Pindolol Augmentation in Depressed Patients Resistant to Selective Serotonin Reuptake Inhibitors: A Double-Blind, Randomized, Controlled Trial

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Background: Studies of pindolol augmentation of antidepressants in major depressive disorder have produced mixed results, and data in treatment-resistant patients are limited. Here, we report on a double-blind, randomized, controlled 6-week study of pindolol augmentation of selective serotonin reuptake inhibitors (SSRIs) in depressed outpatients resistant to SSRI monotherapy.

Method: Forty-two outpatients with DSM-IV major depressive disorder who had an insufficient response to an adequate trial of an SSRI (fluoxetine, paroxetine, or sertraline) were randomly assigned to pindolol, 2.5 mg t.i.d., or sham augmentation, in addition to continued SSRI administration. For separate analysis, the control group underwent a single-blinded switch to pindolol, 2.5 mg t.i.d., from week 4 through week 6, while the active group was continued on pindolol augmentation (hemi-crossover design). Change in Hamilton Rating Scale for Depression (HAM-D) score from baseline to the end of week 3 was the primary outcome measure. Data were gathered from February 1994 to August 1998.

Results: Thirty-eight patients completed at least 1 week on protocol, with 21 and 17 randomly assigned to the pindolol and control groups, respectively. After 3 weeks on protocol, partial response rates (i.e., minimum 50% decrease from baseline in HAM-D score and maximum absolute score of 15) for the pindolol (19% [4/21]) and control (24% [4/17]) groups were comparable. At 3 weeks, the pindolol and control groups demonstrated mean ± SD decreases in HAM-D scores of 6.5 ± 9.8 and 9.7 ± 7.2, respectively. There were no significant differences in antidepressant response or side effects between the 2 groups.

Conclusion: These results do not support the efficacy of pindolol in augmenting clinical response to SSRIs in treatment-resistant depressed patients.

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Advances in pharmacologic treatment of depression have resulted in new agents that, while better tolerated than older medications, are no more effective, with only 40% to 50% of patients achieving remission. Traditionally, hypotheses of the mechanisms of action of antidepressant drugs have focused on the ability of these agents to enhance monoamine (dopamine, norepinephrine, and serotonin) neurotransmission.[1] The most widely used and effective drug treatment combination for treatment-resistant depressed patients is lithium in combination with a variety of antidepressant drugs. The development of this treatment approach was based on the hypothesis that enhancement of serotonin neurotransmission is the key to antidepressant efficacy.[2,3]

Increased knowledge of the mechanisms by which the serotonin neuronal system is regulated may result in novel therapeutic approaches to depression. For example, inhibition of serotonin neuronal activity is mediated by the somatodendritic 5-HT_{1A} autoreceptor. With chronic SSRI administration, the 5-HT_{1A} autoreceptors desensitize, resulting in increased 5-HT neuronal cell firing.[4,5] In theory, therefore, administration of 5-HT_{1A} antagonists may reduce negative feedback and augment the antidepressant effect of SSRIs. Although no selective 5-HT_{1A} receptor antagonists are commercially available, the β-adrenoceptor antagonist pindolol has 5-HT_{1A} receptor–antagonist properties. Previous studies investigating the

utility of pindolol augmentation of antidepressants have yielded mixed results, as have the relatively few double-blind, placebo-controlled trials conducted in treatment-resistant patients.[6,7] In a small (10-subject) 2-week trial, Moreno et al.[8] found no difference between pindolol and placebo augmentation. Perez et al.,[9] in a 10-day trial, also showed no difference between pindolol and placebo augmentation. In a longer (4-week) study, Maes et al.[10] compared pindolol, fluoxetine, and placebo as additions to trazodone; pindolol and fluoxetine augmentation were equally effective and superior to placebo, but the dose of trazodone (100 mg/day) was subtherapeutic. In another double-blind study by the same group, pindolol, mianserin, and placebo were compared for 5 weeks as additions to fluoxetine[11]; pindolol and mianserin augmentation were similarly effective and superior to placebo. In the present study, we examined the effectiveness of the addition of pindolol to an SSRI in treatment-resistant depressed patients, following subjects for as long as 6 weeks in a hemi-crossover design.

