Effect of Pindolol in Hastening Response to Fluoxetine in the Treatment of Major Depression: A Double-Blind, Placebo-Controlled Trial

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Objective: *In two preliminary studies, pindolol produced robust results in hastening clinical response to antidepressant drugs in depressed patients. Validity of those pilot studies was limited by use of an open-label, unblinded study design, and so the authors conducted a double-blind, placebo-controlled trial to assess the effectiveness of pindolol in hastening response to fluoxetine.* *Method:* *Drug-free outpatients with major depression were concurrently treated with fluoxetine (20 mg/day) and either placebo or pindolol (5.0 mg b.i.d. or 2.5 mg t.i.d.), for 6 weeks, in a randomized, double-blind manner. After 6 weeks, all patients received fluoxetine and placebo and were followed for 3 further weeks in a single-blind manner.* *Results:* *Forty-three patients completed at least 1 week of the protocol. Rates of partial remission after 2 weeks of treatment with fluoxetine and either pindolol or placebo were 17% (four of 23 patients) and 20% (four of 20 patients), respectively. At study completion, 65% of the patients (N=28) demonstrated at least a partial remission, and there was no difference between treatment groups. The pindolol group, but not the placebo group, demonstrated significant reductions in blood pressure and pulse rate. The average time to remission and the rates of attrition, overall response, and side effects were similar in the two groups.* *Conclusions:* *These findings do not support the efficacy of pindolol in hastening clinical response in patients treated with fluoxetine.*

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Despite advances in the treatment of depressive illness, a major limitation is that all available antidepressant drugs take at least 2 to 3 weeks to produce substantial clinical effects. This time lag parallels monoaminergic changes, demonstrated in preclinical studies, that are thought to underlie the mechanisms of antidepressant action (1, 2). Recent preclinical electrophysiologic findings on the role of the serotonergic system in antidepressant action have suggested novel strategies for hastening the response to antidepressant treatment.

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Electrophysiologic studies have consistently shown that chronic antidepressant dosing enhances serotonin (5-HT) neurotransmission, by facilitating 5-HT release or increasing postsynaptic responsivity (2). The net increase in 5-HT neurotransmission is much more robust after the chronic administration of monoamine oxidase inhibitors (MAOIs) or selective serotonin reuptake inhibitors (SSRIs) than after use of noradrenergic reuptake inhibitors (2). Chronic administration of SSRIs and MAOIs results in a desensitization of the somatodendritic 5-HT_{1A} autoreceptor (3–5). This desensitization leads to increased 5-HT neurotransmission, which in turn may be responsible for clinical response.

Several electrophysiologic studies based on this model have suggested a strategy for effecting a rapid and robust enhancement of 5-HT function during SSRI administration. Antagonism of the 5-HT_{1A} autoreceptors in rodents with concomitant dosing of SSRIs leads to immediate, sustained increases in extracellular 5-HT concentrations in cortex or hippocampus (6, 7). Dreshfield et al. (8) recently demonstrated that concurrent administration of systemic pindolol and fluoxetine rapidly increases hypothalamic 5-HT content to two or three times the level achieved with fluoxetine alone.

The aforementioned preclinical data, extrapolated clinically, imply that concurrent administration of

SSRIs and 5-HT_{1A} antagonists could accelerate the onset of enhanced 5-HT activity and, hence, potentially result in a rapid improvement of depressive symptoms. Currently there are no selective antagonists of 5-HT_{1A} receptors approved for use in humans. However, some β-adrenergic blockers, such as pindolol, have a high affinity for 5-HT_{1A} receptors (9) and antagonize the presynaptic effects produced by 5-HT_{1A} agonists (9–11).

In open-label pilot investigations (12, 13) the effects of pindolol were examined in depressed patients treated with SSRIs or MAOIs. Five of seven (12) and seven of nine (13) depressed patients who were treated with a combination of paroxetine (20 mg/day) and pindolol (2.5 mg t.i.d.) experienced clinical remissions within 1 week, defined as a reduction of at least 50% in the score on the Hamilton Depression Rating Scale (14).

