Article

Tranylcypromine Versus Venlafaxine Plus Mirtazapine Following Three Failed Antidepressant Medication Trials for Depression: A STAR*D Report

Patrick J. McGrath, M.D.

Jonathan W. Stewart, M.D.

Maurizio Fava, M.D.

Madhukar H. Trivedi, M.D.

Stephen R. Wisniewski, Ph.D.

Andrew A. Nierenberg, M.D.

Michael E. Thase, M.D.

Lori Davis, M.D.

Melanie M. Biggs, Ph.D.

Kathy Shores-Wilson, Ph.D.

James F. Luther, M.A.

George Niederehe, Ph.D.

Diane Warden, Ph.D., M.B.A.

A. John Rush, M.D.

STAR*D Study Team

Objective: The purpose of this study was to compare the effectiveness and tolerability of tranylcypromine and combination treatment with extended-release venlafaxine and mirtazapine in patients with treatment-resistant major depression whose current depressive episode had not responded adequately to treatment in three prior prospective medication trials.

Method: Adult outpatients with nonpsychotic major depressive disorder who had not achieved remission or had withdrawn from treatment because of intolerance in three previous prospective medication trials were randomly assigned to receive open-label treatment with either tranylcypromine (N=58) or extended-release venlafaxine plus mirtazapine (N=51). The primary outcome measure was whether patients achieved remission, which was defined as a score ≤7 at exit on the 17-item Hamilton Depression Rating Scale (HAM-D). The HAM-D was administered by telephone by raters to whom treatment was masked.

Results: Remission rates were not significantly different between the two treatment groups (6.9% for the tranylcypromine group and 13.7% for the venlafaxine plus mirtazapine group). The mean daily dose at exit for tranylcypromine was 36.9 mg (SD=18.5); for venlafaxine, 210.3 mg (SD=95.2); and for mirtazapine, 35.7 mg (SD=17.6). Tranylcypromine was associated with significantly less symptom reduction and greater attrition due to intolerance.

Conclusions: Remission rates were modest for both the tranylcypromine group and the extended-release venlafaxine plus mirtazapine group, and the rates were not statistically different between groups. The lower side effect burden, lack of dietary restrictions, and ease of use of venlafaxine and mirtazapine suggest that this combination may be preferred over tranylcypromine for patients with highly treatment-resistant depression who have not benefited adequately from several prior treatments.

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Major depressive disorder is typically recurrent, chronic, and disabling, with high direct and indirect costs to society (1). Current estimates for lifetime prevalence range from 16.6% to 17.9%, making it one of the most prevalent (2) and disabling (3) psychiatric disorders.

The treatment of depression that has not responded to multiple treatment trials has rarely been systematically studied. ECT has long been considered the primary option for treatment-resistant depression, but high rates of relapse, cognitive side effects, and poor acceptability make this option problematic (4). Monoamine oxidase inhibitors (MAOIs), such as phenelzine and tranylcypromine, have been used as an alternative to ECT for treatment-resistant depression. Tranylcypromine has been more widely studied than other MAOIs, and six studies, including four randomized controlled trials, have examined its efficacy in patients with treatment-resistant depression, reporting a median response rate of 50% (range=29%–75%) (5–10). Two open-label clinical trials reported better efficacy with tranylcypromine when used in doses of 70–120 mg/day, well beyond the maximum of 60 mg/day approved by the Food and Drug Administration (FDA) (8, 9); neither of these studies reported remission rates, however. The current expert consensus is that remission, defined as a virtually complete resolution of symptoms, should be the goal of antidepressant pharmacotherapy (11), because patients who remit function better (12) and have a better longer-term prognosis than those whose depression responds without remission (13).

Treatment with a combination of antidepressants with different pharmacologic profiles has been proposed, under the supposition that such combinations may have ad-

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ditive or synergistic effects (14). The coadministration of venlafaxine, which is a dual reuptake inhibitor of serotonin and norepinephrine, and mirtazapine, which blocks inhibitory α_2-adrenoceptors on both norepinephrine and serotonin neurons, enhances both norepinephrine and serotonin neurotransmission (14, 15).

The multicenter Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study included a series of prospectively conducted randomized clinical trials designed to evaluate the relative effectiveness of antidepressant treatments for adults with nonpsychotic major depressive disorder who did not experience symptom remission with, or were intolerant of, an initial adequate trial of pharmacotherapy (11, 16). Results of the first three treatment steps, Level 1 (17), Level 2 (18, 19), and Level 3 (20; see also Nierenberg et al., in this issue) have already been reported. Participants who did not achieve remission with, or were intolerant of, citalopram and at least two subsequent medication treatments went on to Level 4, in which they underwent randomized assignment to treatment with either tranylcypromine or a combination of extended-release venlafaxine and mirtazapine.

The purpose of this study was to compare the effectiveness and tolerability of tranylcypromine versus combination treatment with extended-release venlafaxine and mirtazapine in patients with highly treatment-resistant major depression.

