Selective Activation of Postsynaptic 5-HT$_{1A}$ Receptors Induces Rapid Antidepressant Response

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It has been reported that the 5-HT$_{1A}$ autoreceptor antagonist pindolol can accelerate the antidepressant response to the selective serotonin (5-HT) reuptake inhibitor (SSRI) paroxetine, presumably by preventing the initial decrease in firing activity of 5-HT neurons produced by the SSRI. The present study was aimed at further exploring this treatment strategy in three groups of 10 patients with unipolar major depression allocated sequentially to three treatment arms for 28 days. The administration of the selective 5-HT$_{1A}$ agonist buspirone (20 mg/day for 1 week and 30 mg/day thereafter) with pindolol (2.5 mg TID) was used to activate selectively postsynaptic 5-HT$_{1A}$ receptors. This combination produced a greater than 50% reduction of depressive symptoms in the first week in 8 of 10 patients and the response was sustained for the remainder of the trial. In contrast, the combination of tricyclic antidepressant drugs devoid of effect on the 5-HT reuptake

process (desipramine or trimipramine, 75 mg/day for 1 week and 150 mg/day thereafter) with pindolol resulted in only one of ten patients achieving a 50% improvement after 28 days. The combination of the SSRI fluvoxamine (50 mg/day for 1 week and 100 mg/day thereafter) with pindolol produced a marked antidepressant effect but did not act as rapidly as the buspirone plus pindolol combination with none, four, and eight patients achieving a 50% amelioration after 7, 14, and 21 days of treatment, respectively. These results provide further evidence that pindolol may accelerate the antidepressant effect of drugs that alter the function of the 5-HT neurons and that the selective activation of postsynaptic 5-HT$_{1A}$ receptors may induce a rapid and robust antidepressant response.
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Two reports provided evidence for an acceleration of the therapeutic effect of the selective serotonin (5-HT) reuptake inhibitor (SSRI) paroxetine by the 5-HT$_{1A}$ and β-adrenoceptor antagonist pindolol in major unipolar depression (Artigas et al. 1994; Blier and Bergeron 1995). This therapeutic strategy was based on electrophysiological data obtained in animals (Blier and de

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Montigny 1983). The rate of firing of 5-HT neurons in the rat dorsal raphe nucleus is markedly reduced by short-term administration of SSRIs, followed by a progressive recovery to normal upon long-term treatment, as a result of a desensitization of cell body 5-HT$_{1A}$ autoreceptors controlling their firing activity. After 2 weeks of treatment, 5-HT neurotransmission is enhanced in the hippocampus because of the normalized firing activity of 5-HT neurons, a desensitization of terminal 5-HT autoreceptors (which role is to inhibit 5-HT release), and sustained 5-HT reuptake blockade (Blier and de Montigny 1994). As the time course for the gradual recovery of the firing activity of 5-HT neurons is congruent with the onset of action of SSRI in major depression, it has been proposed that it could account for

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the delayed onset of action of SSRIs (Blier and Montigny 1983).

Pindolol is a $5\text{-}HT_{1A}$ and β-adrenergic antagonist that can block the cell body $5\text{-}HT_{1A}$ autoreceptor but which is inactive at postsynaptic $5\text{-}HT_{1A}$ receptors mediating the suppression of firing of hippocampus CA_3 pyramidal neurons by 5-HT (Gehlback and VanderMaelen 1987; Romero et al. 1996). It was hypothesized that the concomitant administration of pindolol and of an SSRI should result in a quicker enhancement of 5-HT neurotransmission by preventing the initial suppression of 5-HT neuron firing activity (de Montigny et al. 1993). Preliminary evidence indicated that pindolol can accelerate the antidepressant effect of the SSRI paroxetine (Artigas et al. 1994; Blier and Bergeron 1995). Indeed, two double-blind and placebo-controlled studies show that pindolol accelerates the antidepressant effect of paroxetine and fluoxetine (Artigas et al. 1996; Isaac et al. 1996).

