

A Double-blind, Randomized, Placebo-Controlled Trial of Pindolol Augmentation in Depressive Patients Resistant to Serotonin Reuptake Inhibitors

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Background: Pindolol has been reported to hasten the antidepressant action of selective serotonin reuptake inhibitors in open-label and placebo-controlled trials. Pilot studies also suggested that pindolol could augment the antidepressant response in unresponsive patients. We investigated whether the addition of pindolol can induce a rapid response in treatment-resistant patients.

Methods: After a single-blind lead-in placebo phase of 5 days to exclude placebo responders, 80 outpatients with major depression who did not respond to a minimum of 6 weeks of treatment with clomipramine hydrochloride, 150 mg/d; fluoxetine hydrochloride, 40 mg/d; fluvoxamine maleate, 200 mg/d; or paroxetine hydrochloride, 40 mg/d, were randomly assigned to additionally receive placebo (3 times daily) or pindolol (2.5 mg 3 times daily) for 10 days. The median number of ineffective treatments in the current episode was 2 (range, 1-4). Hamilton Rating Scale for Depression and Montgomery-

Asberg Scale for Depression scores were used as primary measures of efficacy.

Results: At end point, the Hamilton and Montgomery-Asberg scores and change from baseline in Hamilton score were not significantly different in patients taking placebo or pindolol. The response rate was equal in both groups (12.5%). No differences in the clinical outcome were found when the various pretreatment subgroups were considered. At end point, the plasma concentration of pindolol was 9.9 ± 5.1 ng/mL (mean \pm SD; n = 40).

Conclusions: Although pindolol can accelerate the antidepressant action of selective serotonin reuptake inhibitors in previously untreated patients, it does not elicit a rapid clinical response in treatment-resistant patients within a 10-day period.

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DESPITE THE availability of a wide range of antidepressant drugs, clinical trials indicate that 30% to 40% of depressed patients fail to respond to first-line antidepressant treatment despite adequate dosage, duration, and compliance.^{1,2} Indeed, up to 21% of patients with major depression who seek treatment have not recovered 2 years later.³ In an attempt to solve this problem, several augmentation strategies have been devised.⁴ Newer antidepressant drugs, such as the selective serotonin (5-HT) reuptake inhibitors (SSRIs), have a less severe profile of side effects, but their response rate is comparable with or lower than that of tricyclic drugs.⁵⁻⁷ Also, although they can be administered at full effective doses from the initiation of treatment, onset of response requires several weeks of treatment.⁸

Pindolol, a β -adrenoceptor/5-HT_{1A} receptor antagonist, has been used to accelerate the clinical effects of antidepressant drugs with a primary action on serotonergic neurons, including SSRIs.⁹⁻¹³ Re-

cent placebo-controlled studies suggest that pindolol (2.5 mg 3 times daily) accelerates the antidepressant action of the SSRIs fluoxetine hydrochloride and paroxetine.¹⁴⁻¹⁷ In another study, no differences were found in the time to response or response rate between fluoxetine plus placebo and fluoxetine plus pindolol (2.5 mg 3 times daily or 5 mg twice daily).¹⁸

In open-label studies, pindolol was also found to elicit a clinical response in patients treated with but not responding to several antidepressant drugs, including SSRIs (fluoxetine, fluvoxamine maleate, paroxetine), tricyclic drugs (imipramine hydrochloride), and monoamine oxidase inhibitors.^{9,10,19,20} In 1 such study,²¹ no beneficial effect of the addition of pindolol was found in treatment-resistant melancholic patients. Moreover, a recent double-blind crossover trial in a small number of patients showed no significant difference between addition of placebo and pindolol.²² However, the latter authors included patients treated with nonserotonergic antidepressants, whose action is not expected to be synergistically enhanced by addition of 5-HT_{1A} receptor antagonists.

PATIENTS AND METHODS

PATIENTS

Main inclusion criteria were the existence of a major depressive disorder, single or recurrent (*DSM-IV*²³) with a current episode resistant (score on the 17-item Hamilton Rating Scale for Depression [HAM-D] >16) to pharmacological treatment (minimum of 6 weeks) with the SSRIs fluoxetine hydrochloride (40 mg/d), fluvoxamine maleate (200 mg/d), and paroxetine hydrochloride (40 mg/d), or with the nonselective 5-HT reuptake inhibitor clomipramine hydrochloride (150 mg/d). These doses were fixed for at least 2 weeks before admission and for the rest of the trial. All patients except 2 were outpatients, consecutively referred to the study by a collaborative group of psychiatrists (Group for Research in Affective Disorders) working in primary psychiatric care centers in Barcelona, Spain. Age range was 18 to 65 years.