Method

Participants

The study protocol was approved and monitored by the institutional review boards of the National Coordinating Center (University of Texas Southwestern Medical Center in Dallas), the Data Coordinating Center (University of Pittsburgh), each regional center and relevant clinical site, and the Data Safety and Monitoring Board of the National Institute of Mental Health (Bethesda, Md.). All participants provided written informed consent prior to initial enrollment in the study and prior to enrollment in each subsequent treatment level.

The study enrolled outpatients who had a primary diagnosis of nonpsychotic major depressive disorder by DSM-IV criteria, established by routine clinical assessment and confirmed with a checklist completed by the clinical research coordinator. The recruitment of treatment-seeking outpatients and the use of broad inclusion and minimal exclusion criteria were intended to ensure that the study sample was representative of outpatients with major depression typical of those seen in clinical practice. Between July 2001 and April 2004, a total of 4,041 outpatients 18 to 75 years of age were enrolled from 18 primary care and 21 psychiatric care practice settings.

Participants entering this study (STAR*D treatment Level 4) did not achieve remission with, or were intolerant of, each of the first three levels of pharmacotherapy treatment. A subset of this group had also not adequately benefited from cognitive therapy, either alone or combined with citalopram, in addition to three pharmacotherapy trials. As in previous levels, treatment assignment was not masked to patients or treating clinicians.

Symptom remission for clinical decision making was defined as a score ≤5 on the 16-item Quick Inventory of Depressive Symptomatology—Clinician-Rated (QIDS-C) (21, 22). The primary outcome measure was whether participants achieved symptom remission, in this case defined as a total Hamilton Depression Rating Scale (HAM-D) (23) score ≤7 at exit. The HAM-D was administered in structured telephone interviews at entry and exit from each treatment level by independent, trained, certified research outcomes assessors to whom treatment was masked. For secondary outcome measures, the Quick Inventory of Depressive Symptomatology—Self-Report (QIDS-SR) was given at Level 4 baseline and at each subsequent clinic visit to assess whether participants remitted (defined as score ≤5) or responded (defined as a reduction of ≥50% from baseline score).

When participants were enrolled in the first STAR*D treatment step, demographic information was collected and various instruments were administered to collect clinical information. Current general medical conditions were assessed with the Cumulative Illness Rating Scale (24, 25). The presence of 11 potential concurrent axis I disorders was assessed with the Psychiatric Diagnostic Screening Questionnaire (26, 27). The presence of atypical (28) and melancholic features (29) was determined with the 30-item Inventory of Depressive Symptomatology—Clinician-Rated (30) in a telephone interview conducted by a research outcomes assessor, and anxious features were assessed by the anxiety subscale of the HAM-D (31). Measures of functioning and quality of life, collected through a telephone-based interactive voice response system (32, 33), included the 16-item Quality of Life Enjoyment and Satisfaction Questionnaire (34), the mental and physical subscales of the 12-item Short-Form Health Survey (35), and the Work and Social Adjustment Scale (36).

Protocol Treatment

A clinical procedures manual (37) recommended starting doses and dose changes for each medication treatment based on symptom and side effect ratings obtained at each clinic visit in order to deliver measurement-based care (17). Depressive symptom severity over the previous week was assessed using the QIDS-SR and the QIDS-C, which rate the nine diagnostic symptom domains of major depression (21, 22). Side effects were assessed at each visit with self-report measures of side effect frequency, intensity, and burden (11). Didactic instruction, clinical research coordinator support, and a centralized monitoring system (38) with feedback were used to ensure that timely dose increases were made as long as symptom reduction was inadequate and side effects were acceptable.

The aim of treatment was defined a priori as symptom remission (a QIDS-C score ≤5). The protocol recommended that clinic visits take place at baseline and at weeks 2, 4, 6, 9, and 12, with additional visits scheduled if clinically indicated. The planned duration of each treatment trial was 12 weeks. However, participants could leave a trial early if intolerable side effects occurred, if a remission was sustained for at least 2 weeks, or if minimal symptom reduction (QIDS-C total score >9) had occurred after 6 weeks at maximally tolerated doses. Participants who experienced at least a response to treatment (a reduction ≥50% in QIDS-C score at 12 weeks) could continue the treatment for up to 2 additional weeks to determine whether remission would occur with the additional time.

The recommended dosing protocol for tranylcypromine was 10 mg/day for the first 2 weeks, followed by weekly increases of 10 mg/day until a maximum of 60 mg/day was reached. A 2-week washout period after Level 3 was required for participants who were assigned to the tranylcypromine group. For the combination treatment, the dosage of extended-release venlafaxine was 37.5 mg/day for the first week, 75 mg/day for the second week, 150 mg/day for weeks 3–5, 225 mg/day for weeks 6–8, and 300 mg/day thereafter. Mirtazapine was started at 15 mg/day for the first 3 weeks, 30 mg/day for the following 8 weeks, and then 45 mg/day thereafter.

Statistical Methods

For summary statistics, means and standard deviations were computed for continuous variables, and counts and percentages for discrete variables. Student's t tests, Wilcoxon tests, and chi-square tests were used to compare baseline clinical and demographic features, treatment features, side effects measures, and rates of serious adverse events across treatments and for the entire sample.