METHOD

Selection Criteria

Male and female depressed outpatients between the ages of 18 and 75 years were recruited from community advertisements or referred by the Affective Disorders Clinic of the VA Connecticut Healthcare System (West Haven, Conn.) or the Affective Disorders Research Clinic of the Connecticut Mental Health Center (New Haven, Conn.). Data were gathered from February 1994 to August 1998. Screening procedures included the 25-item Hamilton Rating Scale for Depression (HAM-D),[12] the Structured Clinical Interview for DSM-III-R[13] or DSM-IV[14] (SCID), a physical examination, medical and psychiatric histories, routine blood and urine laboratory analyses, and an electrocardiogram.

Patients who met DSM-IV criteria for a major depressive episode (confirmed by the SCID and a research psychiatrist's clinical assessment) and had not demonstrated a sufficient treatment response to an adequate trial of fluoxetine, paroxetine, or sertraline were enrolled. Efforts were made to include predominantly fluoxetine-nonresponding patients for the purpose of maintaining homogeneity of the sample cohort. Patients had a minimum baseline HAM-D score of 25 and had received at least 20 mg of fluoxetine, 20 mg of paroxetine, or 50 mg of sertraline per day for a minimum of 6 weeks prior to study entry. Additionally, patients did not require neuroleptics or demonstrate psychotic features; did not meet DSM-IV criteria for alcohol or substance abuse or dependence in the preceding 3 months; if female, demonstrated a negative urine human chorionic gonadotropin beta subunit test and were adhering to adequate methods of birth control; had no contraindications to the use of β-blockers such as hypotension, reactive airway disease, or medication-controlled diabetes; and had no significant medical illnesses. Patients with comorbid psychiatric diagnoses were included provided that the onset occurred after the development of major depressive disorder and that the symptoms of major depressive disorder were more prominent, as determined by consensus of 3 research psychiatrists. Subjects with bipolar II disorder were included if the hypomanic episodes were not deemed historically prominent.

Written informed consent was obtained from all patients prior to enrollment. The protocol and consent form were approved by the local institutional review board.

Protocol

Patients were maintained on fluoxetine, paroxetine, or sertraline treatment and randomly assigned in a double-blind manner to receive capsules containing either pindolol, 2.5 mg t.i.d., or placebo (lactose powder, 300 mg per capsule) t.i.d. After 3 weeks, patients originally assigned to sham augmentation were switched in a single-blind manner to pindolol, 2.5 mg t.i.d., for an additional 3 weeks. The patients originally assigned to active pindolol stayed on that regimen for an additional 3 weeks. Thus, the duration of the study was 6 weeks.

During the study period, patients were assessed weekly for mood and side effects by a research assistant and psychiatrist, and weekly orthostatic vital signs were measured. Weekly ratings included the 25-item HAM-D; a side effect checklist (SECL)[15]; Beck Depression Inventory (BDI),[16] also performed on days 4, 11, 25, and 32; and the Hamilton Rating Scale for Anxiety (HAM-A).[17] The SECL is a questionnaire assessing 23 potential side effects and their severity over the previous week, with ordinal scores from 0 ("none at all") to 3 ("severe"). Items assessed include dry mouth, trouble concentrating, headache, constipation, nausea or vomiting, poor memory, difficulty sitting still, irregular or pounding heartbeat, drowsiness, blurred vision, increased appetite, decreased appetite, difficulty starting urination, frequent need to urinate, tremors or shakiness, nightmares, diarrhea, rash, ringing in the ears, sweating, fainting or light-headedness, poor coordination, and muscle stiffness.

