzine.

Results: Of the 77 patients, 67 (87%) completed the trial, of whom 35 (52%) responded. No significant differences in response between both drugs were observed. Seventeen (44%) of 39 patients responded to tranylcypromine and 18 (47%) of 38 to phenelzine (≥ 50% reduction in Hamilton Rating Scale for Depression [HAM-D] score). The mean reduction in HAM-D score was 10.4 ± 8.3 for the tranylcypromine sample versus 8.3 ± 8.4 for the phenelzine-treated patients. Only a few patients (10%) used concomitant psychotropic medication. A substantial number of patients experienced severe side effects, mainly dizziness, agitation, and insomnia; the incidence was the same in both samples (21%).

Conclusion: No difference in efficacy was observed between both monoamine oxidase inhibitors in a sample of patients with severe antidepressant-refractory depression. Phenelzine appears to be a suitable alternative to tranylcypromine.

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The use of nonselective monoamine oxidase inhibitors (MAOIs) is limited by several factors, particularly dietary restrictions, reports of toxic interactions, and their supposed inferior efficacy in patients with melancholic depression in comparison with tricyclic antidepressants (TCAs).[1] MAOIs are used frequently in the treatment of depressed patients that have not responded to TCAs. Several uncontrolled open studies[2–4] have supported the efficacy of tranylcypromine in TCA-refractory depression.

Nolen et al.[5,6] found tranylcypromine to be superior to both L-5-hydroxytryptophan (L-5-HTP) in an open randomized study[5] and nomifensine in a double-blind study.[6] In both studies, 50% of the highly refractory patients responded to tranylcypromine. Similar efficacy was reported after a double-blind comparative study with the reversible inhibitor of MAO-A (RIMA) brofaromine.[7] Two other double-blind studies[8,9] found an even higher efficacy (about 75%) for tranylcypromine in refractory depression. However, a considerable proportion of patients taking tranylcypromine experience serious adverse effects, such as orthostatic hypotension, agitation, and insomnia. There clearly is a need for an effective MAOI that is better tolerated than tranylcypromine. The RIMA brofaromine may have been a promising alternative to tranylcypromine[7,9] but has been withdrawn from further development. Another RIMA, moclobemide, has not been well studied in refractory depression; according to the clinical impression of some investigators,[10,11] it probably is not an effective alternative to tranylcypromine.

Both tranylcypromine and phenelzine are irreversible inhibitors of both the A and B form of the MAO enzyme. Phenelzine has been studied most extensively in so-called atypical depression. This type of depression requires preserved reactivity of mood and at least 2 additional atypical symptoms. A series of studies carried out by Columbia University in New York (for review, see Quitkin et al.[12]) showed phenelzine to be superior to both placebo and imipramine in outpatients with atypical depression. Phenelzine has been studied in outpatients with atypical depression that had not responded to a TCA,[13] but studies of inpatients with TCA-refractory melancholic depression are lacking.

Phenelzine and tranylcypromine show differences in both chemical structure and pharmacologic characteristics. In contrast with phenelzine, tranylcypromine is not a hydrazine derivative and is structurally related to amphetamine. Tranylcypromine is more likely to provoke a hypertensive reaction.[14]

The present study consists of a double-blind comparison of tranylcypromine versus phenelzine in antidepressant-refractory severely depressed inpatients. This study, the first to compare the efficacy of these 2 MAOIs, was designed to assess whether phenelzine might be a suitable alternative to tranylcypromine in patients with severe antidepressant-refractory depression.

METHOD

The study was performed between November 1996 and July 2001 at the inpatient depression unit of 2 centers: Parnassia Psychomedical Centre, The Hague (T.K.B.), and the Department of Psychiatry, Erasmus University Hospital, Rotterdam (W.W.vdB., J.A.B.), the Netherlands. Both units have a supraregional function for the treatment of treatment-resistant depressed patients. It is routine practice to discontinue psychotropic drugs after admission. Depressed patients were screened for inclusion and exclusion criteria. The study protocol was approved by the medical ethical boards of both centers, and the study was conducted in accordance with the Declaration of Helsinki. Eligible patients provided written informed consent after study procedures were fully explained.