All analyses included all participants who underwent randomized assignment. Remission was defined as a HAM-D score ≤7 and a QIDS-SR score ≤5 at exit from treatment. The remission threshold of ≤5 for the QIDS-SR was established using item response theory analysis and was chosen because it corresponds to a score of ≤7 on the HAM-D (22). Logistic regression models were used to compare the remission and response rates after adjusting for the effect of baseline clinical and demographic factors that were not balanced across treatment groups (medication treatment received in Level 3 and whether a participant exited Level 3 because of intolerance). Additional exploratory logistic regression analyses were conducted to determine whether there was a treatment effect after excluding participants who exited the study during the tranylcypromine washout period and whether there was a differential treatment effect in various Level 3 treatment subgroups (e.g., those intolerant to their Level 3 treatment). The time to first remission was defined as the first clinic visit with a QIDS-SR score ≤5, and time to first response was defined as the first clinic visit with a reduction ≥50% from the baseline QIDS-SR score. Log-rank tests were used to compare the cumulative proportions of participants who remitted and who responded across the two treatment groups. An additional exploratory analysis was conducted to determine whether presentation of major depressive disorder with atypical features was associated with remission.

Participants whose exit HAM-D scores were missing were assumed not to have achieved remission. Sensitivity analyses were conducted to determine whether this method of addressing the missing data had an impact on the results of the study. An additional method of addressing these missing data used an imputed value generated from an item response theory analysis of the relationship between the HAM-D and the QIDS-SR.

Results

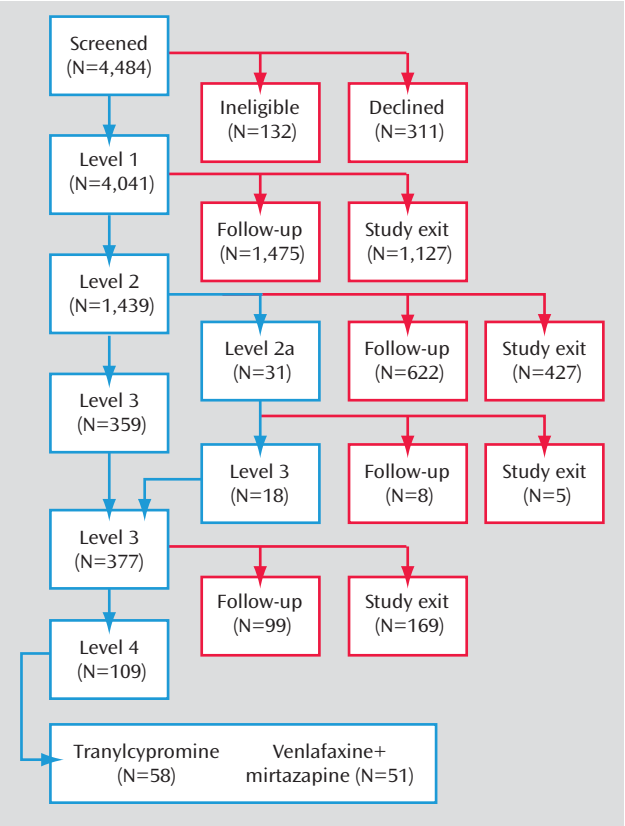
Participant Disposition

Figure 1 illustrates the flow of participants through the STAR*D study. Of 4,041 participants enrolled in the STAR*D trial, 109 entered Level 4, 58 of whom were assigned to receive tranylcypromine and 51 to receive combination treatment with extended-release venlafaxine and mirtazapine.

Demographic and Clinical Characteristics

Table 1 summarizes the demographic and clinical characteristics of Level 4 participants. About half were female, over 40% had their first major depressive episode before age 18, and three-quarters had recurrent major depressive disorder. The average HAM-D score at entry to Level 4 was nearly 20, indicating moderate to severe depression; this score represented minimal improvement from when these participants entered Level 1 (mean=23.4, SD=5.9). The duration of the current major depressive episode was fairly long, with a median of 9.1 months, and for about 30% of participants, it had lasted 2 or more years.

FIGURE 1. Participant Flow (CONSORT Chart) for the STAR*D Study[a]



[a] In Level 1, all participants received citalopram. In Level 2, participants could be assigned to treatment switch, in which case citalopram was stopped and participants could receive sustained-release bupropion, sertraline, extended-release venlafaxine, or cognitive therapy, or they could be assigned to one of three augmentation treatments, in which case citalopram was continued and sustained-release bupropion, buspirone, or cognitive therapy was added. In Level 2A, which was available only to Level 2 participants who had received either cognitive therapy alone or cognitive therapy plus citalopram, participants switched either to sustained-release bupropion or to extended-release venlafaxine. In Level 3, participants either switched to nortriptyline or mirtazapine or received augmentation treatment with lithium or T_3.

Comorbidity was substantial. Scores on the Quality of Life Enjoyment and Satisfaction Questionnaire, the mental and physical subscales of the Short-Form Health Survey, and the Work and Social Adjustment Scale indicated substantial reductions in quality of life. According to the Cumulative Illness Rating Scale, 64.2% had at least one general medical condition at baseline. The Psychiatric Diagnostic Screening Questionnaire indicated that 76% had at least one additional axis I comorbid disorder, and over 19% had at least four disorders.