Statistical Analysis

Intergroup differences in demographic characteristics were assessed by 2-tailed Fisher exact or unpaired t tests. The primary hypothesis tested was that, in patients with major depressive disorder who had failed to respond sufficiently to an adequate trial of fluoxetine, paroxetine, or sertraline monotherapy, addition of pindolol for 3 weeks would reduce depressive symptoms to a greater extent than continuation of the SSRI alone. The corollary hypothesis was that this response would be sustained over the 6-week trial period. Change in HAM-D score from baseline to the end of week 3 was the primary outcome mea-

sure. Continuous efficacy variables (HAM-D, BDI, and HAM-A) were analyzed with repeated-measures analysis of variance (ANOVA) for weeks 0 through 3 and weeks 4 through 6. Partial response (primary binomial variable) and full response were analyzed with the Fisher exact test. Partial response was defined as a minimum HAM-D score reduction of 50% from the baseline week and maximum endpoint HAM-D score of 15, and full response was defined as a minimum HAM-D score reduction of 50% from the baseline week and maximum endpoint HAM-D score of 8. Analyses were repeated on an intent-to-treat basis (i.e., last observation carried forward).

Secondary outcome measures included the 23 assessed side effects from the SECL, sitting and standing blood pressures, and weight, obtained through the end of week 6. Repeated-measures ANOVAs were used to test for significance.

Two-tailed Fisher exact tests were performed to compare intergroup differences in the percentages of patients demonstrating at least partial response and full response, performed serially for weeks 1 through 6. For the Fisher exact tests, significance levels for multiple comparisons were purposely reported at the uncorrected $p < .05$ level to favor the detection of potentially significant results.

RESULTS

Patient Attributes and Disposition

Forty-two subjects received at least 1 dose of study medication (pindolol or sham augmentation). One patient in the control group was excluded from the analyses because ratings had not been obtained during medication treatment, and another patient in the control group was excluded due to a protocol violation resulting in termination in week 2. One patient each in the pindolol and control groups was terminated in week 1 due to side effects and was excluded. Demographic attributes of the 38 subjects completing at least 1 week of the protocol are listed in Table 1. In the active group, 14 subjects were taking daily doses of fluoxetine, 20 mg, and 1 each were taking fluoxetine, 30, 40, and 60 mg; 2 were taking paroxetine, 20 mg; and 1 each were taking sertraline, 150 and 200 mg. In the control group, 10 subjects were taking daily doses of fluoxetine, 20 mg, and 1 each were taking fluoxetine, 40 and 60 mg; 2 each were taking paroxetine, 20 and 40 mg; and 1 was taking sertraline, 50 mg.

In the pindolol group, 20 (95%) of 21 patients completed 6 weeks of the study, as did 14 (82%) of the 17 patients in the control group (Fisher exact test, $p = .31$). The patient in the pindolol group was terminated from the study after week 3 due to nonresponse. Reasons for noncompletion in the control group included poor response by 2 patients (terminated after weeks 4 and 5) and protocol violation (1 patient terminated after week 3). One patient in the pindolol group was terminated from the study due to a positive pregnancy test result after week 3; she elected to continue with open-label treatment after consulting with her private obstetrician, completing ratings through week 6 in an open-label manner and achieving full response. Her ratings were included for the most conservative analysis.[18]

Baseline HAM-A ratings were not obtained for 3 subjects, and a baseline BDI rating was not obtained for 1 subject; these subjects were not included in the respective analyses.