Patient Selection

The study was a 5-week randomized double-blind comparison of tranylcypromine and phenelzine, preceded by a washout of 1 week. Included were inpatients aged 18 to 65 years with a depressive disorder according to DSM-IV criteria and a score ≥ 14 on the 17-item Hamilton Rating Scale for Depression (HAM-D).[15] Furthermore, they were nonresponders to either a double-blind study comparing imipramine and fluvoxamine, of which the doses were adjusted according to predefined plasma levels, or open treatment with a TCA with adequate plasma levels. All patients had achieved stable plasma levels of ≥ 200 ng/mL for imipramine + desmethylimipramine, ≥ 150 ng/mL for fluvoxamine, ≥ 100 ng/mL for amitriptyline + nortriptyline, ≥ 150 ng/mL for clomipramine + desmethylclomipramine, or 50 to 150 ng/mL for nortriptyline during at least 4 weeks. Nonresponse was defined as a HAM-D reduction by less than 50% and a posttreatment HAM-D score ≥ 14. Excluded were patients with schizophrenia, bipolar or schizoaffective disorder, organic brain syndrome, alcohol or drug abuse during more than 6 months, relevant somatic illness, pregnancy or inadequate contraception for women in the fertile age, refractoriness to previous adequate treatment with an MAOI, or an immediate indication for electroconvulsive therapy. None of the patients had been using fluoxetine in the 5 weeks before study entry. Preparation of the study medication capsules and randomization from a random number table were done by the Department of Pharmacy of the second center.

Treatments

The study medication comprised capsules of tranylcypromine and phenelzine of identical appearance, taste, and weight, containing 10 mg of the MAOI. Antidepressants were withdrawn at least 1 week before the start of MAOI administration.

Treatment was started at a daily dose of 20 mg, divided in 2 equal dosages given at 8:00 a.m. and 8:00 p.m. After 3, 7, 10, and 14 days, the daily doses could be increased to 40, 60, 80, and 100 mg, respectively, in case of insufficient response (i.e., HAM-D reduction by less than 50%). When side effects were severe, doses were not increased or decreased. Moreover, dihydroergotamine could be given in case of orthostatic hypotension. The use of concurrent psychotropic medication was prohibited, with the exception of lorazepam (maximum dose 3 mg daily). All patients were kept on a tyramine-restricted diet.

Study Assessments

The diagnosis was assessed by performing the depression part of the Schedule for Affective Disorders and Schizophrenia.[16] The severity of depression was scored weekly on both the HAM-D and the Clinical Global Impressions scale (CGI)-Severity of Illness and -Change.

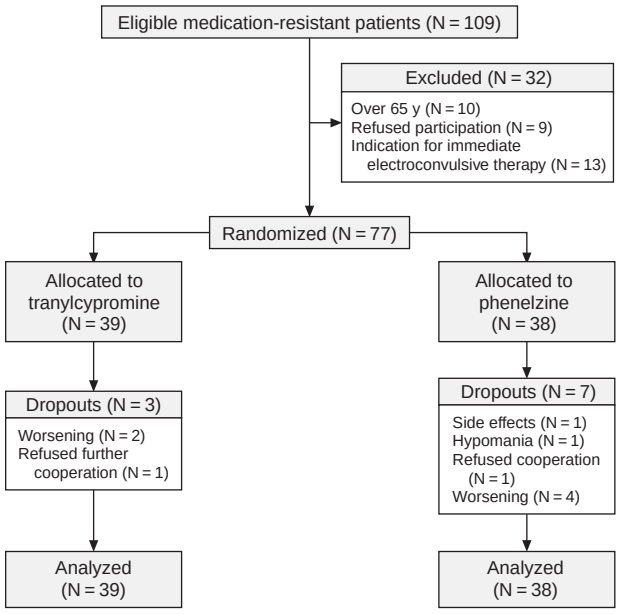
All assessments were done by the 3 research psychiatrists (W.W.vdB., J.A.B., T.K.B.). To ensure comparable ratings, interrater reliability sessions took place 6 times per year during the study. Excellent interrater reliability ($\kappa = 0.95$) was achieved between the participating psychiatrists regarding the total score on the HAM-D.

In all patients, blood pressure and pulse rate were measured twice daily in both lying and standing positions at 7:00 a.m. and 9:00 p.m. The well-known side effects of both MAOIs were evaluated weekly, i.e., dizziness, headache, agitation, drowsiness, and insomnia. In addition, other spontaneously reported side effects were also recorded. When side effects either prevented dose increment or led to the prescription of concurrent medication, they were rated "severe." Side effects were considered present when they appeared or worsened after baseline.