The two treatment groups did not differ on most variables (Table 1), including rates of comorbidity (data not shown). Significant differences were observed in treat-

TABLE 1. Demographic and Clinical Characteristics of Outpatients With Major Depressive Disorder Receiving Either Tranylcypromine or Venlafaxine (Extended-Release) and Mirtazapine in STAR*D Level 4, by Treatment[a]

Characteristic	Total (N=109)		Treatment: Tranylcypromine (N=58)		Treatment: Venlafaxine and Mirtazapine (N=51)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	46.0	11.1	46.6	11.6	45.3	10.6
Age at onset of first episode (years)	25.0	14.1	27.3	15.3	22.4	12.2
Number of episodes	9.0	15.7	7.1	10.4	11.0	20.0
Duration of current episode (months)	43.5	80.4	33.1	67.9	55.7	92.2
	N	%	N	%	N	%
Female gender	56	51.4	33	56.9	23	45.1
Race						
White	89	81.7	46	79.3	43	84.3
Black	17	15.6	10	17.2	7	13.7
Other	3	2.8	2	3.4	1	2.0
Hispanic	17	15.6	8	13.8	9	17.6
Employment status						
Employed	52	47.7	26	44.8	26	51.0
Unemployed	53	48.6	30	51.7	23	45.1
Retired	4	3.7	2	3.4	2	3.9
Medical insurance						
Private	44	41.1	23	40.4	21	42.0
Public	14	13.1	5	8.8	9	18.0
None	49	45.8	29	50.9	20	40.0
Marital status						
Never (single)	22	20.2	12	20.7	10	19.6
Married or cohabiting	48	44.0	22	37.9	26	51.0
Divorced or separated	33	30.3	19	32.8	14	27.5
Widowed	6	5.5	5	8.6	1	2.0
Psychiatric care setting	65	59.6	34	58.6	31	60.8
Age <18 years at onset of first episode	45	41.7	22	38.6	23	45.1
At least one prior episode	73	74.5	38	73.1	35	76.1
Family history of depression	57	52.3	32	55.2	25	49.0
Ever attempted suicide	24	22.0	11	19.0	13	25.5
Duration of current episode ≥2 years	33	30.8	15	25.9	18	36.7
	Mean	SD	Mean	SD	Mean	SD
Quality of Life and Enjoyment Satisfaction Questionnaire	36.4	15.3	36.8	15.9	36.1	14.9
Short-Form Health Survey, mental subscale	28.6	9.1	29.6	10.0	27.7	8.3
Short-Form Health Survey, physical subscale	43.0	12.2	43.0	12.0	43.1	12.4
Work and Social Adjustment Scale	27.8	7.9	28.2	8.2	27.4	7.6
Hamilton Depression Rating Scale	19.6	6.7	19.6	7.6	19.7	5.5
Inventory of Depressive Symptomatology—Clinician-Rated	37.4	12.2	37.7	13.2	37.0	11.0
Quick Inventory of Depressive Symptomatology—Clinician-Rated	14.4	4.3	14.1	4.7	14.8	3.9
Quick Inventory of Depressive Symptomatology—Self-Report	14.2	4.7	13.6	5.1	14.9	4.1
Percentage change in Quick Inventory of Depressive Symptomatology—Self-Report score during Level 3	1.8	33.2	3.1	37.9	0.3	27.3
	N	%	N	%	N	%
Anxious features	49	49.5	28	51.9	21	46.7
Atypical features	21	21.2	13	24.1	8	17.8
Melancholic features	24	24.0	14	25.5	10	22.2
Level 3 treatment[b]						
Mirtazapine	31	28.4	10	17.2	21	41.2
Nortriptyline	40	36.7	26	44.8	14	27.5
Lithium augmentation	22	20.2	13	22.4	9	17.6
T_3 augmentation	16	14.7	9	15.5	7	13.7
Exited Level 3 because of intolerance of treatment[b]	35	32.1	24	41.4	11	21.6
	Mean	SD	Mean	SD	Mean	SD
Level 3 treatment duration (weeks)	10.0	4.3	9.4	4.6	10.5	3.9

[a] Sums do not always equal N because of missing data; percentages are based on number of subjects for whom data were available.
[b] Difference between treatment groups, $p<0.05$.

TABLE 2. Treatment and Outcome Measures for Outpatients With Major Depressive Disorder Receiving Either Tranylcypromine or Venlafaxine (Extended-Release) and Mirtazapine in STAR*D Level 4, by Treatment

Variable	Total (N=109)		Treatment: Tranylcypromine (N=58)		Treatment: Venlafaxine and Mirtazapine (N=51)	
	N	%	N	%	N	%
Time in treatment <4 weeks[a]	21	19.3	17	29.3	4	7.8
Time in treatment <8 weeks[a]	38	34.9	27	46.6	11	21.6
	Mean	SD	Mean	SD	Mean	SD
Number of postbaseline visits	4.0	1.9	4.0	2.1	3.9	1.8
Time to first postbaseline visit (days)[b]	20.0	14.0	16.7	7.4	23.1	17.6
Tranylcypromine dose (mg/day) at exit			36.9	18.5		
Venlafaxine dose (mg/day) at exit					210.3	95.2
Mirtazapine dose (mg/day) at exit					35.7	17.6
Time on tranylcypromine exit dose (days)			30.5	21.0		
Time on venlafaxine exit dose (days)					51.2	34.1
Time on mirtazapine exit dose (days)					66.3	36.0

[a] Difference between treatment groups, p<0.01.
[b] Difference between treatment groups, p<0.05.