The preceding clinical results are generally consistent with the hypothesis that the enhancement of 5-HT neuronal function is an important component of the mechanism of action of antidepressant drugs. The findings are provocative in that they suggest that a pindolol-antidepressant combination may be a rapidly acting antidepressant treatment and may be helpful for treatment-resistant patients. However, these studies were not placebo-controlled and involved small numbers of subjects. Therefore, we examined the effectiveness of a pindolol-fluoxetine combination in depression by using a placebo-controlled, double-blind design with a larger group of depressed patients.

METHOD

Selection Criteria

Depressed outpatients were either recruited from advertisements in local newspapers or referred by the Affective Disorders Clinic of the West Haven Veterans Administration Medical Center. The screened patients included depressed men and women between the ages of 18 and 70 years who met the DSM-IV criteria for major depression. Screening procedures included administration of the 25-item Hamilton Depression Rating Scale, the Structured Clinical Interview for DSM-III-R (SCID) (15), a physical examination, medical and psychiatric histories, routine blood and urine laboratory analyses, and an electrocardiogram.

Eligible patients 1) met the DSM-IV criteria for major depression, as determined through clinical assessment by a research psychiatrist and confirmed by consensus opinion of three program psychiatrists or the SCID, depending on patient availability; 2) had a screening score of at least 18 on the 25-item Hamilton depression scale; 3) had no history of alcohol or substance abuse in the month preceding initiation of medication; 4) were not pregnant, as determined by a test of serum human chorionic gonadotropin (β-HCG) the week before initiation of medication when indicated, and were adhering to adequate methods of birth control; 5) were free of contraindications to the use of β blockers, such as hypotension, reactive airway disease, or medication-controlled diabetes; and 6) did not have seizure disorders, impaired hepatic function, impaired renal function, untreated thyroid disease, cardiac conduction abnormalities, congestive heart failure, history of myocardial infarction, or other illnesses determined from routine workup deemed to necessitate acute medical treatment. Patients were excluded if they had comorbid DSM-IV psychotic disorders. Patients with other comorbid psychiatric diagnoses were included provided that the onset occurred after the development of the major depression (for axis I diagnoses) and that the symptoms of major depression were more prominent (for axis I and II diagnoses), as determined by consensus of three research psychiatrists.

After complete discussion of the study, written informed consent was obtained. The protocol and consent forms were approved by the institutional review board of the West Haven Veterans Administration Medical Center.

Protocol

After the psychiatric and medical screening just described, qualifying depressed patients were randomly assigned to treatment with fluoxetine (20 mg/day) and capsules containing either pindolol or placebo (lactose powder, 300 mg per capsule). Dosing for the first nine patients was 5.0 mg of pindolol twice daily (four subjects) or placebo twice daily (five subjects). For the subsequent 35 patients the dosing was altered to 2.5 mg of pindolol thrice daily or placebo thrice daily, in order to coincide with the dosing strategy of the pilot studies (12, 13). After 6 weeks on this double-blind regimen, the patients receiving fluoxetine and pindolol were blindly switched to fluoxetine and placebo, for a duration of 3 weeks. The patients initially assigned to fluoxetine and placebo were kept on this regimen for a total of 9 weeks. Hence, the first 6 weeks of the study were double-blind, and the following 3 weeks were single-blind to allow for evaluation of pindolol discontinuation.