Statistical Analysis

The primary response criterion is defined a priori as a reduction of at least 50% of the HAM-D score compared with baseline, and the secondary response criterion is defined as "much improved" or "very much improved" on

Figure 1. Flow of 77 Antidepressant-Refractory Depressed Inpatients



the CGI. The criterion for remission is a HAM-D final score ≤ 7. Response is analyzed separately according to both the primary and the secondary criterion. All statistical analyses are intent-to-treat analyses; for patients who dropped out, the score of the last week with treatment is carried forward to week 5. Dichotomous variables are analyzed with Fisher exact test; the t test is used for comparing continuous variables with a Gaussian-shaped distribution. For the response definition—50% reduction in the HAM-D score—we analyzed the difference in time to response between the 2 treatment groups, using a Cox proportional hazards model. The duration of treatment until the primary response criterion was met is the survival time variable. Dropouts were censored at the time of dropout. Analysis for testing difference in response between the 2 treatments was adjusted for 3 prespecified covariables (duration of the index episode, psychotic features, and previous treatment during index episode) and stratified for center.

Mean reduction in the HAM-D score at week 5 compared with baseline was compared between the 2 treatment samples using analysis of covariance (ANCOVA) with the baseline HAM-D score as covariate. CGI-Change scale scores between the 2 samples were compared using logistic regression including the prespecified covariables mentioned above. With regard to tolerability, we assumed that if one of the MAOIs would cause more serious adverse effects, this could lead to a higher discontinuation rate or to suboptimal dosing in nonresponders. Therefore, we analyzed both dropout rate and final MAOI dose in nonresponders. Statistical significance was defined as $p < .05$. Statistical analyses were performed using SPSS for Windows, version 10 (SPSS Inc., Chicago, Ill.)

Table 1. Demographic and Clinical Characteristics of 77 Antidepressant-Refractory Depressed Inpatients

Variable	Tranylcypromine (N = 39)	Phenelzine (N = 38)	Total (N = 77)
Age, range, y	31–65	32–64	31–65
Age, mean ± SD, y	54.1 ± 8.7	53.1 ± 9.5	53.6 ± 9.0
Sex, M/F	13/26	8/30	21/56
Prior nonresponse to lithium addition, N (%)	12 (31)	11 (29)	23 (30)
Duration index episode > 1 y, N (%)	21 (54)	26 (68)	47 (61)
Psychotic features, N (%)	16 (41)	7 (18)	23 (30)
Baseline HAM-D score, mean ± SD	27.2 ± 4.9	25.7 ± 4.2	26.5 ± 4.6
Dose for nonresponders, mean ± SD, mg/d	50.5 ± 3.2	77.4 ± 2.8	N/A

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, N/A = not applicable.

RESULTS

Of the 59 eligible patients with an antidepressant-refractory depressive disorder at the first center (Parnassia), 8 patients (14%) fulfilled 1 or more exclusion criteria, 6 patients (10%) refused participation, and 45 patients (76%) participated. In the second center (Erasmus), 50 patients were diagnosed with an antidepressant-refractory depressive disorder, of which 15 (30%) fulfilled at least 1 exclusion criterion, 3 (6%) refused participation, and 32 (64%) participated (Figure 1).

A total of 77 depressed inpatients were randomly assigned to either tranylcypromine (N = 39) or phenelzine (N = 38). Twenty-three patients (30%) had been nonresponders to fixed plasma level treatment with imipramine or fluvoxamine,[17] followed by lithium addition. The remaining 54 patients (70%) had not responded to open treatment with a TCA with therapeutic plasma levels. Subclassification according to the DSM-IV reveals that 23 patients (30%) were suffering from depression with mood-congruent psychotic features. Table 1 shows the demographic and clinical characteristics of the total sample. The 2 treatment groups were balanced for age, previous treatment, and entry HAM-D score. There was a nonsignificant greater number of men in the tranylcypromine-treated sample than in the phenelzine-treated sample (13 and 8, respectively). Moreover, there was a trend toward patients with psychotic features being overrepresented in the tranylcypromine-treated sample compared with the phenelzine-treated sample (16 vs. 7; $p = .06$).