TABLE 3. Remission and Response Measures Among Outpatients With Major Depressive Disorder Receiving Either Tranylcypromine or Venlafaxine (Extended-Release) and Mirtazapine in STAR*D Level 4, by Treatment[a]

Measure	Total (N=109)		Treatment: Tranylcypromine (N=58)		Treatment: Venlafaxine and Mirtazapine (N=51)	
	N	%	N	%	N	%
Remission, defined as score ≤7 on Hamilton Depression Rating Scale	11	10.1	4	6.9	7	13.7
Remission, defined as score ≤5 at exit on Quick Inventory of Depressive Symptomatology—Self-Report	16	14.7	8	13.8	8	15.7
Response, defined as ≥50% reduction from baseline score on Quick Inventory of Depressive Symptomatology—Self-Report	19	17.4	7	12.1	12	23.5
	Mean	SD	Mean	SD	Mean	SD
Exit score on Quick Inventory of Depressive Symptomatology—Self-Report	11.8	5.8	12.3	5.9	11.2	5.6
Percentage change in score on Quick Inventory of Depressive Symptomatology—Self-Report[b]	–15.0	35.2	–6.2	36.9	–25.0	30.4

[a] Sums do not always equal N because of missing data; percentages are based on number of subjects for whom data were available.
[b] Difference between treatment groups, p<0.05, adjusted for Level 3 treatment and exiting Level 3 due to intolerance.

ment received in Level 3 (more of the participants in the group receiving combination treatment with extended-release venlafaxine and mirtazapine had received mirtazapine in Level 3) and the proportion who exited Level 3 because of intolerable side effects (more of those assigned to the tranylcypromine group experienced intolerable side effects in Level 3). There was no difference between the two treatment groups in the proportion who had received venlafaxine or venlafaxine plus either lithium or T_3 augmentation in Level 3.

Treatment Characteristics

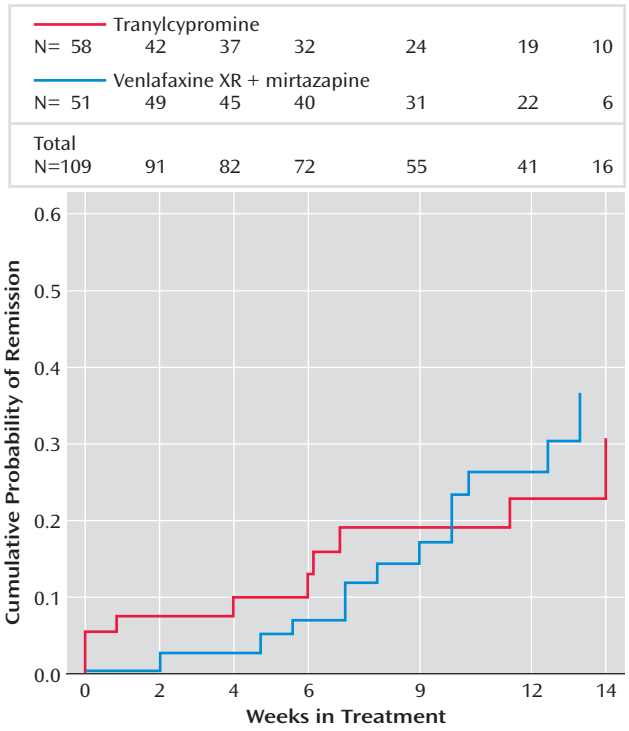
While both groups received Level 4 treatment for a substantial time (mean=9.4 weeks, SD=5.1), participants in the tranylcypromine group tended to remain in the treatment for less time than those in the combination group (about 8 versus 11 weeks on average). Significantly more of those receiving tranylcypromine (29% versus 8% receiving the combination treatment) had less than 4 weeks of treatment (Table 2)—and these treatment durations include the required 2-week washout period before tranylcypromine could be initiated. Although the doses taken were comparable for the two regimens and were substantial relative to the recommended maximum dosages, neither treatment group achieved the relatively high levels thought to be optimal for highly treatment-resistant patients. Dosage and duration of treatment did not differ between primary and specialty care sites.

Outcomes

Remission rates as indicated by both the HAM-D (6.9% for tranylcypromine and 13.7% for extended-release venlafaxine and mirtazapine) and the QIDS-SR (13.8% and 15.7%, respectively) were not statistically different between groups. Response rates were also low and not significantly different. The percentage reduction in QIDS-SR score between baseline and exit was greater for those taking venlafaxine and mirtazapine than for those taking tranylcypromine (Table 3).