During the 9-week study period, the patients met weekly with a research assistant and psychiatrist for the assessments of mood and side effects. Limited, brief supportive contact was provided by the research psychiatrist. Weekly schedules and self-administered questionnaires included the 25-item Hamilton depression scale, a side effect checklist (16), the Beck Depression Inventory (17), and the Hamilton Anxiety Rating Scale (18). The side effect checklist is a questionnaire assessing 23 potential side effects over the previous week, with ordinal scores from 0 ("none at all") to 3 ("severe"). The assessed items include headache, constipation, poor memory, nausea or vomiting, drowsiness, blurred vision, increased appetite, difficulty starting urination, trouble concentrating, nightmares, difficulty sitting still, irregular or pounding heartbeat, diarrhea, frequent need to urinate, dry mouth, decreased appetite, tremors or shakiness, rash, ringing in the ears, sweating, faintness or lightheadedness, poor coordination, and muscle stiffness. Additionally, research assistants measured orthostatic vital signs weekly.

Statistical Analysis

Intergroup differences in demographic characteristics were assessed by means of two-tailed Fisher's exact or Student's t tests.

The primary hypothesis tested was that the pindolol-fluoxetine combination would result in a more rapid improvement in depressive symptoms than would the placebo-fluoxetine combination. Primary efficacy variables were analyzed both as continuous variables (i.e., scores on the Hamilton depression scale, Beck Depression Inventory, and Hamilton anxiety scale) and as discrete variables (i.e., full, partial, and no response). Full response was defined as a maximum posttreatment Hamilton depression score of 10, a minimum reduction in Hamilton depression score of 50% from the baseline week, and agreement among the treaters that further medication changes were not indicated. Partial response was defined as a maximum posttreatment Hamilton depression score of 15 and a minimum reduction in Hamilton depression score of 50% from the baseline week.

For the continuous primary efficacy variables, analyses of variance (ANOVAs) were performed with repeated measures (weeks 0 through 6) on data for all of the patients entering the protocol (i.e., last observation carried forward), and endpoint analyses of patients completing at least 6 weeks of the protocol were also conducted. When time effects were significant, follow-up Student-Newman-Keuls tests were applied to determine significant divergence from baseline scores. To determine group differences in side effects or vital sign changes, repeated-measure ANOVAs (for weeks 0 through 6) were performed for each of the side effects on the checklist, diastolic blood pressure, systolic blood pressure, and heart rate.

The effect of treatment group on time to remission in the eventual responders was determined by means of a survival analysis. Time to

remission was defined as the number of weeks of combined treatment before the patient met the criteria for partial remission. Patients who did not meet those criteria during the study were not included in this analysis (19). The two-tailed Fisher's exact test was performed serially, for weeks 1 through 9, to compare the intergroup differences in proportion of patients demonstrating responses (partial and full). For the Fisher's exact tests, significance levels for multiple comparisons were purposely reported at the uncorrected 0.05 level to favor detection of potentially significant results.

TABLE 1. Demographic and Clinical Characteristics of Patients With Major Depression Who Received Fluoxetine Plus Either Pindolol or Placebo

Characteristic	Pindolol Group (N=23)		Placebo Group (N=20)		p[a]
	Mean	*SD*	*Mean*	*SD*	
Continuous variables					
Age (years)	43.0	11.3	40.7	9.1	0.48
Weight (kg)	83.8	21.3	82.6	26.9	0.84
Duration of current depressive episode (years)[b]	5.6	6.8	5.7	8.0	0.98
Baseline symptom ratings					
Hamilton Depression Rating Scale score	31.7	5.7	31.1	7.7	0.76
Beck Depression Inventory score	28.4	9.8	28.1	11.0	0.93
Hamilton Anxiety Rating Scale score	16.6	4.1	16.1	5.0	0.71
	N		*N*		
Categorical variables					
Gender					1.00
Male	13		11		
Female	10		9		
Race					1.00
Black	1		1		
White	22		20		
Military status					0.53
Veteran	8		5		
Nonveteran	15		15		
Diagnosis					
Unipolar depression	21		20		1.00
Bipolar depression	2[c]		0		0.49
Chronic subtype	12		10		1.00
Melancholic subtype	1		2		0.60
Atypical subtype	4		1		0.35
Comorbid panic disorder	4		2		0.67
Comorbid social phobia	0		1		0.47
Comorbid obsessive-compulsive disorder	1		0		1.00
Past psychiatric history					
Previous psychiatric hospitalizations	2		0		0.49
No previous treatment	9		14		0.07
History of substance abuse or dependence	11		10		1.00
History of suicide attempts	3		3		1.00
First-degree relative with suspected history of major depressive disorder[d]	11		9		1.00

