The Use of Pindolol to Potentiate Antidepressant Medication

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Serotonin (5-HT) selective reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors are thought to have a delayed onset of antidepressant action attributable in part to the decrease in firing activity of 5-HT neurons they produce upon treatment initiation. As cell body 5-HT_{1A} autoreceptors desensitize, 5-HT neuronal firing is restored. The agent pindolol, through its 5-HT_{1A} receptor blocking property, has been shown to prevent the initial decrease in firing of rat 5-HT neurons associated with SSRI treatment. Four open-label studies put into evidence a significant acceleration of the antidepressant effect of SSRIs when combined with pindolol. Four of five placebo-controlled studies have confirmed this observation. Controlled trials indicate that a greater rate of response may be obtained by combining pindolol from the beginning of the SSRI treatment. The strategy of adding pindolol to the regimen of SSRI-resistant patients also appears to produce a therapeutic effect in a significant proportion of patients.
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Research endeavors to elucidate the mechanism of action of antidepressant treatments have led to the development of strategies to potentiate the antidepressant response of these medications. One of these approaches consists in combining pindolol with a serotonin (5-HT) selective reuptake inhibitor (SSRI) or a monoamine oxidase inhibitor (MAOI) from the beginning of a treatment to obtain a more rapid onset of antidepressant action, and perhaps also a greater percentage of responders.[1,2] The addition of pindolol to the therapeutic regimen of depressed patients treated with but not responding to one of these two classes of agents has also been reported to exert a rapid improvement in a significant proportion of cases.[2,3] In contrast to most other agents used as augmentation strategies, which by themselves are endowed with intrinsic antidepressant activity, such as lithium, paradoxically pindolol belongs to a class of compounds, the β-adrenoceptor antagonists, that has classically been associated with an increased use of antidepressant drugs.[4] However, the use of pindolol as an adjuvant in depressed patients stemmed not from its β-adrenergic properties, but from its 5-HT_{1A} receptor antagonistic property. The rationale for this use of pindolol is summarized below.

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EFFECTS OF ANTIDEPRESSANT TREATMENTS ON 5-HT NEUROTRANSMISSION

Extensive electrophysiologic investigations carried out in our laboratory have documented that several types of antidepressant treatments enhance 5-HT neurotransmission in the rat hippocampus.[5] This net effect, which is common to the major types of antidepressant treatments, is, however, mediated via different mechanisms (Figure 1, Table 1). All tricyclic antidepressant (TCA) drugs, independent of their capacity to inhibit the reuptake of 5-HT and/or norepinephrine, progressively enhance the responsiveness of postsynaptic 5-HT_{1A} receptors in the hippocampus with a time course that is congruent with the delayed onset of action of these drugs in major depression.[6] It has also been demonstrated by our group and other laboratories that this enhanced responsiveness to 5-HT also occurs in other, but not all, brain regions and that the sensitivity of 5-HT receptor subtypes other than the 5-HT_{1A} receptors is also altered. For instance, in the facial motor nucleus, the effect of 5-HT is mediated by 5-HT_2 receptors and that of norepinephrine by α_1-adrenoceptors, yet both types are sensitized following repeated TCA drug administration.[7] Repeated, but not single, electroconvulsive shocks also induce this sensitization of 5-HT_{1A} receptors in the dorsal hippocampus.[8,9] This finding is consistent with the clinical effectiveness of repeated electroconvulsive therapy (ECT) sessions.

MAOIs, SSRIs, and 5-HT_{1A} agonists all induce an initial attenuation of the firing activity of 5-HT neurons upon treatment initiation because they increase the degree of activation of the somatodendritic 5-HT_{1A} autoreceptors,

Table 1. Effects of Long-Term Administration of Antidepressant Treatments on 5-HT Neurotransmission in Rat Hippocampus*

Treatment	Responsiveness: Somatodendritic Autoreceptor[a]	Responsiveness: Terminal Autoreceptor[b]	Responsiveness: Postsynaptic[a]	Net Effect[c]
Tricyclic antidepressants	0	0	↑	↑
Electroconvulsive shocks	0	0	↑	↑
Monoamine oxidase inhibitors	↓	0	0/↓	↑
Selective 5-HT reuptake inhibitors	↓	↓	0	↑
5-HT_{1A} agonists	↓	0	↑	↑[d]