The present open study was undertaken to explore further this therapeutic strategy. A first group of patients was administered the $5\text{-}HT_{1A}$ agonist buspirone and pindolol to achieve a selective activation of postsynaptic $5\text{-}HT_{1A}$ receptors because the blockade of somatodendritic $5\text{-}HT_{1A}$ autoreceptors by pindolol would prevent the initial suppression of firing of 5-HT neurons by $5\text{-}HT_{1A}$ agonists (de Montigny and Blier 1991). Sustained administration of selective $5\text{-}HT_{1A}$ agonists initially attenuates the firing activity of 5-HT neurons as SSRIs do (Blier and de Montigny 1987; Godbout et al. 1991). The coadministration of buspirone and pindolol was thus aimed at verifying the hypothesis that the selective activation of postsynaptic $5\text{-}HT_{1A}$ receptors plays a pivotal role in the antidepressant response. A second group of patients received pindolol in combination with tricyclic antidepressant drugs that do not block the reuptake of 5-HT. The rationale for using such a combination is that the therapeutic response of tricyclic drugs, such as desipramine and trimipramine, should not be

accelerated by pindolol because they do not decrease the firing activity of 5-HT neurons as they lack affinity for the 5-HT transporter (Scuvée-Moreau and Dresse 1979; Hyttel 1982). As paroxetine was the only SSRI used in combination with pindolol to accelerate the antidepressant response in drug-naive patients in the first two studies, the SSRI fluvoxamine was used because, like paroxetine, it has a short half-life and thus rapidly achieves steady state (Lund et al. 1982; De-Bree et al. 1983).

METHODS

Patients

Thirty outpatients (10 males and 20 females) were included in the study. All were diagnosed as suffering from major unipolar depression according to DSM-IV criteria. They were all at least moderately ill: on the 21-item Hamilton Rating Scale for Depression (HAM-D) their scores at baseline were between 26 and 35 in the buspirone group and 26 and 33 in the fluvoxamine and in the tricyclic groups. None were highly suicidal (score of 2 or less on item 3 of the HAM-D scale) or presented psychotic symptoms. Although several patients had had prior episodes of depression, they were not receiving any antidepressant drugs when they entered into the trial. The mean duration of their present episode was of 18 ± 3 weeks (range: 6 to 42 weeks). Further patient characteristics are given in Table 1. At the time of the trial, none of the patients had a medical condition necessitating pharmacological treatment. It was ensured that they did not have a history of asthma, severe drug or food allergy, or low blood pressure because they would receive the β-adrenoceptor antagonist pindolol.

Treatment Regimens and Assessments

Buspirone was given in three divided doses: 5 mg BID with meals and 10 mg at bedtime for the first week

Table 1. Patients Profile

	Buspirone	Tricyclics	Fluvoxamine
Age (years and range)	38 ± 4 (21–61)	40 ± 3 (24–56)	37 ± 3 (23–52)
Sex (M/F)	4/6	3/7	3/7
Weight (kg and range)	M: 76 ± 4 (69–82); F: 62 ± 4 (50–76)	M: 70 ± 4 (66–77); F: 59 ± 3 (52–76)	M: 67 ± 6 (49–75); F: 61 ± 4 (54–77)
Patients with melancholia	3	2	4
Patients with prior episode(s)	3	2	2
Patients taking clonazepam (0.5 mg PRN to a maximum of 1 mg/day)	3	1	4

(daily dose: 20 mg) and then 10 mg TID at the same times for the remainder of the trial (daily dose: 30 mg). Desipramine and trimipramine were initiated at 75 mg per day at bedtime for the first week and then increased to 150 mg daily for the rest of the study. Fluvoxamine was given with a meal at a dose of 50 mg per day for the first week and then increased to 50 mg BID for the remainder of the trial (daily dose: 100 mg). Pindolol was given to all patients at a regimen of 2.5 mg TID. The patients were allocated to each of the three groups sequentially. Three patients received pindolol plus paroxetine (20 mg/day) after an unsuccessful attempt to treat them with pindolol plus desipramine, and four patients received pindolol plus buspirone after failing to respond to pindolol plus trimipramine.

The intensity of the depressive syndrome was assessed using the 21-item HAM-D scale every 7 days. The raters were not blind to the treatment regimens. Response to treatment was defined as a 50% or greater decrease in HAM-D score and remission as a score of 9 or less. Results are expressed as means ± SEM and in the figures as intent to treat with the last observation carried forward. The data were analyzed with one-way analysis of variance for repeated measures preceded by the Bartlett's test to ensure absence of variance heterogeneity.

RESULTS

Eight patients discontinued their medication during the first week of treatment: all five in the desipramine group, two out of 10 in the fluvoxamine group, and one out of 10 in the buspirone group. In the desipramine group, three stopped because of increased irritability and two for increased anxiety and accrued insomnia. In the buspirone group, the one patient who discontinued his medication reported increased anxiety. In the fluvoxamine group, one stopped also for the latter reason and the other because of lack of efficacy. Otherwise the drug combinations were well tolerated. As previously reported in two studies from our group on a total of 41 patients (Blier and Bergeron 1995, 1996), there was no clinically significant alteration in pulse or blood pressure that required tapering of the pindolol regimen (data not shown).