[a]The continuous variables were analyzed by means of two-tailed Student's t tests. The categorical variables were analyzed by means of two-tailed Fisher's exact tests.
[b]The median duration of the current episode was 3.8 years for the pindolol group and 4.8 years for the placebo group.
[c]One subject had bipolar I disorder, and the other had bipolar II disorder.
[d]As determined from clinical interview.

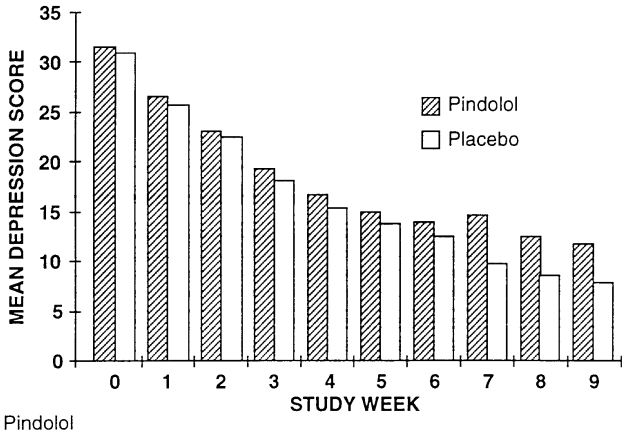
RESULTS

Patient Characteristics and Disposition

Table 1 lists demographic attributes of all subjects completing at least 1 week of the protocol. Nonstudy medications that were started a minimum of 3 weeks before the study and were not deemed as contributing to the onset of depression included benzodiazepines (placebo, N=2; pindolol, N=1), atenolol for hypertension (pindolol, N=1), lovastatin for hypercholesterolemia (pindolol, N=1), terazosin for hypertension (placebo, N=1), and estrogen replacement (placebo, N=1). Axis one disorders other than major depression were deemed secondary, by consensus opinion of three research psychiatrists. Among the patients with histories of substance abuse, the duration of remission ranged from 1 month to 20 years (median, 5 years) for the pindolol group and from 4 months to 20 years (median, 8 years) for the placebo group. Previous fluoxetine trials were reported by eight and three subjects from the pindolol and placebo groups, respectively (Fisher's exact test, p=0.18). In the pindolol group, six subjects reported previously responding to fluoxetine trials lasting longer than 4 weeks, whereas one patient did not tolerate a trial and another reported no response after a 3-week trial. Two other patients from this group reported previous trials of other SSRIs; both reported responses. In the placebo group, three patients reported responding to previous fluoxetine trials; one other patient reported responding to a trial of paroxetine, and another reported not tolerating a trial of sertraline.

Forty-four patients enrolled in the study and received at least one dose of study medication. One patient was excluded from the analyses because ratings had not been obtained during medication administration. Of the 23 patients who received pindolol, 20 (87%) completed at least 6 weeks of the study, as did 15 (75%) of the 20 patients in the placebo group. Reasons for noncompletion for the placebo group included protocol violations by three patients (after weeks 2, 4, and 5) and an allergic skin reaction (week 5) and intervening illness (manifesting labile hypertension at week 2, which persisted after discontinuation of medications) for one patient each. Reasons for noncompletion for the pindolol group included protocol violations for two patients (after week 3) and an adverse reaction for another (edema and hair loss after week 2). The rates of noncompletion were similar in the two groups (Fisher's exact test, p=0.44).