Response to Treatment

With response defined as a 50% reduction in the HAM-D score, 17 (44%) of 39 patients taking tranyl-

Table 2. Influence of Treatment and Covariables on Response in 77 Antidepressant-Refractory Depressed Inpatients

Variable	Hazard Ratio	p Value	95% Confidence Interval
Type of treatment (tranylcypromine)	1.01	.97	0.54 to 1.99
Psychotic features (yes)	0.73	.42	0.34 to 1.56
Duration of index episode (> 1 y)	0.89	.76	0.43 to 1.83
Pretreatment with lithium addition (yes)	0.79	.53	0.37 to 1.66

Table 3. Number of Responders/Remitters Among 77 Antidepressant-Refractory Depressed Inpatients on Various Outcome Criteria

	HAM-D Score Reduction ≥ 50%		CGI-Change Score		Final HAM-D Score ≤ 7	
Treatment Group	N	%	N	%	N	%
Tranylcypromine (N = 39)	17	44	16	41	7	18
Phenelzine (N = 38)	18	47	15	39	4	11
Total (N = 77)	35	46	31	40	11	14

Abbreviations: CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression.

cypromine and 18 (47%) of 38 patients taking phenelzine were responders (Fisher exact test: p = .82).

Only 7 (18%) of 39 patients taking tranylcypromine and 4 (11%) of 38 patients taking phenelzine met the criterion for remission, defined as a final HAM-D score ≤ 7 (Fisher exact test: p = .52). The mean ± SD reduction in HAM-D score was 10.4 ± 8.3 for the tranylcypromine sample versus 8.3 ± 8.4 for the phenelzine-treated patients (ANCOVA phenelzine-tranylcypromine = –2.34, standard error = 1.94, df = 76, p = .23).

With response defined as a ≥ 50% reduction in the HAM-D score, the Cox proportional hazards model, stratified for center with adjustment for 3 prespecified covariables (previous antidepressant treatment, psychotic features, and duration of the index episode), showed no significant difference in time to response (hazard ratio = 1.01, 95% CI: 0.54 to 1.99, p = .97). This analysis showed a small nonsignificant negative effect on response of 2 illness characteristics, psychotic features and duration of the index episode. The exact hazard ratios are presented in Table 2.

Sixteen (41%) of 39 patients taking tranylcypromine and 15 (39%) of 38 patients taking phenelzine met the response criterion "much improved" or "very much improved" on the CGI (likelihood ratio test p = .94).

Thus no differences in efficacy between the 2 drugs were detected. The numbers of responders by the various response criteria are shown in Table 3.

Dropouts

Ten patients did not complete the study, 3 patients taking tranylcypromine (3/39 = 8%) and 7 taking phenelzine (7/38 = 18%). Thus, overall discontinuation amounts to 10 (13%) of 77. Six patients (2 taking tranylcypromine and 4 taking phenelzine) dropped out due to a deteriorating condition. One patient taking phenelzine dropped out because of hypomania, and 2 patients (1 taking phenelzine) refused further cooperation.

Doses

The mean daily dose in the total sample was 60.5 ± 2.9 mg for tranylcypromine and 79 ± 2.7 mg for phenelzine (2-tailed Mann-Whitney test; p = .004). The dose range was 30 to 100 mg for tranylcypromine and 50 to 100 mg for phenelzine. Thirty-two (84%) of 38 patients taking phenelzine received at least 60 mg daily for 4 weeks. Twenty-four (62%) of 39 patients taking tranylcypromine received at least 60 mg daily for 4 weeks.

The mean daily dose in nonresponders was 50.5 ± 3.2 mg for tranylcypromine and 77.4 ± 2.8 mg for phenelzine (2-tailed Mann-Whitney test; p = .012). Side effects (mainly orthostatic hypotension) prevented dose increment in 8 patients taking tranylcypromine and 5 taking phenelzine.

Atypical Features

Six patients (8%) showed a preserved reactivity of mood, which is the core symptom of atypical depression. One of them met the criteria for definite atypical depression, which requires 2 additional criteria. Another suffered from probable atypical depression, which requires 1 additional criterion. The overall MAOI response of these mood-reactive patients was 83% (5 of 6 patients).

Concomitant Medication

Four patients taking tranylcypromine (4/39) and 3 patients taking phenelzine (3/38) were prescribed lorazepam 1 to 2 mg daily for intolerable anxiety. One psychotic patient taking phenelzine was treated with 3 mg of haloperidol as well as lorazepam. Although this patient is actually a protocol violator, because she is the only one, this patient is not excluded from statistical analyses. The total number of patients using concurrent psychotropic medication was 8/77 (10%), which has been ignored in the analyses because of the small number of patients.