Eight of the ten patients who received pindolol plus buspirone had a greater than 50% reduction of their HAM-D scores after seven days of treatment. All nine patients who pursued this regimen beyond the first week had reached the latter response criterion at Day 14 and attained the remission criterion at Day 21 (HAM-D of 9 or less).

Pindolol plus desipramine was given to the first five patients in the tricyclic group (HAM-D prior to de-

sipramine: 29 ± 2, n = 5). None of them, quite unexpectedly, tolerated this drug combination. Three of the dropouts who stopped taking their medications during the first 7 days accepted to try another drug combination with pindolol. They were given the SSRI paroxetine with the same pindolol regimen. After 7 days of this combination, they were already markedly improved (HAM-D score prior to paroxetine: 28 ± 2; score at day 7: 17 ± 3, n = 3) one patient exhibiting an improvement of more than 50%. After 21 days of this paroxetine plus pindolol regimen, there was further improvement (HAM-D score: 9 ± 1, n = 3), and two out of the three patients were in remission (HAM-D of 9 or less).

None of the five patients administered pindolol plus trimipramine improved by more than three points on the HAM-D scale after 7 days of treatment. There was a significant group effect at Days 21 and 28, but two patients failed to present any clinically significant improvement (i.e., a decrease of at least five points on the HAM-D scale). None of the patients on this treatment regimen attained the remission criterion at day 28. Aside from the only patient who had a greater than 50% response to pindolol plus trimipramine, the four other patients were subsequently administered the pindolol plus buspirone regimen. Three of these four patients had improved after 1 week on this drug regimen (HAM-D score prior to pindolol plus buspirone: 21 ± 3; seven days after: 16 ± 1, n = 4), but none had reached the 50% improvement criterion. However, 2 weeks later (day 21 of the pindolol plus buspirone treatment) all four patients were in remission (HAM-D score: 7 ± 1).

In the pindolol plus fluvoxamine group, there was a small, but significant, improvement after 1 week of treatment, and the improvement occurred gradually over the first 21 days of treatment with three, four, and seven of the 10 patients on this regimen achieving remission after 14, 21, and 28 days of treatment, respectively. The cumulative number of responders (HAM-D scores decreased by 50% or more) after each week of treatment is given in Table 2.

DISCUSSION

The most interesting observation in the present study is the remarkably rapid response of the patients administered the 5-HT$_{1A}$ agonist buspirone with pindolol (Figure 1A). Although buspirone has been shown to have antidepressant efficacy in placebo-controlled studies, even in patients with melancholia (Robinson et al. 1990), it is generally considered not to be as efficacious as classical antidepressant drugs. However, in combination with pindolol in the present study it exhibited both an efficacy and an onset of action that were superior to those of the pindolol plus fluvoxamine or the

Table 2. Cumulative Number of Patients Presenting a 50% or Greater Decrease in the Severity of Depression on the 21-Item Hamilton Rating Scale for Depression When Concomitantly Treated with Pindolol

	Buspirone	Tricyclics	Fluvoxamine
Day 7	8/9	0/5	0/8
Day 14	9/9	0/5	4/8
Day 21	9/9	0/5	8/8
Day 28	9/9	1/5	8/8

Pindolol was administered at a regimen of 2.5 mg TID to 10 patients in each group. Buspirone was given at a total daily dose of 20 mg TID. The tricyclics desipramine and trimipramine were given at a dose of 75 mg at bedtime for the first week and 150 mg thereafter. Fluvoxamine was given at a dose of 50 mg daily for the first week and 50 mg BID thereafter. All the patients who discontinued their medication because of side effects did so in the first week, including all five patients of the desipramine group. Note that the response was sustained over the 28-day treatment period.

pindolol plus trimipramine combinations in the present study (Table 2 and Figure 1) and were at least similar to those obtained with the SSRI paroxetine plus pindolol in a previous study (Blier and Bergeron 1995). It is important, however, to underscore that none of the 10 patients who were administered the pindolol plus buspirone combination were drug-resistant and that seven had no history of prior depressive episode. Nevertheless, the three patients meeting the criteria for melancholia responded as well as the other patients. Therefore, this robust effect was not limited to the less severely ill patients. It also is noteworthy that the four patients who failed to respond to the pindolol plus trimipramine combination subsequently responded to pindolol plus buspirone, although not as rapidly as in the buspirone group of untreated patients.