After referral, these patients were examined by a team of 4 psychiatrists in an affective disorders unit at the Hospital de Sant Pau, Barcelona. None of the patients had previous knowledge about the possibility of participating in a clinical trial. The study was approved by the Ethics Committee of the Hospital de Sant Pau and the Spanish Ministry of Health. Written informed consent was obtained from all subjects, with the use of a consent form approved by the institutional review board, after all procedures were fully explained.

Patients with bipolar disorder type I or II and patients at suicide risk, with a score of 3 or more on item 3 of the HAM-D, were excluded. Pregnant or breast-feeding women and women of childbearing potential not using adequate contraceptive measures were also excluded. All

patients were required to be free of other serious medical conditions. Other exclusion criteria were the presence of organic mental disorders, delusions, or hallucinations; a history of drug abuse including alcohol abuse; treatment with psychotropic medications other than benzodiazepines, β -blockers, and catecholamine-depleting agents (eg, amphetamine-like compounds); and any concomitant psychiatric illness of Axis I of *DSM-IV* or Axis II disorder clusters A and B. The use of benzodiazepines was allowed only when patients were taking them before entering the study, but their dose and frequency was not changed. Patients were not allowed to receive structured psychotherapy during the trial. To exclude the presence of individuals with chronic depression, the duration of the current episode had to be less than 9 months, with a preceding asymptomatic period of at least 3 months.²⁴ Patients must not have participated in any other trial in the 3 months preceding inclusion in the present study. Before the patient entered the study, plasma levels of antidepressants were monitored to check for compliance with current antidepressant drug regimens.

The degree of treatment resistance was determined according to the classification of Thase and Rush.² A median of 2 (range, 1-4) was obtained (**Table 1**). This indicated that, on average, patients had been treated before the current 5-HT reuptake inhibitor with an adequate dose (and for a sufficient time) of another antidepressant drug of a different family without obtaining an adequate response.

Sample size was calculated considering a response to placebo of 20% in treatment-resistant patients,²⁵ a hypothetical response to pindolol of 50%, and a 10% loss of patients after randomization. Eighty patients were required for $\beta = .20$ and $\alpha = .05$. Finally, 88 white patients with a primary diagnosis of major depression according to *DSM-IV*

We conducted the present double-blind, placebo-controlled study to examine whether pindolol can augment the short-term antidepressant response in patients resistant to treatment with 5-HT reuptake inhibitors. These included the SSRIs fluoxetine, fluvoxamine, and paroxetine and the nonselective tricyclic drug clomipramine hydrochloride, a potent blocker of 5-HT reuptake.

RESULTS

The percentage of patients completing the study was 98% (39/40) in both treatment arms. Of the 80 patients who began the double-blind phase of the study, 1 patient abandoned the study by her own decision (placebo group) and another patient because of violation of the protocol (pindolol group). There were no significant differences in the number of patients who spontaneously complained of adverse events during the 10 days of the active phase of the study, although the number of patients in the pindolol group was higher than that in the placebo group (8 vs 4; **Table 2**). Of the vital signs examined, only heart rate was differentially affected in the 2 groups. There was a mean reduction of 7.5 beats/min in the 5-HT reuptake inhibitors plus pindolol group vs 1.9 beats/min in the 5-HT reuptake inhibitors plus placebo group. Blood pressure was unaffected by pindolol addition.

Two-way analysis of variance showed a significant effect of time on severity scores, as assessed by Hamilton and Montgomery-Asberg scales and the CGI

($F_{2,156} = 17.2, P < .001$ for HAM-D; $F_{2,156} = 19.1, P < .001$ for MADRS; and $F_{2,156} = 5.6, P < .004$ for CGI scores) and a nonsignificant effect of the treatment and the time \times treatment interaction in all of them (**Figure**). The percentage of responder patients was the same in the 2 treatment arms (12% [10/80]). Remission rate was 12% (10/80) in the placebo group and 10% (8/80) in the pindolol group (nonsignificant difference). The change in severity, as assessed by the fall in the HAM-D score from day 0 to day 10, was not significantly different in patients treated with placebo or with pindolol (**Table 3**). No differences emerged when the different treatment subgroups were considered (SSRIs together or individually and clomipramine) (**Table 3**). At end point, the HAM-D and MADRS scores in the groups treated with placebo and pindolol were 15.7 ± 6.0 and 17.3 ± 5.7 (HAM-D) and 21.6 ± 8.6 and 24.2 ± 8.9 (MADRS), respectively.