Table 1. Demographic Data of 38 Depressed Patients Receiving SSRI Treatment

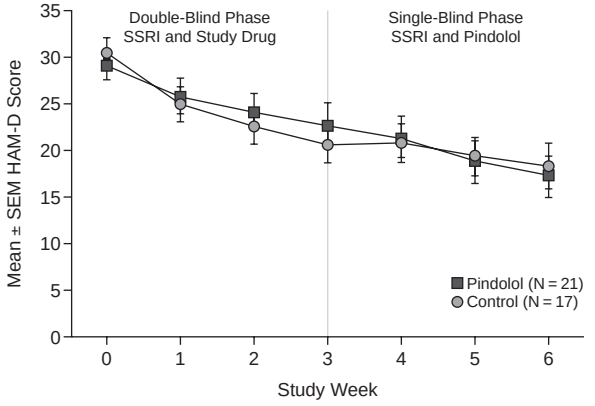
Characteristic	Pindolol Group (N = 21)	Control Group (N = 17)	p
Age, mean ± SD, y	49 ± 13	43 ± 11	.15
Weight, mean ± SD, lb	153 ± 31	156 ± 35	.85
Gender, male:female, N	5:16	5:12	.73
Race, black:white, N	0:21	0:17	1.00
Veterans, N	4	2	.67
Antidepressant, N			
Fluoxetine	17	12	.70
Paroxetine	2	4	.38
Sertraline	2	1	1.00
Mood disorder diagnosis, N			
Major depressive disorder	21	16	.45
Bipolar I disorder, most recent episode depressed	0	0	1.00
Bipolar II disorder, most recent episode depressed	0	1	.45
Chronic specifier	6	7	.50
Melancholic specifier	1	2	.58
Atypical specifier	3	0	.24
Comorbid diagnosis			
Panic disorder	2	0	.49
Social phobia	0	1	.45
Obsessive-compulsive disorder	0	0	1.00
Duration of current depressive episode, mean ± SD, y	3.4 ± 6.5	3.4 ± 3.6	1.00
Duration of current depressive episode, median, y	2.0	2.0	
Psychiatric history, N			
No previous medication treatment	2	0	.49
No previous depressive episodes	1	0	1.00
History of substance abuse or dependence	11	5	.20
History of suicide attempt	3	7	.08
Previous psychiatric hospitalizations	5	2	.43
First-degree relative with suspected history of major depressive disorder	12	9	1.00
Baseline ratings, mean ± SD			
HAM-D	29 ± 7	30 ± 7	.63
HAM-D item 1 (mood)	2.7 ± 0.7	2.4 ± 0.6	.44
Beck Depression Inventory	24 ± 11	26 ± 9	.61

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

Efficacy

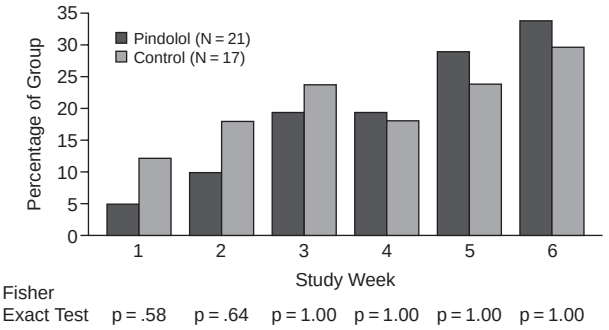
Mean HAM-D scores for pindolol and control groups through the first 3 study weeks are depicted in Figure 1.

Figure 1. HAM-D Scores for Pindolol and Control Groups (all subjects), Weeks 0–6



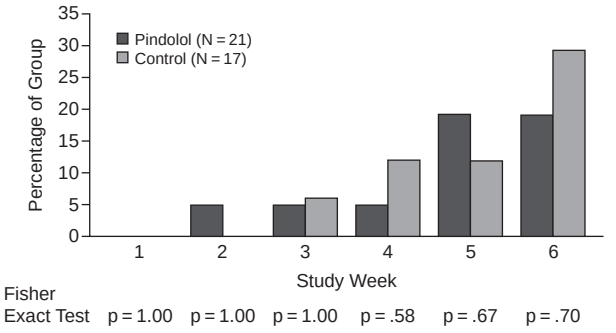
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

Figure 2. Percentage of Subjects Demonstrating at Least Partial Response (≥ 50% reduction on HAM-D), Weeks 1–6



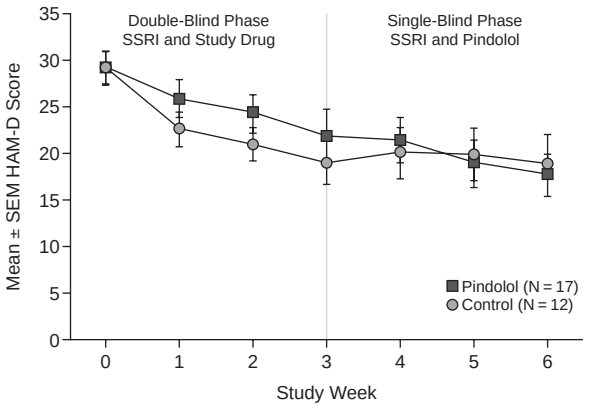
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 3. Percentage of Subjects Demonstrating Full Response (HAM-D score ≤ 8 and ≥ 50% score reduction), Weeks 1–6



Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 4. HAM-D Scores for Pindolol and Control Groups (fluoxetine subjects only), Weeks 0–6



Abbreviations: HAM-D = Hamilton Rating Scale for Depression, SSRI = selective serotonin reuptake inhibitor.

As with other efficacy ratings, there were no significant intergroup differences, as analyzed by intent-to-treat repeated-measures ANOVAs. Treatment group effects were as follows: HAM-D, $F = 0.14$, $df = 1,36$; $p = .71$; HAM-D core mood item, $F = 2.80$, $df = 1,36$; $p = .10$; BDI, $F = 0.33$, $df = 1,35$; $p = .57$; HAM-A, $F = 1.21$, $df = 1, 33$; $p = .28$. Group-by-time effects were as follows: HAM-D, $F = 0.76$, $df = 3,108$; $p = .52$; HAM-D core mood item, $F = 0.81$, $df = 3,108$; $p = .49$; BDI, $F = 0.03$, $df = 3,105$; $p = .99$; HAM-A, $F = 0.47$, $df = 3,99$; $p = .71$. Main effects of time were as follows: HAM-D, $F = 18.7$, $df = 3,108$; $p < .01$; HAM-D core mood item, $F = 10.0$, $df = 3,108$; $p < .01$; BDI, $F = 9.14$, $df = 3,105$; $p < .01$; HAM-A, $F = 12.90$, $df = 3,99$; $p < .01$.

Mean HAM-D scores through the last 3 weeks, in which both groups received pindolol in addition to SSRI, are depicted in Figure 1. This allowed examination of the pindolol group over 6 weeks of active treatment, while permitting the control group to receive pindolol for 3 weeks as well. Similar to the first 3 weeks, there were no significant intergroup differences in the efficacy ratings by intent-to-treat repeated-measures ANOVAs. Treatment group effects were as follows: HAM-D, $F = 0.01$, $df = 1,36$; $p = .93$; HAM-D core mood item, $F = 0.46$, $df = 1,36$; $p = .50$; BDI, $F = 1.09$, $df = 1,35$; $p = .30$; HAM-A, $F = 0.51$, $df = 1,33$; $p = .48$. Group-by-time effects were as follows: HAM-D, $F = 0.80$, $df = 3,108$; $p = .50$; HAM-D core mood item, $F = 0.76$, $df = 3,108$; $p = .52$; BDI, $F = 1.07$, $df = 3,105$; $p = .37$; HAM-A, $F = 0.17$, $df = 3,99$; $p = .92$. Main effects of time were as follows: HAM-D, $F = 5.56$, $df = 3,108$; $p < .01$; HAM-D core mood item, $F = 2.03$, $df = 3,108$; $p = .12$; BDI, $F = 0.91$, $df = 3,105$; $p = .44$; HAM-A, $F = 2.98$, $df = 3,99$; $p = .04$.

As shown in Figures 2 and 3, the percentages of subjects demonstrating at least partial response and full re-

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sponse (intent-to-treat) were similar for each of the study weeks (Fisher exact test, $p > .05$ in all cases).

HAM-D scores were also examined for fluoxetine patients alone, since they were the largest group. Mean HAM-D scores for patients treated with fluoxetine in the first 3 weeks and last 3 weeks are shown in Figure 4. Results were similar to the scores for all patients, with no significant intergroup differences by intent-to-treat repeated-measures ANOVAs. Treatment group effects were as follows: weeks 0 through 3, $F = 0.94$, $df = 1,27$; $p = .34$; weeks 3 through 6, $F = 0.03$, $df = 1,27$; $p = .86$. Group-by-time effects were as follows: weeks 0 through 3, $F = 0.62$, $df = 3,81$; $p = .61$; weeks 3 through 6, $F = 1.09$, $df = 3,81$; $p = .36$. Main effects of time were as follows: weeks 0 through 3, $F = 13.8$; $df = 3,81$; $p < .01$; weeks 3 through 6, $F = 1.54$, $df = 3,81$; $p = .21$.