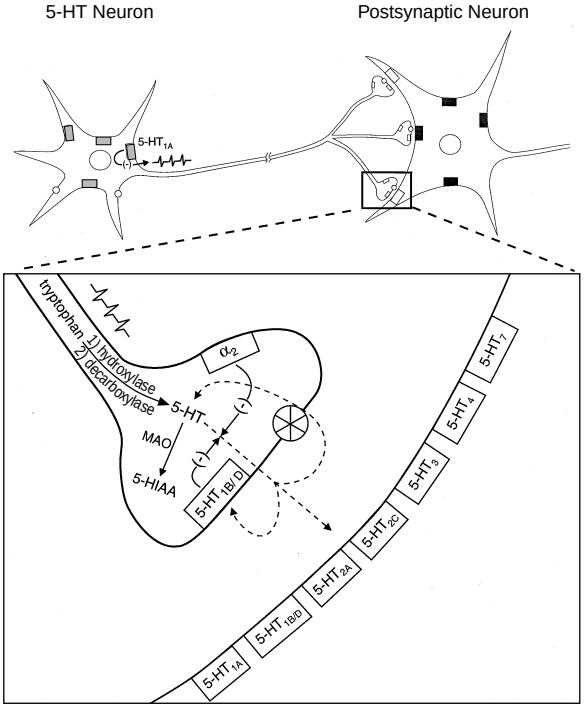
*From reference 5. Rats were treated for at least 14 days.
Symbols: ↑ = increased, ↓ = decreased, 0 = no change.
[a]Assessed by microiontophoresis or systemic injection of 5-HT receptor agonists.
[b]Assessed by comparing the effect of agonists or antagonists in control and treated rats.
[c]Determined from the firing activity of the presynaptic neurons and the effect of stimulating 5-HT fibers.
[d]Effect obtained by an enhanced tonic activation of postsynaptic 5-HT_{1A} receptors resulting from a normal amount of 5-HT (normalized 5-HT neuronal firing) and the presence of the exogenous 5-HT_{1A} agonist.

which control the firing rate of 5-HT neurons.[10–12] This is followed by a gradual recovery to normal firing activity of 5-HT neurons when the treatment is continued for 2 to 3 weeks due to a desensitization of the 5-HT_{1A} autoreceptors (see Table 1). At this point in time, MAOIs enhance 5-HT transmission by increasing the amount of 5-HT released per action potential as a result of a greater concentration of 5-HT in the terminals.[13] SSRIs produce the same effect, not by augmenting the releasable pool of 5-HT as MAOIs do, but rather by desensitizing terminal $5\text{-HT}_{1B/1D}$ autoreceptors, which exert a negative influence on the amount of 5-HT that is released per impulse.[14,15] 5-HT_{1A} agonists produce an enhanced tonic activation of postsynaptic 5-HT_{1A} receptors as a result of a normalized firing activity of 5-HT neurons (and of 5-HT release as well) in the presence of the exogenous 5-HT_{1A} agonist, which acts on normosensitive postsynaptic 5-HT_{1A} receptors.[12]

EFFECT OF PINDOLOL ON PRE- AND POSTSYNAPTIC 5-HT_{1A} RECEPTORS

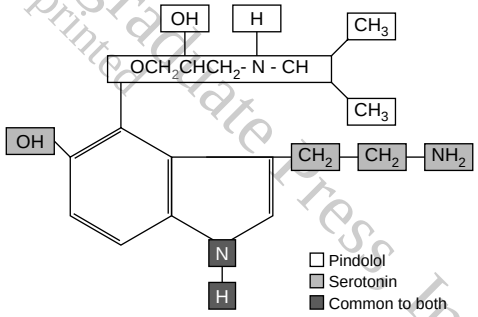
According to the above-mentioned data, the delayed onset of antidepressant action of SSRIs and MAOIs, and perhaps of 5-HT_{1A} agonists as well,[13] would be attributable in part to the capacity of 5-HT neurons to regain their normal firing activity in the presence of the sustained activation of their 5-HT_{1A} autoreceptors. Consequently, if this hypothesis were correct, a drug capable of antagonizing this 5-HT_{1A} autoreceptor on the cell body of 5-HT neurons should produce a more rapid onset of action by preventing the initial decrease of the firing activity of 5-HT neurons at the beginning of the treatment. It has been reported that

Figure 1. Presynaptic and Postsynaptic Factors Regulating the Efficacy of Serotonin (5-HT) Neurotransmission*



*From reference 5. Only the subtypes of 5-HT receptors for which an electrophysiologic response has been identified in unitary recording studies are depicted. 5-HT_{1A} receptors on the cell body of 5-HT neurons mediate an inhibitory effect on firing activity. 5-HT release from nerve terminals is inhibited by the activation of α_2-adrenoceptors, 5-HT_{1B} in rats and mice, and 5-HT_{1D} receptors in humans.