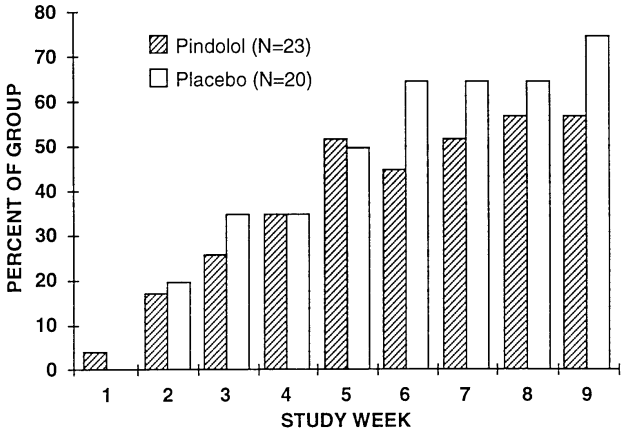
FIGURE 1. Mean Scores on the Hamilton Depression Rating Scale of Patients With Major Depression Who Received Fluoxetine Plus Either Pindolol or Placebo[a]



Pindolol Group N =	23	23	23	22	20	20	20	18	18	17
Placebo Group N =	20	20	20	18	18	16	15	15	15	15

[a]Intergroup differences were not significant. All intragroup differences between baseline and subsequent weeks were significant (Student-Newman-Keuls Test, $p<0.05$).

FIGURE 2. Occurrence of at Least Partial Remission[a] in Patients With Major Depression Who Received Fluoxetine Plus Either Pindolol or Placebo



[a]Partial remission was defined as a maximum Hamilton Depression Rating Scale score of 15 and a minimum reduction in score from baseline of 50%.

Efficacy

As depicted in figure 1, the mean Hamilton depression scores by week for the two treatment groups were similar. Ratings of clinical improvement during the initial 6 weeks of medication were similar for all outcome measures assessed (intent-to-treat comparisons), with no treatment group effects—Hamilton depression scale: $F=0.22$, df=1, 41, $p=0.64$; Beck Depression Inventory: $F=0.70$, df=1, 41, $p=0.41$; Hamilton anxiety scale: $F=0.46$, df=1, 41, $p=0.50$. Similarly, no group-by-time interactions were significant—Hamilton depression scale: $F=0.06$, df=6, 246, $p=1.00$; Beck Depression Inventory: $F=0.43$, df=6, 246, $p=0.86$; Hamilton anxiety scale: $F=0.50$, df=6, 246, $p=0.81$. Main effects of time were highly significant—Hamilton depression scale: $F=77.81$, df=6, 246, $p=0.0001$; Beck Depression Inventory: $F=37.88$, df=6, 246, $p=0.0001$; Hamilton anxiety scale: $F=52.92$, df=6, 246, $p=0.0001$. Analyses that included only subjects who completed at least 6 weeks of the protocol yielded similar results. For the Hamilton depression scale, significant changes from baseline were noted in both treatment groups by week 1 (Student-Newman-Keuls tests, $p<0.05$).

As depicted in figure 2, the proportions of patients from the two treatment groups who demonstrated partial or greater remissions were similar for all study weeks. At the end of the study, partial remission had been achieved by 28 (65%) of the 43 total patients, 13 (57%) of the 23 patients in the pindolol group and 15 (75%) of the 20 in the placebo group (Fisher's exact test, $p=0.34$). Full remission by study completion was present in 23 (53%) of the total patients, 11 (48%) of the patients who received pindolol and 12 (60%) of the patients who received placebo (Fisher's exact test, $p=0.54$).