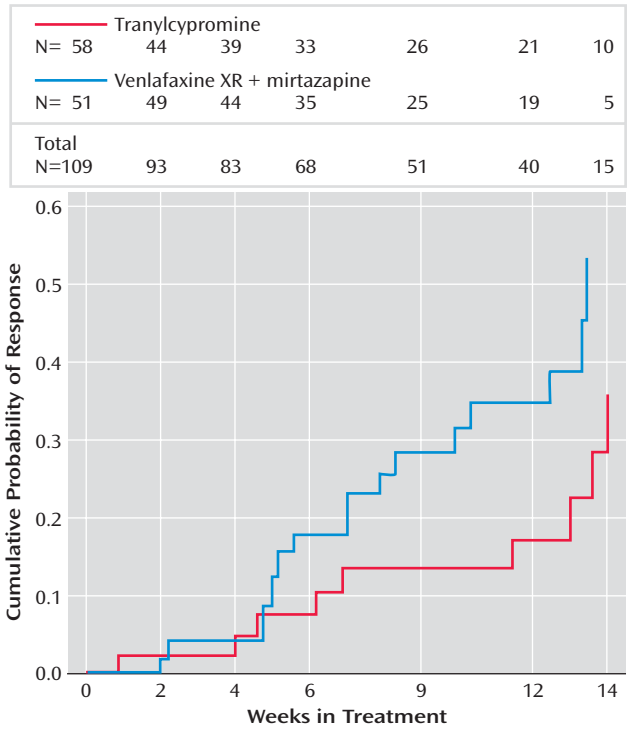
The treatments did not differ significantly in either time to remission (log rank χ^2=0.015, p=0.90) (Figure 2) or time to response (log rank χ^2=2.77, p=0.10) (Figure 3). Remission and response were measured from time of randomization, including the tranylcypromine washout period,

FIGURE 2. Cumulative Probability of Remission[a] for Outpatients With Major Depressive Disorder Receiving Tranylcypromine or Venlafaxine (Extended-Release) and Mirtazapine in STAR*D Level 4, by Time in Treatment



[a] Remission was defined as a score ≤5 on the Quick Inventory of Depressive Symptomatology—Self-Report.

FIGURE 3. Cumulative Probability of Response[a] for Outpatients With Major Depressive Disorder Receiving Tranylcypromine or Venlafaxine (Extended-Release) and Mirtazapine in STAR*D Level 4, by Time in Treatment



[a] Response was defined as the first reduction ≥50% from baseline Quick Inventory of Depressive Symptomatology—Self-Report score.

on the basis of QIDS-SR scores. Among patients who had a remission according to the results on the QIDS-SR, the mean time to remission was 8.6 weeks (median=8.8) for those taking tranylcypromine and 8.1 weeks (median=8.4) for those taking sustained-release venlafaxine and mirtazapine. Similarly, among patients who had a response according to the results on the QIDS-SR, the mean time to response was 11.4 weeks (median=13.0) among those taking tranylcypromine and 8.6 weeks (median=7.0) among those taking venlafaxine and mirtazapine.

As noted, a sensitivity analysis was conducted to evaluate the methods used to address missing values for the exit HAM-D. The use of values imputed from the exit QIDS-C score based on item response theory revealed remarkably similar findings, indicating that the analyses were not sensitive to the missing data methodology.

Tolerability and Adverse Events

There were no significant differences between groups in the maximum ratings of frequency, intensity, or burden of side effects participants gave over the course of treatment or in the rate of serious adverse events. The groups differed only in the proportion who exited treatment because of side effects (χ^2=4.89, p<0.03). Participants taking tranylcypromine were more likely to exit the study because of side effects than those taking the combination of extended-release venlafaxine and mirtazapine (Table 4).

Relationship Between Level 3 and Level 4 Treatment Outcomes

Thirty-five Level 4 participants had exited Level 3 because of medication intolerance, and their remission rates in Level 4 (11.4%) were nearly identical to those of Level 4 participants who had not exited Level 3 because of intolerance (11.7%). There were no differences in outcome between those with and without intolerance in Level 3, and no significant relationship was found between intolerance in Level 3 and intolerance in either Level 4 treatment. Participants who were assessed on initial enrollment in STAR*D as having atypical symptom features (N=21) did not have significantly different remission rates with tranylcypromine than participants without such features (N=88) (9.5% versus 11.5%).