Figure 2. Chemical Structures of Pindolol and Serotonin*



*Note that pindolol has an indole nucleus, which confers its affinity for serotonin receptors, unlike other β-adrenoceptor antagonists, which have totally different structures.

pindolol (Figure 2) blocks the cell body 5-HT_{1A} autoreceptors but, very importantly, not the postsynaptic 5-HT_{1A} receptors in the hippocampus.[14] Otherwise, the simultaneous blockade of all pre- and postsynaptic 5-HT_{1A} receptors would prevent a net increase in 5-HT neurotransmission via postsynaptic 5-HT_{1A} receptors, which are present in a particular high density in the limbic system and are

thought to play an important role in the antidepressant response.

Obviously, such a statement relies on knowledge of the distinct pharmacologic profile of 5-HT_{1A} receptors. Although only a single amino acid sequence encoding the 5-HT_{1A} receptor has thus far been identified, several lines of evidence have been gathered that clearly show that 5-HT_{1A} receptors are heterogenous. First, most exogenous 5-HT_{1A} agonists, such as buspirone, are full agonists at presynaptic sites but partial agonists in the hippocampus. Second, upon long-term administration of 5-HT_{1A} agonists, 5-HT_{1A} autoreceptors become desensitized, whereas 5-HT_{1A} receptors in the hippocampus remain normosensitive.[5] Third, the 5-HT_{1A} antagonist spiperone, as well as pindolol, readily blocks the 5-HT_{1A} autoreceptor in the dorsal raphe but not the 5-HT_{1A} receptors in the dorsal hippocampus, whereas the buspirone derivative BMY-7378 blocks the post- but not the presynaptic 5-HT_{1A} receptors in the same two brain structures.[14,16,17] Finally, the potent and selective 5-HT_{1A} antagonist WAY-100635 blocks 5-HT_{1A} receptors on the cell body of 5-HT neurons in the dorsal raphe and of pyramidal neurons in the hippocampus but not those located in the orbitofrontal cortex.[18–20] Taken together, these four lines of evidence indicate that there would be at least three pharmacologically distinct subtypes of 5-HT_{1A} receptors.

STUDIES ON THE USE OF PINDOLOL TO POTENTIATE SELECTED ANTIDEPRESSANT DRUGS

Open-Label Studies

Four open-label studies have examined the capacity of pindolol to accelerate the therapeutic effect of antidepressant drugs (Table 2). In the first trial, by Artigas et al.,[2] five of seven patients had a greater than 50% improvement within 1 week of initiating paroxetine (20 mg/day) and pindolol (2.5 mg t.i.d.). In a subsequent trial, seven of nine patients presented a greater than 50% improvement after 1 week using the same therapeutic regimen (Figure 3).[3] Viñar et al.[21] documented an acceleration of the antidepressant response to the same SSRI when individuals, presenting a second depressive episode, were concomitantly treated with pindolol. The onset of action was shorter in 15 of 22 patients. Bakish et al.[22] have observed a rapid improvement in patients receiving the weak 5-HT reuptake blocker nefazodone together with pindolol in comparison with historical controls treated with nefazodone alone in one of their previous trials.