The effect of discontinuing pindolol at the end of week 6 did not have significant group effects on independent clinical measures, except for the Beck Depression Inventory, among completers of the full 9 weeks of the study—Hamilton depression scale: $F=3.73$, df=1, 30, $p=0.06$; Beck Depression Inventory: $F=4.25$, df=1, 30, $p=0.05$; Hamilton anxiety scale: $F=0.94$, df=1, 30, $p=0.34$. Group-by-time interactions were nonsignificant—Hamilton depression scale: $F=0.24$, df=2, 60, $p=0.78$; Beck Depression Inventory: $F=0.43$, df=2, 54, $p=0.65$; Hamilton anxiety scale: $F=0.80$, df=2, 60, $p=0.80$. Changes in Hamilton depression score between week 6 and each of weeks 7, 8, and 9 were, for the pindolol and placebo groups, respectively, –1.2 versus 2.8, 0.18 versus 3.33, and 0.94 versus 4.53. Changes in scores on the Beck Depression Inventory during these periods were –1.7 versus 2.0, 0.59 versus 3.0, and 0.53 versus 4.41, respectively, for the pindolol and placebo groups. Notably, three patients in the pindolol group demonstrated clinical deterioration during week 7, with increases in Hamilton depression score of 9, 17, and 18 points, respectively.

Among the eventual responders, time to remission did not differ between the two groups (pindolol: mean=4.1 weeks, SD=2.0; placebo: mean=4.4 weeks, SD=2.2) ($F=0.13$, df=1, 28, $p=0.73$). A survival analysis of time to full remission (log-rank chi-square test; $\chi^2=0.21$, df=1, $p=0.64$) and time to partial remission ($\chi^2=0.07$, df=1, $p=0.80$) did not show significant differences.

Side Effects

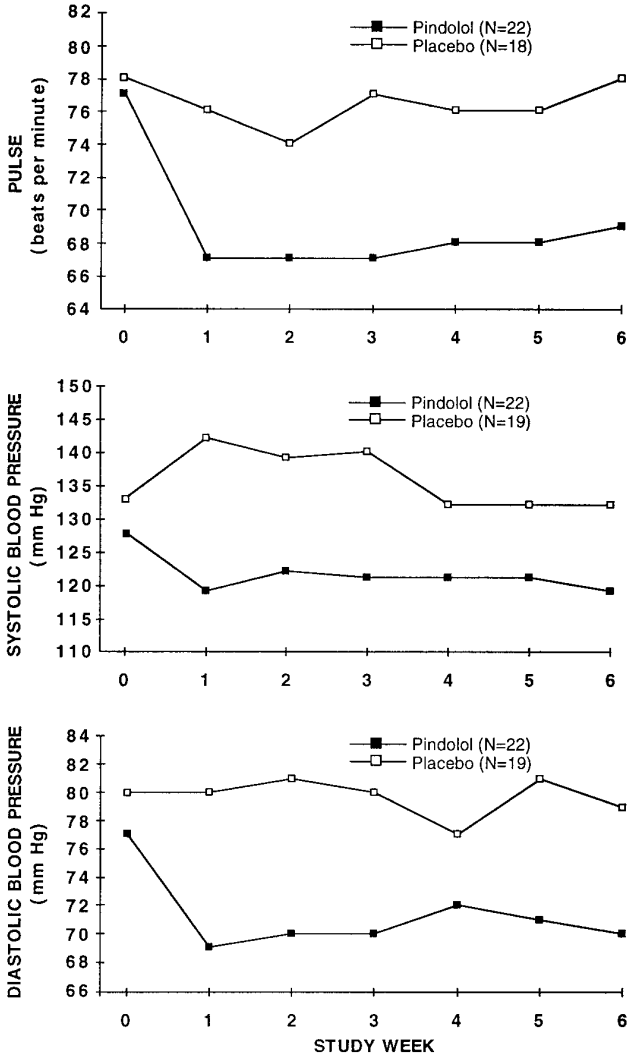
Adverse experiences were determined through the clinician interviews and completion of the side effect checklist. Adverse effects precipitated study discontinu-