Adverse Effects

Only 1 patient taking phenelzine dropped out due to adverse effects. Nevertheless, side effects were a major cause for concern, since severe forms of dizziness, agitation, and insomnia were reported by 21% of the patients. Table 4 shows the exact frequencies of the specific adverse effects. The frequency of severe adverse effects was virtually the same in both samples. Severe drowsiness occurred more frequently with phenelzine than with tranylcypromine, although not at a significant level.

Table 4. Adverse Effects (AEs) in 77 Antidepressant-Refractory Depressed Inpatients

	Tranylcypromine (N = 39)		Phenelzine (N = 38)	
Effect	No. of AEs	%	No. of AEs	%
Mild/moderate dizziness	10	26	5	13
Severe dizziness	7	18	7	18
Mild/moderate agitation	3	8	2	5
Severe agitation	8	21	7	18
Mild/moderate headache	3	8	1	3
Severe headache	4	10	3	8
Mild/moderate drowsiness	2	5	4	11
Severe drowsiness	0	0	3	8
Mild/moderate insomnia	4	10	2	5
Severe insomnia	8	21	6	16

DISCUSSION

In this report, we describe the first randomized study to compare the efficacy and tolerability of phenelzine with those of tranylcypromine in severe antidepressant-refractory depression. No indication of differences in efficacy between the 2 MAOIs was found. The present study has limited power to detect such differences, and definite conclusions should await the results of larger studies. The strict criteria required for treatment resistance restrict the number of patients available for such studies; therefore, it is questionable whether a larger study than the present one will ever be performed. The overall intent-to-treat MAOI response (45%) in our study can be considered a satisfactory result in patients with severe treatment-resistant depression and is comparable with the results of previous studies.[18] In such treatment-resistant patient samples, a placebo response is assumed to be 10% by some investigators.[4,9] If we would agree with this assumption, the efficacy of both MAOIs in the present study is beyond doubt. The response rate amounts to 40% to 50% for both MAOIs (HAM-D, 45%; CGI-Change score, 40%). The mean reduction in HAM-D score was larger in the tranylcypromine sample (10.4 vs. 8.3) but not at a significant level. Since the present study has a flexible-dose design, nonresponders could be expected to receive high doses (90–100 mg of either compound), unless side effects would have prevented increasing the dose. Apparently, the mean dose in nonresponders to tranylcypromine was significantly lower compared with phenelzine nonresponders, which might reflect a better tolerability of phenelzine even though the number of patients suffering from severe adverse effects did not differ between the 2 samples.

Furthermore, the relatively low dose in nonresponders to tranylcypromine may have prevented the exertion of its full therapeutic potential in some patients. The optimal dosages for MAOI treatment are not exactly known. According to an extensive meta-analysis,[19] there is no evidence to support the efficacy of MAOIs at daily doses lower than 30 mg for tranylcypromine and 45 mg for phenelzine. Since further information is lacking, it is impossible to examine whether the dosages used in the present study were optimal.

With regard to our definition of antidepressant resistance, it should be noted that the plasma level–response relationship has been established firmly for imipramine and nortriptyline, and to a lesser extent for amitriptyline and clomipramine.[20] Such relationship has not been proven for fluvoxamine, but the target plasma level technique itself results in excluding low and possibly subtherapeutic plasma levels in fast metabolizers.[21]

Concerning various illness characteristics, patients with a longer duration of the index episode and/or psychotic features showed reduced response but not at a significant level. A remarkably high MAOI response rate (5/6 = 83%) was found in patients with preserved reactivity of mood, which is known to be the core symptom of atypical depression; this is in accordance with previous studies.[12] However, the number of patients manifesting these features was small, which is not surprising in an inpatient setting.[6]

In conclusion, treatment with both MAOIs was found to be effective and rather well tolerated in our sample of severely depressed inpatients that had been refractory to previous treatment with antidepressants, including those patients with psychotic features. No major differences between both drugs were found. Our results provide further support for treatment with nonselective MAOIs if the depression does not respond to TCAs and other antidepressants. Because tranylcypromine has been studied more extensively than phenelzine in antidepressant-resistant depression, we consider it first choice in so-called Stage 3 refractory depression. Phenelzine appears to be a useful alternative, especially if side effects prevent the administration of higher doses of tranylcypromine.

Drug names: amitriptyline (Elavil and others), amphetamine (Adderall, Dexedrine, and others), clomipramine (Anafranil and others), dihydroergotamine (Migranal and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), imipramine (Tofranil and others), lorazepam (Ativan and others), nortriptyline (Pamelor, Aventyl, and others), phenelzine (Nardil), tranylcypromine (Parnate).

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