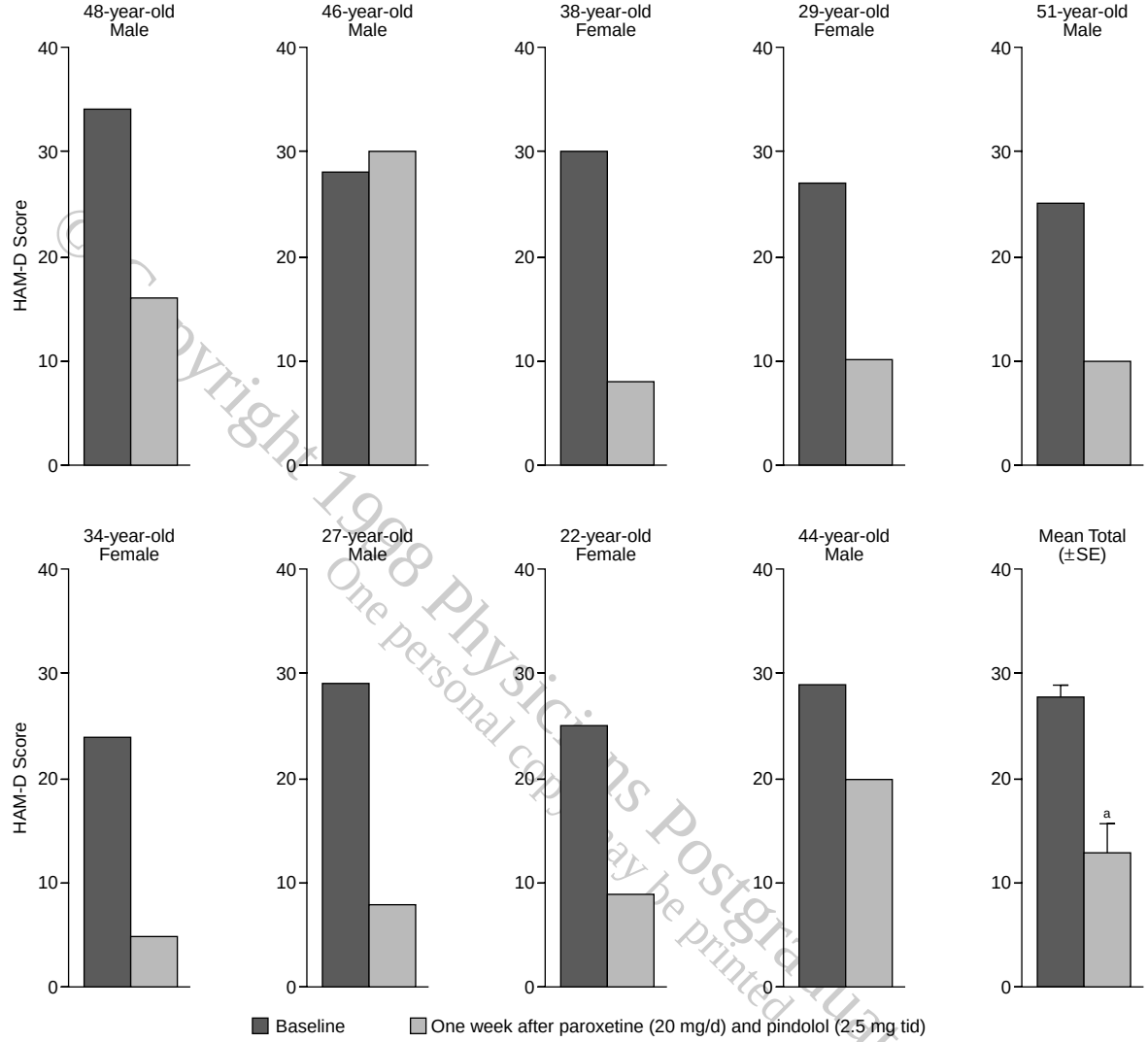
In order to provide further evidence that pindolol accelerates the antidepressant effect of SSRIs via the preferential antagonism of the cell body 5-HT_{1A} autoreceptor, the capacity of pindolol to potentiate the antidepressant effect of the 5-HT_{1A} agonist buspirone was examined.[23] Buspirone, in a dose range higher than that used for the treatment of generalized anxiety disorder, has been shown to be an antidepressant drug in a large placebo-controlled trial, exerting a more robust effect in patients meeting the criteria for melancholia.[13] Since buspirone activates both pre- and postsynaptic 5-HT_{1A} receptors, and since the desensitization of the autoreceptor leads to the enhancement of 5-HT neurotransmission, it was postulated that its combination with pindolol would lead to a preferential activation of postsynaptic 5-HT_{1A} receptors. This approach was postulated to exert a rapid antidepressant effect before the beneficial effect of pindolol was first reported.[24] After 1 week of this treatment regimen (buspirone 20 mg/day plus pindolol 2.5 mg t.i.d.), 8 of 10 patients with major depression presented a 50% or greater degree of improvement on the Hamilton Rating Scale for Depression (HAM-D). These results provide further evidence that the 5-HT_{1A} antagonist pindolol must not block all the 5-HT_{1A} receptors that the 5-HT_{1A} agonist buspirone is activating; otherwise, this drug combination would have been inactive. In the same trial, 10 patients were also treated with pindolol and TCA drugs that do not block the reuptake of 5-HT. The hypothesis for this combination was that pindolol should not accelerate the antidepressant effect of these drugs because they do not initially decrease the firing rate of 5-HT neurons (Figure 4). The use of the selective norepinephrine reuptake blocker desipramine with pindolol led all five patients to discontinue their medication in the first 7 days due to an exacerbation of their anxiety, irritability, or insomnia. The combination of trimipramine, a TCA that does not block the reuptake of either 5-HT or norepinephrine, produced a gradual but modest antidepressant effect