The plasma concentration of pindolol was determined in plasma samples taken at the fourth visit (10 days after initiation of the active treatment) and was found to be 9.9 ± 5.1 ng/mL (mean \pm SD). We did not find any significant correlation between clinical response and pindolol concentration.

COMMENT

The data of the present study do not support the hypothesis that the addition of pindolol results in a rapid aug-

criteria were qualified to enter the study. Table 1 shows the demographic data and psychiatric characteristics of patients in both groups. No statistically significant differences in age, sex ratio, or severity at admission were found between the patients in the 2 groups.

STUDY DESIGN

After giving informed consent, patients entered a placebo run-in period of 5 days (from day -5 to day 0, the day of randomization) to exclude responders to placebo. Eight patients showed a reduction of 25% or greater of their admission HAM-D score or to a HAM-D score lower than 16 during this period and were excluded from the study. After randomization and beginning of the active phase of the study (day 0), patients had visits at days 5 and 10. During the process of referral, evaluation, and admission to the study, the patients' medications were not changed. Patients had blood samplings on days 0 and 10 for biochemical analysis. The plasma concentration of pindolol was analyzed in samples from day 10 by high-performance liquid chromatography with the use of fluorometric detection of the indole ring²⁶ (excitation and emission wavelengths of 280 and 340 nm, respectively).

On day 0, patients were randomly assigned to either of 2 treatment arms: 5-HT reuptake inhibitors plus pindolol, 7.5 mg/d (2.5 mg 3 times daily) or 5-HT reuptake inhibitors plus placebo (3 times daily). Pindolol and placebo capsules had the same appearance. An independent researcher (Ignasi Gich, MD, Department of Clinical Pharmacology, Hospital de Sant Pau) not involved in the clinical trial carried out the randomization by means of computer-generated random numbers. The design was balanced

on the admission HAM-D score to avoid group differences in this variable.

Severity was assessed at each visit by the 17-item HAM-D, the Montgomery-Asberg Scale for Depression (MADRS), and the Clinical Global Impression (CGI) and Patient Global Impression scales (except visit 1 by the CGI improvement and Patient Global Impression scales). Raters were blind to treatment status. Safety was evaluated by assessment of treatment-emergent adverse events, clinical laboratory tests, and vital signs. Response was defined as a 50% reduction in the admission HAM-D score. Remission was defined as a reduction of the HAM-D score to 8 or below.

STATISTICAL ANALYSIS

On the basis of the working hypothesis initially tested in pilot studies (see the introduction), the main objective of the study was to compare the efficacy of the addition of pindolol to a previous ineffective treatment with 5-HT reuptake inhibitors. We therefore assessed efficacy by measuring the change from baseline to end point in HAM-D, MADRS, and CGI severity, and end point CGI improvement and Patient Global Impression scores. Severity scores were computed by means of a last observation carried forward approach. The effect of the addition of pindolol was examined by repeated-measures analysis of variance with time as repeated factor and treatment (placebo or pindolol) as independent factor. Treatment differences in the severity change from baseline to end point and end point scores were assessed by means of *t* tests. Treatment differences in percentages of responders and remitters were assessed by Pearson χ^2 test or Fisher exact test. Significance was set at $P < .05$ (2 tailed).

mentation of the effects of 5-HT reuptake inhibitors (SSRIs and clomipramine) in depressed patients resistant to treatment. Response and remission rates and change from baseline to end point in HAM-D and MADRS scores were not significantly different in resistant patients treated with placebo or pindolol, 2.5 mg 3 times daily, for 10 days. These data agree with a recent placebo-controlled crossover study with a small number of treatment-resistant patients with major depression that showed no beneficial effect of addition of pindolol to serotonergic and nonserotonergic antidepressants.²² Yet they are in contrast with data reported by our group and others indicating a rapid remission in SSRI-resistant patients after the addition of pindolol (2.5 mg 3 times daily) in open-label trials.^{9,10,19,20} That pindolol may be beneficial for some treatment-resistant patients is also supported by circumstantial evidence of relapses after withdrawal of pindolol and further improvement after its reintroduction (V.P., E.A., and F.A., unpublished observations, 1997).