The rapid and robust antidepressant effect of pindolol plus buspirone lends further support to the hypothesis that postsynaptic 5-HT$_{1A}$ receptors play an important role in the antidepressant response. Indeed, with pindolol blocking the cell body 5-HT$_{1A}$ autoreceptors, but not postsynaptic 5-HT$_{1A}$ receptors (Romero et al. 1996), the 5-HT$_{1A}$ agonist buspirone would not produce an initial decrease in firing activity of 5-HT neurons and thus activate selectively postsynaptic 5-HT$_{1A}$ receptors, such as those mediating the hyperpolarization of dorsal hippocampus pyramidal neurons by 5-HT. It will be important to test other 5-HT$_{1A}$ agonists in combination with pindolol, particularly more potent agonists and also agonists, which, unlike buspirone, do not generate the metabolite 1-pirimidinyl-piperazine (1-PP) which is an α_2-adrenoceptor (Blier et al. 1991). Flesinoxan would be a good candidate in that respect (Oliver et al. 1991). Indeed, α_2-adrenoceptor antagonists, such as yohimbine, can produce anxiety (Price et al. 1995). One can then wonder
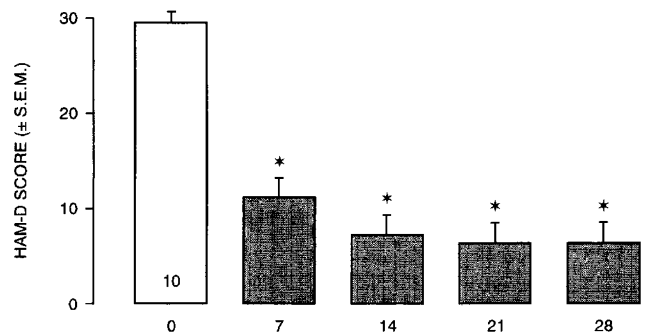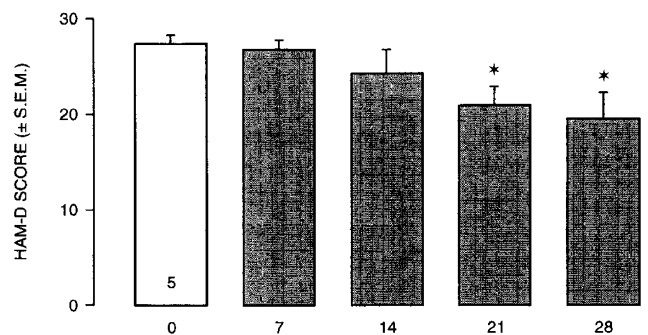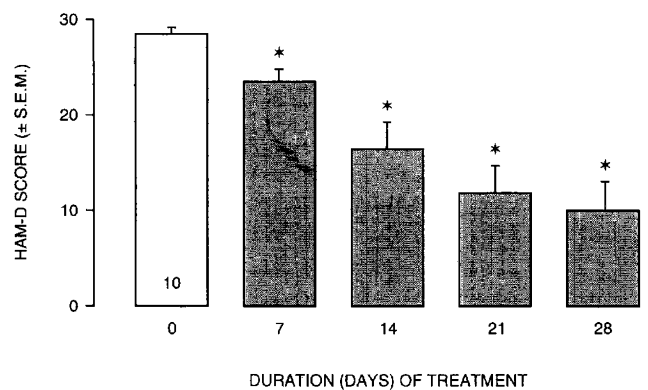

Figure 1. Mean intensity of the depressive symptoms on the 21-item Hamilton Rating Scale for Depression. The number at the bottom of the first column represents the number of patients studied. The results are depicted as intent to treat with the last observation carried forward. Pindolol was given at a dose of 2.5 mg TID in the three groups. Buspirone was given TID at total daily doses of 20 mg for the first week and of 30 mg thereafter. Trimipramine was given at bedtime at doses of 75 mg for the first week and of 150 mg thereafter. Fluvoxamine was administered at a dose of 50 mg per day for the first week and of 50 mg BID thereafter. *$p < .05$ using ANOVA for repeated measures.

whether the 1-PP generated by buspirone may somewhat dampen the therapeutic effect of buspirone itself.