Table 2. Reported Data on the Possibility That Pindolol Potentiates (Acceleration/Augmentation) Antidepressant Drugs*

Study	N[a]	Rapid Onset[b]	Greater Efficacy[b]
Open-labeled studies			
Artigas et al (1994)[2]	15	+	+
Blier and Bergeron (1995)[3]	28	+	+
Viñar et al (1996)[21]	27	+	n/a
Blier and Bergeron (1996)[30]	11	–	+
Moreno et al (1996)[32]	10	–	–
Bakish et al (1997)[22]	20	+	+
Blier et al (1997)[23]	30	+	+
Placebo-controlled studies[c]			
Maes et al (1996)[31]	33	–	+
Perez et al (1997)[26]	111	+	+
Tome et al (1997)[27]	80	+	–
Berman et al (1997)[29]	43	–	–
Thomas et al (1997)[28]	101	+	–
Zanardi et al (1997)[25]	63	+	+

*Symbols: + = yes, – = no, n/a = Not available because there were no comparative groups and treatment-resistant patients were not included.
[a]Total number of patients.
[b]As assessed by a greater percentage of patients achieving either a 50% degree of improvement or statistically different (lower) score on the Hamilton Rating Scale for Depression in the pindolol-treated group than in the placebo-treated group.
[c]These patients were not treatment-resistant, with the exception of those in the first study.

Figure 3. Intensity of Depressive Symptoms on the 21-Item Hamilton Rating Scale for Depression (HAM-D) in Nine Patients With Unipolar Depression at Baseline (Without Medication) and 7 Days After the Administration of Paroxetine and Pindolol*

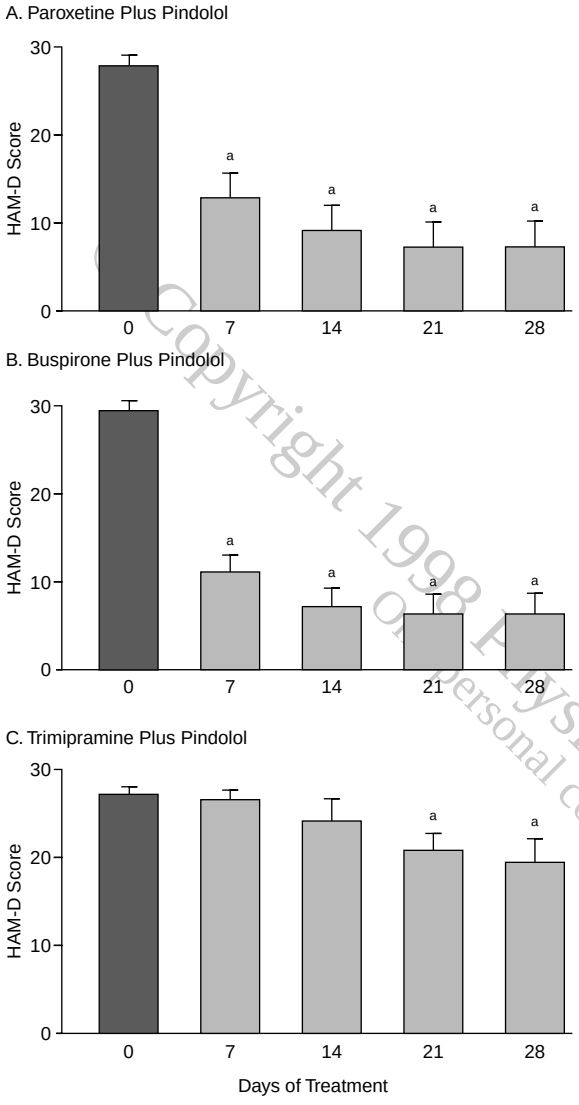


*Data from reference 3. Subject number 2 (46-year-old male) stopped pindolol treatment after 3 days because of increased anxiety and irritability.
[a]$p < .05$, paired Student's t test.