The failure of pindolol in the present study to elicit a rapid response in treatment-resistant patients cannot be attributed to an insufficient plasma concentration of pindolol. At day 10, this was 9.9 ± 5.1 ng/mL, a value close to that found in patients treated with fluoxetine plus pindolol in a previous study.¹⁴ In these patients, a mean plasma concentration of approximately 7 ng/mL was already attained at day 3 (first time point) and remained stable until day 42 of treatment.²⁷ These observations are

entirely consistent with the rapid pharmacokinetics of pindolol after single or repeated (3 times daily) oral administration (half-life less than 5 hours).²⁸ Also, patients treated with pindolol had a more pronounced fall in heart rate, indicative of the action of pindolol at β -adrenoceptors. The long period with stabilized antidepressant treatments also suggests that the patients admitted had reached steady-state concentrations of SSRIs.

In a previous trial conducted by the same team in the same clinical setting, pindolol reduced the time to onset and enhanced the response rate of the SSRI fluoxetine at 6 weeks in untreated patients with major depression.¹⁴ Thus, it is unlikely that methodological reasons (eg, differences in the diagnosis or psychiatric ratings) can account for the different outcome of pindolol-treated patients in both studies.

The accelerating effect of pindolol has been attributed to the prevention of the self-inhibition of midbrain serotonergic neurons that results from the treatment with 5-HT reuptake inhibitors.^{29,30} These drugs elevate the extracellular concentration of 5-HT in the mesencephalic raphe nuclei, which contain the vast majority of serotonergic neurons projecting to forebrain.³¹⁻³⁵ This results in activation of somatodendritic 5-HT_{1A} autoreceptors, reduction of the firing activity of serotonergic neurons, and diminished 5-HT release in forebrain. Because the application of 5-HT reuptake inhibitors in the raphe nuclei reduced 5-HT release in forebrain,^{30,31} 5-

Table 1. Demographic Characteristics of the Patients*

Characteristic	All Patients (N = 80)	SRI Plus Placebo (n = 40)	SRI Plus Pindolol (n = 40)
Sex, No. M:F	23:57	13:27	10:30
Age, y	47.1 ± 10.1	48.0 ± 10.7	46.2 ± 9.6
HAM-D score	20.5 ± 4.1	20.0 ± 4.2	20.9 ± 3.9
Duration of current episode, wk	25.7 ± 10.1	25.3 ± 11.1	27.0 ± 8.8
Melancholic patients, %	15	12	18
No. of previous episodes	3.3 ± 3.3	3.8 ± 3.2	2.7 ± 3.3
No. of previous unsuccessful treatments in current episode†	2 (1-4)	2 (1-4)	2 (1-4)
Duration of current SRI treatment, wk	17.0 ± 8.8	16.9 ± 10.1	17.2 ± 7.7
Pindolol plasma concentration, ng/mL	NA	NA	9.9 ± 5.1

*Data are given as mean ± SD except number of previous unsuccessful treatments, given as median (range), and melancholic patients (in percentage). SRI indicates serotonin reuptake inhibitor; HAM-D, Hamilton Rating Scale for Depression; and NA, not applicable

†Determined according to the classification of Thase and Rush.²

Table 2. Frequency of Treatment-Emergent Adverse Events*

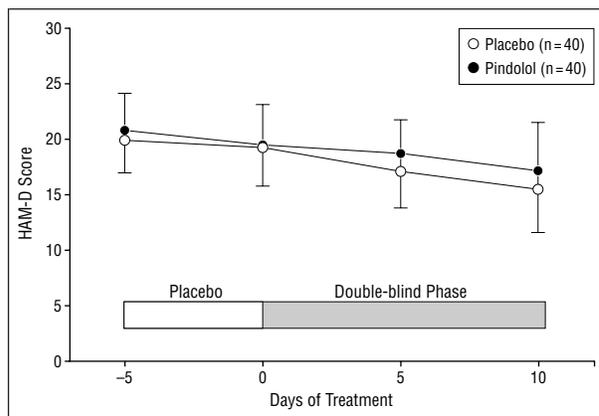
	No. of Events	
	SRI Plus Placebo (n = 40)	SRI Plus Pindolol (n = 40)
All Events	4	8
Somnolence	1	1
Nausea and/or vomiting	2	2
Pruritus	1	1
Postural hypotension	0	2
Sweating	0	1
Dry mouth	0	1

*SRI indicates serotonin reuptake inhibitor. Nonsignificant differences between treatment groups were found.