Discussion

To our knowledge, this is the first report of a randomized treatment trial with patients prospectively observed not to have obtained satisfactory benefit with three prior consecutive medication trials. The results of this study are generalizable to the broad range of outpatients in typical practice

TABLE 4. Side Effect Measures, Adverse Events, and Treatment Intolerance Among Outpatients With Major Depressive Disorder Receiving Either Tranylcypromine or Venlafaxine (Extended-Release) and Mirtazapine in STAR*D Level 4, by Treatment[a]

Measure	Total (N=109)		Treatment			
			Tranylcypromine (N=58)		Venlafaxine and Mirtazapine (N=51)	
	N	%	N	%	N	%
Maximum side effect frequency[b]						
No side effects	44	42.7	22	40.7	22	44.9
10–25% of the time	22	21.4	14	25.9	8	16.3
50–75% of the time	21	20.4	9	16.7	12	24.5
90–100% of the time	16	15.5	9	16.7	7	14.3
Maximum side effect intensity[b]						
No side effects	44	42.7	22	40.7	22	44.9
Minimal to mild	20	19.4	13	24.1	7	14.3
Moderate to marked	24	23.3	11	20.4	13	26.5
Severe to intolerable	15	14.6	8	14.8	7	14.3
Maximum side effect burden[b]						
No side effects	49	47.6	26	48.1	23	46.9
Minimal to mild	26	25.2	15	27.8	11	22.4
Moderate to marked	21	20.4	9	16.7	12	24.5
Severe to intolerable	7	6.8	4	7.4	3	6.1
At least one serious adverse event[c]	3	2.8	2	3.4	1	2.0
At least one psychiatric serious adverse event[c]	1	0.9	1	1.7	0	0.0
Exited Level 4 because of intolerance of treatment[d]	35	32.1	24	41.4	11	21.6

[a] Sums do not always equal N because of missing data; percentages are based on number of subjects for whom data were available.
[b] The maximum side effect frequency, intensity, and burden refer to the highest ratings participants gave these measures over the course of all clinic visits they made while receiving Level 4 treatment.
[c] Adverse events were all judged to be unrelated to the study medication. One participant taking tranylcypromine who did not have a history of cardiac disease had a myocardial infarction; another developed psychotic symptoms and suicidal ideation. One participant taking venlafaxine and mirtazapine exited the study for preplanned elective surgery.
[d] Difference between treatment groups, $p<0.05$.

settings who have chronic major depression and psychiatric and medical comorbid disorders.

Remission rates, as assessed by the HAM-D and the QIDS-SR, were low (7%–16%) and not significantly different between treatment groups. Likewise, we identified no significant group differences in response rate as defined by QIDS-SR score or in time to response and time to remission as defined by QIDS-SR score. A significant limitation of this comparison is that the intensity of tranylcypromine treatment achieved was limited. When the 2-week washout period is subtracted from the total time in treatment, nearly 30% of participants in the tranylcypromine group had less than 2 weeks of treatment with this medication, and almost half had less than 6 weeks of treatment. Participants who received the combination of extended-release venlafaxine and mirtazapine had longer courses of treatment on study medication, yet there was no significant difference between groups in the frequency, intensity, or global burden of side effects.

Participants who received tranylcypromine were more likely to exit the trial early and more likely to exit because of side effects. Possible reasons for this result include a lower comfort level with tranylcypromine treatment, among both participants and clinicians; a lower tolerance of, or slower accommodation to, tranylcypromine-associated side effects; and the loss of five participants from the tranylcypromine group during the 2-week washout period. Previous studies of tranylcypromine for treatment-resistant depression suggest that using doses higher than the FDA-recommended maximum may produce better outcomes (8, 9). It may be that higher remission rates would be achieved with higher doses of tranylcypromine prescribed by specialists who have experience with MAOIs and are comfortable with them. In any case, our data suggest that psychopharmacologists may be needed to give MAOIs an adequate trial.

The power of the study to detect a difference between treatments was calculated by estimating how great a superiority the study could detect for the combination treatment compared with what was actually observed for tranylcypromine. The study had a power of 0.80 to detect a 22% superiority of extended-release venlafaxine and mirtazapine compared with the observed tranylcypromine rate. Participants who received the combination treatment had a modest but significantly greater improvement in symptoms as measured with the QIDS-SR than those who received tranylcypromine (25% versus 6% overall reduction in symptom severity). The greater improvement in those who received the combination treatment is somewhat surprising given that almost half of the participants receiving extended-release venlafaxine and mirtazapine had previously received mirtazapine, and some had previously received extended-release venlafaxine. A possible explanation is that with the early attrition of participants taking tranylcypromine, scores for this group at study exit did not have the same opportunity to improve with treatment as compared with those for the combination treatment group. Another is that participants in the combination treatment group received two pills, which could have increased placebo response in this group. Finally, the

Patient Perspective

"Mr. B," 50 years old, married, and unemployed, sought psychiatric evaluation for chronic depression, anhedonia, anxiety, and irritability. He was a Vietnam veteran, and his symptoms had been recurrent since his discharge from the army more than 30 years earlier. Since his service in Vietnam, he had also experienced recurrent nightmares, intrusive combat memories, avoidant behavior, and hyperarousal. Mr. B was diagnosed as having severe, nonpsychotic, chronic, recurrent major depressive disorder and posttraumatic stress disorder (PTSD). He enrolled in the STAR*D study and began treatment with citalopram in Level 1. Despite 9 weeks of good adherence to treatment, with the dose of citalopram titrated to 60 mg/day by week 4, he experienced minimal improvement in his symptoms.