after 4 weeks of treatment. The lack of a potentiation of the antidepressant response of trimipramine when pindolol is used also supports the notion that the β-adrenergic properties of pindolol do not contribute to the beneficial effect of this adjunct in the treatment of depression. Furthermore, Zanardi et al.,[25] in a group of ten depressed patients, did not observe a more rapid onset of action of the SSRI paroxetine when metoprolol, a β-adrenoceptor antagonist devoid of affinity for 5-HT_{1A} receptors, was administered concurrently. Taken together, the last two series of observations clearly indicate that the beneficial effect of pindolol as an adjunct is not due to its β-adrenergic property.

Not only is pindolol addition an accelerating strategy, but it has also been reported in open-labelled trials to produce an antidepressant effect in patients not responding to an SSRI or an MAOI. In the initial study by Artigas et al.,[2] five patients not responding to the SSRI paroxetine, one to the SSRI fluvoxamine, one to the TCA imipramine, and one to the MAOI phenelzine presented a marked improvement within 1 week after pindolol was added. In a second study, 19 drug-resistant unipolar depressed patients were selected.[3] With only one exception, they had undergone at least one of the following augmentation strategies: lithium, desipramine, or buspirone. Eleven patients had undergone one augmentation trial; 5 patients, two; and 2 patients had received three different strategies. Ten patients had a reduction greater than 50% on the HAM-D after 1 week of pindolol addition (2.5 mg t.i.d.; see Figure 5). An

Figure 4. Mean Intensity of the Depressive Symptoms on the 21-Item Hamilton Rating Scale for Depression (HAM-D)*



*(A) from reference 3. (B) and (C) from reference 23. The results are depicted as intent-to-treat with the last observation carried forward. Pindolol was given at a dose of 2.5 mg p.o. t.i.d. in the three groups. Paroxetine was given throughout the study period at a dose of 20 mg/day (N = 9). Buspirone was given on a t.i.d. basis at a total daily dose of 20 mg for the first week, and at 10 mg t.i.d. thereafter (N = 10). Trimipramine was given at bedtime for the first week at a dose of 75 mg and of 150 mg (N = 5) thereafter.
[a]p < .05, ANOVA for repeated measures.

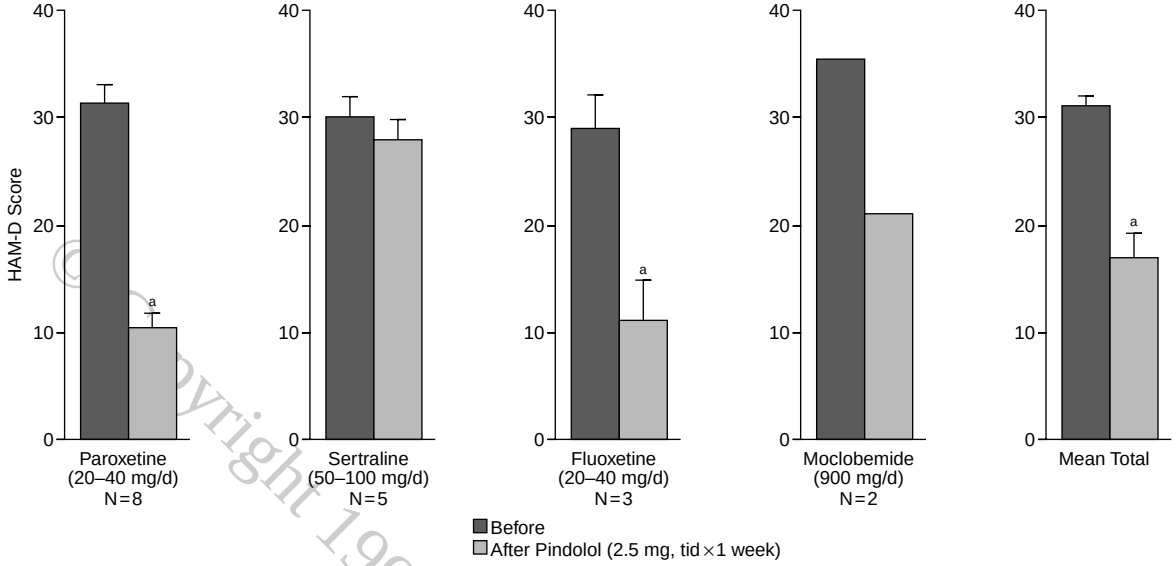
unexpected finding, however, was that none of the sertraline-treated patients responded to pindolol addition after 1 week. As the treatment was prolonged for 28 days for the 4 patients who continued taking pindolol, they improved, but only marginally (mean HAM-D ± SE score before pindolol treatment = 30 ± 2; after pindolol treatment = 23 ± 2). The HAM-D score of the sertraline-treated patient with the most notable improvement gradually decreased from 31 to 19 after 28 days of pindolol addition. It may be argued, however, that suboptimal doses of sertraline were used in these patients. Three of these sertraline-treated patients did not respond to a doubling of the dose of pindolol, but were markedly improved when they were switched to paroxetine while taking the initial dose of pindolol. Of the 14 drug-resistant patients taking an antidepressant drug other than sertraline, the most significant improvement occurred after 1 week of treatment (mean HAM-D ± SE scores before pindolol treatment = 31 ± 1; after pindolol treatment = 10 ± 1). There was further improvement in these 14 patients during the second week (mean ± SE score = 6 ± 1).