HT_{1A} receptor antagonists could prevent this negative feedback, enabling 5-HT release to normalize.²⁹ In this manner, the use of 5-HT_{1A} receptor antagonists was proposed to “reduce the therapeutic delay (and perhaps to increase the antidepressant efficacy).”³⁶ Whereas most placebo-controlled studies support the first hypothesis,^{14-17,37} the present data cast reasonable doubts about the ability of pindolol to rapidly augment the efficacy of 5-HT reuptake inhibitors in treatment-resistant patients. It should be emphasized that the patients included in the present study exhibited a moderate to high degree of treatment resistance, as exemplified by the median number of different unsuccessful treatments in the current episode (stage 2 in the classification by Thase and Rush²).

These differences in outcome lie conceivably in the different type of patients included in studies assessing time to onset (mostly untreated) and in the present study (treatment resistant). This is also supported by the failure of pindolol to accelerate the effect of fluoxetine in a sample with a large percentage of chronically ill patients.¹⁸

Despite the comparable outcome of placebo- and pindolol-treated patients found herein, it cannot be excluded



Evolution of the 17-item Hamilton Rating Scale for Depression (HAM-D) score in patients resistant to selective serotonin reuptake inhibitors treated additionally with placebo (3 times daily) or pindolol (2.5 mg 3 times daily) during the active phase of the trial. Data points are means ± SDs of 40 patients per group. No significant difference was noted between placebo and pindolol groups (2-way repeated-measures analysis of variance).

Table 3. Change in HAM-D Score After 10 Days of Treatment*

Treatment	SRI Plus Placebo (n = 40)	SRI Plus Pindolol (n = 40)	P
All treatments (N = 80)	3.7 ± 5.9 (40)	2.2 ± 4.4 (40)	.22
All selective SRIs (n = 54)	2.3 ± 3.7 (28)	1.3 ± 3.8 (26)	.35
Fluoxetine hydrochloride (n = 28)	2.8 ± 2.5 (14)	1.6 ± 3.5 (14)	.30
Paroxetine (n = 20)	2.1 ± 5.3 (11)	1.2 ± 4.8 (9)	.68
Fluvoxamine maleate (n = 6)	0.7 ± 0.6 (3)	0.7 ± 2.3 (3)	.99
Clomipramine hydrochloride (n = 26)	6.8 ± 8.6 (12)	3.9 ± 5.0 (14)	.29

*Data are mean ± SD, with number of patients in each group given in parentheses. P values were obtained with Student's t test. HAM-D indicates Hamilton Rating Scale for Depression; SRI, serotonin reuptake inhibitor.

that longer treatment times might result in differences between the 2 groups. Yet, a difference in response rates between placebo- and pindolol-treated patients was noted early in double-blind trials assessing time to onset.^{14-17,38}

This difference in the action of pindolol may indicate a different neurobiological substrate (for instance, major depressive patients exhibit a hippocampal atrophy that correlates with the duration of the illness³⁸) or, more specifically, differences in the regulation of 5-HT_{1A} receptors, such as inability to induce a sufficient desensitization of 5-HT_{1A} autoreceptors.³⁹ In the latter case, higher doses of pindolol or more potent 5-HT_{1A} receptor antagonists might be required. In support of the latter possibility, a higher density of 5-HT_{1A} autoreceptors in the dorsal raphe of depressed patients who committed suicide compared with controls has been reported recently.⁴⁰ Individuals expressing a high density of such receptors might experience an inhibition of the activity of serotonergic neurons greater than average, resulting in an insufficient increase of the serotonergic function in forebrain and failure to respond to treatment.

Long-term SSRI treatments increase synaptic 5-HT in experimental animals.⁴¹ The 5-HT_{1A} receptor antagonists augment the 5-HT increase produced by short- and long-term treatment with SSRIs,^{29,42} which suggests a lim-

ited extent of 5-HT_{1A} receptor desensitization after SSRI treatments. The inability of pindolol to bring about a rapid clinical response in SSRI treatment-resistant patients may indicate an abnormal regulation of 5-HT_{1A} receptors by these agents (see above). It may also suggest that an increased serotonergic activity is not sufficient to elicit a clinical response in these patients, who may require interventions through other transmitter systems.

In summary, the present data do not support an efficacy of pindolol greater than placebo in depressed patients resistant to treatment with 5-HT reuptake inhibitors. Whether this is because of an insufficient treatment time with pindolol in this type of patients or reflects the limitations of serotonin-based therapies in resistant depression awaits further investigation.

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