ation for two subjects: one patient in the pindolol group developed transient edema and hair loss after 2 weeks in the study protocol, and one patient in the placebo group developed an allergic skin reaction requiring oral prednisone after 5 weeks in the protocol. Other side effects were mild to moderate and included, in descending order of frequency, headaches (44%), nausea (33%), diarrhea (28%), dry mouth (26%), faintness or lightheadedness (23%), sweating (12%), tremors or shakiness (7%), ringing in the ears (7%), blurred vision (5%), and bruxism (5%). No differences between treatment groups were significant (Fisher's exact test, $p>0.30$ in all cases). From the pindolol group, one patient reported a metallic taste during the 6 weeks of pindolol administration, and another reported increased frequency of yawning. Rates of sexual side effects were not reliably determined.

Repeated ANOVAs for each of the items in the side effect checklist revealed no significant group or group-by-week effects with Bonferroni correction. Without correction for multiple comparisons, group effects were found for faintness/lightheadedness (the pindolol group scored higher than the placebo group, but the difference was accounted for by baseline differences; $F=8.45$, $df=1, 40$, $p=0.006$) and for skin rash (higher scores in the placebo group; $F=3.99$, $df=1, 40$, $p=0.05$); a group-by-time interaction was found for constipation ($F=2.88$, $df=6, 240$, $p=0.01$).

As depicted in figure 3, the pindolol treatment group showed significant decreases in vital signs, whereas the placebo group did not. Sitting systolic blood pressure and heart rate both demonstrated significant group, time, and group-by-time effects. Sitting diastolic blood pressure demonstrated a significant group effect.

FIGURE 3. Vital Signs of Patients With Major Depression Who Received Fluoxetine Plus Either Pindolol or Placebo[a]



[a]Depicted vital signs were measured with the patients sitting. There were significant group differences in systolic blood pressure ($F=7.07$, $df=1, 39$, $p=0.01$), diastolic blood pressure ($F=6.93$, $df=1, 39$, $p=0.01$), and pulse ($F=5.49$, $df=1, 38$, $p=0.02$). For systolic blood pressure, there were also significant time ($F=2.21$, $df=6, 234$, $p=0.04$) and group-by-time ($F=3.01$, $df=6, 234$, $p=0.008$) effects. For pulse, there were also significant time ($F=6.01$, $df=6, 228$, $p=0.0001$) and group-by-time ($F=2.45$, $df=6, 228$, $p=0.03$) effects.

DISCUSSION

The drug-free depressed patients who began treatment with fluoxetine and pindolol concurrently did not experience a more rapid response than did similar patients who concurrently began treatment with fluoxetine and placebo. Furthermore, the rates of response did not differ between groups.

These results are not in accord with the findings from two preliminary studies (12, 13) examining the use of pindolol (2.5 mg t.i.d orally) with paroxetine (20 mg/day orally). In those two studies a total of 12 of 16 patients demonstrated decreases in Hamilton depression scores of at least 50% by the end of the first week of treatment. Factors potentially accounting for this discrepancy include inadequate study power and differences in study methods, patient characteristics, and SSRIs.

A power analysis, based on the collected data (pindolol: SD=8.56, N=23; placebo: SD=7.66, N=20), indicated that there was a 77% chance of detecting a group difference in Hamilton depression score of as much as 6 points by week 2 and a 95% chance of detecting as much as an 8-point group difference by week 2. This analysis suggests that the power of the study was adequate for determining clinically significant group differences.

The preliminary trials used an open-label design, lacking placebo control groups. Such a method is susceptible to bias in both patient reporting and observer assessment. Nevertheless, the robust preliminary results found by two groups exceeded the expected bias attributable to open-label design.