In Level 2, Mr. B was randomly assigned to treatment with sertraline. His dose was titrated to 150 mg/day by week 6, but after 9 weeks, his depression continued. In addition, he felt a growing sense of hopelessness and anger, so he started attending supportive psychoeducational groups for people with PTSD. He also began taking 50 mg of trazodone or 0.5 mg of clonazepam at bedtime for insomnia, a treatment he continued thereafter.

In Level 3, Mr. B was assigned to treatment with mirtazapine. By week 4, with the dose at 30 mg/day, his mood had improved, and he was delighted to find that his sleep was better and that his appetite had increased after a period of steady weight loss. When the dose was increased to 45 mg/day, however, his anxiety worsened, so the dose was returned to 30 mg/day. Mr. B continued to experience a gradual improvement in his symptoms, and he was enjoying greater social involvement. Even with his improvement, at week 6 the depressive episode was not considered to be in full remission, so Mr. B's daily dose of mirtazapine was once again increased to 45 mg, and then to 60 mg. This time Mr. B tolerated the dose increases, and by week 12 his depressive symptoms were substantially improved, although the improvement was not sustained.

After 14 weeks of treatment with mirtazapine, Mr. B went on to Level 4, in which he was assigned to combination treatment with venlafaxine (extended-release) and mirtazapine. He continued with the same dose of mirtazapine he had been taking in Level 3, and the dose of venlafaxine was gradually titrated to 300 mg/day. By week 4, Mr. B's symptoms remitted (his QIDS-SR score was 3), and his remission was sustained through the remaining 8 weeks of Level 4. Mr. B was then entered into the STAR*D follow-up phase, during which his remission continued.

longer time on medication with extended-release venlafaxine and mirtazapine, given the washout period needed for tranylcypromine, may be an explanation.

Study limitations include the lack of a placebo arm, which could have helped us determine whether observed improvement was due to nonspecific aspects of treatment. However, a placebo arm was not needed to compare these two treatments or to determine an upper bound for the expected rate of response for either treatment. Moreover, we believed that including a placebo arm in a study for participants who had not responded adequately to three consecutive treatment trials would have raised insurmountable ethical concerns. Another limitation was that treatment was open-label, although for the primary outcome measure, the HAM-D was administered by assessors to whom treatment was masked.

In addition, medication doses in this study did not approach the upper limit of the protocol-recommended dosing, perhaps because of clinicians' unfamiliarity with tranylcypromine or the combination of extended-release venlafaxine and mirtazapine or a propensity to discontinue these less familiar treatments in the face of side effects. The requirement of a washout period for participants receiving tranylcypromine may have had a negative impact on treatment adherence, as participants might have been more inclined to discontinue treatment prematurely because they had to wait to begin the next treatment. There was no significant difference in outcome when those participants who were assigned to receive tranylcypromine but did not actually take it were excluded.

In summary, we found no significant difference in remission rates or symptom improvement between treatment with tranylcypromine and combination treatment with extended-release venlafaxine and mirtazapine for patients with major depressive disorder who had three previous unsuccessful medication trials. However, tranylcypromine was less well tolerated, and many patients assigned to receive tranylcypromine did not achieve an adequate trial of this medication. The low remission rates we observed in both treatment groups suggest that switching antidepressants after failure to achieve remission in three successive antidepressant medication trials provides only modest chances of remission. However, this conclusion must be tempered by the fact that the doses used in this study did not approach the maximum recommended doses as well as by data (8, 9) suggesting that using doses of tranylcypromine higher than the maximum recommended by the FDA may be more effective than standard dosing. Although remission was uncommon with either of the study treatments, clinically satisfactory responses can be attained with both treatments (see the clinical vignette), and either one is worth trying in patients with highly treatment-resistant depression. The lower side effect burden, lack of dietary restrictions, and ease of use of venlafaxine and mirtazapine suggest that this combination may be preferred over tranylcypromine for patients

with highly treatment-resistant depression who have not benefited adequately from several prior treatments.

Further studies are needed to assess earlier use of alternative strategies for treatment of nonresponsive major depression, such as combining antidepressant medications, augmenting antidepressant medications, and using somatic treatments such as ECT (4) or vagus nerve stimulation (39, 40).

Received April 17, 2006; revisions received June 16, 2006; accepted July 7, 2006. From the Department of Psychiatry, University of Texas Southwestern Medical Center; Epidemiology Data Center, Graduate School of Public Health, University of Pittsburgh; New York State Psychiatric Institute, New York City; Department of Psychiatry, Columbia College of Physicians and Surgeons, New York City; Clinical Psychopharmacology Unit, Massachusetts General Hospital, Boston; Department of Psychiatry, University of Pittsburgh School of Medicine; and NIMH, Bethesda, Md. Address correspondence and reprint requests to Dr. McGrath, Depression Evaluation Service, New York State Psychiatric Institute, 1051 Riverside Dr., Unit #51, New York, NY 10032; mcgrath@pi.cpmc.columbia.edu (e-mail).

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Melanie M. Biggs, Ph.D., has received honoraria for consultations to Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck, and Pfizer.

Diane Warden, Ph.D., M.B.A., owns shares of Pfizer stock and has owned shares of Bristol-Myers Squibb stock.

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