The present results suggest that the combination of pindolol with a tricyclic antidepressant drug that is inactive on 5-HT reuptake does not confer additional efficacy. Furthermore, the combination of pindolol with the selective norepinephrine reuptake blocker desipramine proved deleterious, as it exacerbated anxiety, irritability, and insomnia. These side effects may have resulted from the selective activation of α-adrenoceptors by enhanced norepinephrine levels in the presence of the blockade of the norepinephrine reuptake carriers and of β-adrenoceptors. One possibility that has been raised for the potentiating effect of pindolol used in combination with certain antidepressant drugs is the favorable effect that β-adrenoceptor antagonists exert on some symptoms of anxiety, particularly the peripheral manifestations (Bailly 1996). It is quite striking, however, that all but one patient who stopped taking their medication in the first week of this study did so specifically because of increased irritability and anxiety. This also was the case in our previous study, in which three of the 28 depressed patients stopped taking their medication because of these side effects (Blier and Bergeron 1995). It is therefore unlikely that the potentiating effect of pindolol is related to its β-adrenoceptor antagonist property (Blier and Bergeron 1996).

The combination of pindolol and fluvoxamine produced a clear antidepressant effect, although it occurred more slowly than in the pindolol plus buspirone group (Figure 1). These results preclude the conclusion that pindolol can accelerate the antidepressant effect of this SSRI. Two factors, however, have to be taken into account. First, the dose of fluvoxamine administered during the first week of treatment was probably too low to achieve a therapeutically significant blockade of 5-HT reuptake. Although there are no fixed-dose studies available for this drug in major depression, the modal dose of fluvoxamine in the worldwide data bank collected for 34,587 patients is of 100 mg per day. Consequently, pindolol probably had little neurobiological effect of this SSRI to potentiate in the first week of treatment. Nevertheless, this drug was given at a regimen of 50 mg per day for 1 week and then increased to 100 mg for week 2 onward because this titration is common in outpatients and recommended by the manufacturer. Indeed, if one looks at the number of responders in this group (Table 2), half of the patients who were still on this combination at Day 14, that is, after 1 week of 100 mg/day of fluvoxamine, had achieved the response criterion and after 2 weeks of the latter regimen all were responders. These data suggest that the degree of 5-HT reuptake blockade is an important factor in the accelerating effect of the pindolol. The lack of a pharmacokinetic interaction in the combination of pindolol

plus fluvoxamine also might account for the lack of rapid onset of this combination. In fact, in one of our previous studies, the addition of pindolol to patients treated with, but not responding to, the potent SSRI sertraline was not effective in contrast to the rapid response obtained in patients receiving paroxetine or fluoxetine (Blier and Bergeron 1995). Among SSRIs, fluoxetine and paroxetine are two most potent inhibitors of the P450 2D6 cytochrome (Nemeroff et al. 1996). This property of paroxetine may thus have contributed to enhancing the plasma and brain levels of pindolol. However, fluvoxamine is a potent inhibitor of the P450 1A2 cytochrome. This isoform also may be involved in the metabolism of β-adrenoceptor antagonists (Ono et al. 1995). Consequently, in the absence of plasma levels of pindolol, the most likely explanation for the relatively slow onset of action in the fluvoxamine plus pindolol remains that the dose of fluvoxamine was too low in the first week of treatment.

In conclusion, the results of the present study provided preliminary evidence that the potentiation of the antidepressant response by pindolol may occur only with drugs that act via 5-HT neurons because pindolol was ineffective to enhance the antidepressant effect of the tricyclic drugs desipramine and trimipramine that do not block the reuptake of 5-HT. The results obtained with fluvoxamine suggest that the degree of 5-HT reuptake blockade achieved with an SSRI also appears to be an important factor in the potentiating effect of pindolol. That the 5-HT$_{1A}$ agonist buspirone produced a rapid antidepressant effect when used with pindolol it provides further evidence that the selective activation of postsynaptic 5-HT$_{1A}$ receptors plays an important role in the antidepressant response. Obviously, the present results will have to be confirmed under double-blind conditions, in particular the striking results obtained with the pindolol and buspirone combination. Given the prior reports of the effectiveness of adding pindolol (Artigas et al. 1994; Blier and Bergeron 1995), it is likely that pindolol addition is effective in at least some patients. The percentage of patients who can be expected to respond to pindolol addition remains to be determined. That question should be answered by the several ongoing double-blind studies. It would be of the utmost interest to unveil the clinical and/or biological parameters differentiating responders from nonresponders to pindolol addition.

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