Another source of discordant results may be putative differences in study groups. The five responders described by Artigas et al. (12) included four women and

two melancholic patients, and the subjects' baseline Hamilton depression scores ranged from 21 to 30. The study group described by Blier and Bergeron (13) did not differ from ours by gender or previous history of depression; however, that group included no patients with chronic depression. In contrast, approximately one-half of our study group met criteria for chronic depression, but inspection of our data did not reveal a correlation between duration of episode and rapidity of response to treatment. Furthermore, our subjects proved to be responsive to treatment; 65% demonstrated at least a partial response to treatment. This response rate is in accord with findings from previous studies using fluoxetine.

Our patients may have been significantly heavier than the subjects in the two preliminary studies (Artigas and Blier, personal communications, 1996). Given that all three studies used the same dose of pindolol, the greater body mass of our study group raises the question of whether the pindolol dosing we used was inadequate. Reanalyses of our data after exclusion of the patients over 80 kg did not yield significant intergroup differences in treatment response. Furthermore, the findings of significant changes in the vital signs in the pindolol group but not in the placebo group suggest that the dose was sufficient to exert β-adrenergic blocking effects. Blier and Bergeron (13) did not find such effects in their pindolol-treated patients and, therefore, asserted that patients are more sensitive to the serotonergic effects of pindolol than to β-adrenergic effects. If that is the case, then the pindolol levels achieved in this study should have been sufficient to block 5-HT_{1A} receptors.

That the discrepancy between our results and those from previous studies may be attributable to the use of fluoxetine instead of paroxetine is not supported by preclinical and clinical evidence. Preclinical studies have demonstrated two- to threefold increases in hypothalamic 5-HT content in rat brain after the addition of pindolol to fluoxetine (8); hence, the pindolol-fluoxetine combination should increase 5-HT transmission in humans. Further, pindolol augmentation of a fluoxetine-resistant depression resulted in rapid (by 1 week) remission in three patients (13); this latter finding is difficult to reconcile but may suggest that pindolol addition in refractory depression may work through mechanisms other than those thought to hasten the response in drug-free patients. Additionally, it is commonly believed that paroxetine and fluoxetine yield similar rates of response, and this belief is supported by the largest comparative study to date (20); however, some studies suggest that paroxetine may have modestly higher rates of response (21, 22).

Our results show that pindolol administration is associated with decreases in vital signs, contrasting with the results of two previous studies. Although low doses of pindolol were used in this study, concurrent administration of fluoxetine may have resulted in inhibition of the cytochrome P450, 2D6 isoenzyme (CYP4502D6), the liver enzyme responsible for degradation of many β-adrenergic blockers (23). Hence, the blood levels of pindolol achieved may have been higher than if pindolol had been given without an agent that inhibited CYP4502D6 function. In fact, the decreases in vital sign variables suggest that the pindolol blood levels achieved were high enough to attain β-adrenergic activity, thereby suggesting that the pindolol plasma levels were higher in this study group than were those in the preliminary studies. That higher pindolol levels would prevent hastening of clinical response through blocking of postsynaptic 5-HT_{1A} receptors is not supported by preclinical electrophysiologic studies (24).

Overall, our data do not suggest the routine use of a pindolol-fluoxetine combination to hasten clinical response in the treatment of drug-free depressed subjects. Our current study would have benefited from assessment of pindolol blood levels and markers for enhanced serotonergic transmission, such as 5-HT metabolite levels in cerebral spinal fluid. Although in this study concurrent administration of an antidepressant and a putative 5-HT_{1A} antagonist failed to hasten clinical response, it remains to be determined whether 5-HT transmission was indeed enhanced. Therefore, we believe that the use of a 5-HT_{1A} antagonist remains a compelling pharmacologic strategy, meriting further evaluation. Future studies of 5-HT_{1A} antagonists in depression should assess varied antidepressant agents (e.g., paroxetine and MAOIs) in randomized clinical trials, assess therapeutic activity for augmentation of ineffective antidepressant regimens, use potentially higher doses of pindolol, or use penbutolol as a potentially more potent 5-HT_{1A} antagonist, with a greater half-life requiring only once-daily dosing.

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