Adverse Events

Adverse events were determined through clinician interview and weekly completion of the SECL. Analysis of all 23 items on the SECL with intent-to-treat repeated-measures ANOVAs revealed no statistically significant group or group-by-time effects with Bonferroni correction.

DISCUSSION

The addition of pindolol to an SSRI in treatment-resistant depressed outpatients did not result in a difference in response over the course of 3 weeks compared with that of a similar group who were continued on SSRI treatment without pindolol. Furthermore, the addition of pindolol to the SSRI in the latter group resulted in a mean ± SD decrease of 2.5 ± 9.2 in HAM-D scores in the last 3 weeks, not a clinically significant improvement. There was no difference in response between the 2 groups at the end of 6 weeks.

These results are consistent with some,[8,9] but not all,[11] reports from other double-blind controlled trials. The failure of this study to demonstrate the efficacy of pindolol for SSRI augmentation in treatment-resistant depressed patients may be explained by type II error, dosing issues, or confounding patient characteristics.

A post hoc 1-sided power analysis based on observed variances for decrease in HAM-D score from week 0 to week 3 (pindolol group: SD = 9.8, N = 21; control group: SD = 7.2, N = 17) suggested that there was an 81% chance of detecting a minimum 7-point HAM-D score difference favoring the pindolol-treated group, assuming an alpha level of .05. Our study was therefore adequately powered to establish the efficacy of pindolol in our patient population by detecting a clinically significant change in HAM-D score. The p value of .52 observed for group-by-time effect was not significant, and the mean ± SD decrease in HAM-D score from week 0 to week 3 was greater for the control group (9.7 ± 7.2) than the pindolol group (6.5 ± 9.8), which further supports that the absence of significant group-by-time interaction was not due to lack of power.

The mean decreases in sitting pulse of 5.6 ± 11.0 beats per minute and in standing pulse of 7.0 ± 9.8 beats per minute observed in the pindolol group after 1 week indicate that the blood pindolol levels achieved were high enough to attain β-adrenergic activity, consistent with previous results from our group.[19] However, more recent positron emission tomography findings suggest that the 7.5-mg/day dose of pindolol used in this and other studies results in occupancy of 5-HT_{1A} receptors that is low and highly variable between subjects,[7] which could explain the observed lack of efficacy of pindolol augmentation.

As discussed elsewhere,[19] differences in patient characteristics of our sample compared with those reported in other studies may have confounded our results. All of the control patients and all but 1 of the pindolol patients had recurrent depression. In addition, 7 of the 17 control patients and 6 of the 21 pindolol patients met criteria for the chronic specifier of major depressive episode, with duration of current episode of 3.4 ± 3.6 years in the control group and 3.4 ± 6.5 years in the pindolol group.

Overall, our results do not support the routine use of pindolol to augment clinical response to SSRIs in treatment-resistant depressed patients. It is possible, however, that the strategy of 5-HT_{1A} antagonism for SSRI augmentation has not been fully exploited. The pindolol model, although supported by preclinical data showing increased 5-HT levels when pindolol is combined with SSRIs, may be limited by partial agonist actions of pindolol at the 5-HT_{1A} autoreceptor.[20] Alternatively, 5-HT_{1A} antagonism may be useful for hastening clinical response to SSRIs, but not for augmentation in treatment-resistant depressed patients. Selective antagonists of 5-HT_{1A} receptors, when available, may prove to be more efficacious.

Drug names: fluoxetine (Prozac and others), paroxetine (Paxil and others), pindolol (Visken and others), sertraline (Zoloft), trazodone (Desyrel and others).

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