Double-Blind Studies

Five placebo-controlled trials have addressed the putative accelerating effect of pindolol in nonresistant patients (Table 2). Four studies confirm it, and one was negative. In the trial carried out in Barcelona,[26] there were 55 patients in the fluoxetine (20 mg/day) plus placebo group and 56 in the fluoxetine plus pindolol (2.5 mg t.i.d.) group. The mean time to a sustained response (a 50% or more improvement on the HAM-D) was 29 days in the placebo-treated group and 19 days in the pindolol-treated group. In the trial carried out in London,[27] the mean time to response using the criterion of 50% improvement on the HAM-D was 24 days in the SSRI (paroxetine 20 mg/day) plus placebo group and 10 days in the SSRI plus pindolol group (2.5 mg t.i.d.). A group from France[28] reported, as in the previous study, a significant acceleration of the antidepressant response at Days 5 and 10 in patients receiving paroxetine plus pindolol when compared with those given paroxetine plus placebo. The percentage of responders at the end of this 30-day trial was, however, identical in both groups.[28] In contrast, Zanardi et al.[25] in Italy observed both a more rapid onset of the antidepressant response and a greater percentage of responders in hospitalized depressed individuals given the same regimen of paroxetine and pindolol in a 4-week trial.

In the negative study, the mean time to a 50% improvement was 28 days both with fluoxetine (20 mg/day) plus placebo and with fluoxetine plus pindolol (2.5 mg t.i.d. or 5 mg b.i.d.).[29] There are two factors that may account for the negative results obtained in the latter study. First, the mean weight of the patients was 84 kg, whereas in most other studies patients on average were about 15 kg lighter.[23] Since the optimal dose of pindolol is not known, it is conceivable that these patients did not receive a dose sufficient to block the 5-HT_{1A} autoreceptor. However, the authors claim that an adequate dose was administered; they observed a significant decrease in pulse and blood pressure in the patients receiving pindolol. In contrast, we have never observed such changes of cardiovascular parameters.[3,23,30] Consequently, obese patients may be more sensitive to the β-adrenergic properties of pindolol than individuals of normal weight. The fact that several of these patients were overweight also suggests that perhaps more

Figure 5. Intensity of the Depressive Symptoms as Assessed Using the 21-Item Hamilton Rating Scale for Depression (HAM-D) Before and After 1 Week of Pindolol Addition in Drug-Resistant Patients*



*From reference 3. Except for the selective and reversible type A monoamine oxidase inhibitor moclobemide, which was given thrice daily, the drug regimens indicated below the histograms were given on a once-a-day basis for at least 4 weeks and were not altered once pindolol was initiated. One patient taking sertraline and one taking moclobemide stopped taking pindolol after 2 and 3 days, respectively, because of increased irritability. All but one patient had undergone at least one augmentation trial with lithium, desipramine, or buspirone.
[a]$p < .05$, one-way ANOVA. Results are expressed as means ± SE (last observation carried forward for the results obtained after pindolol treatment).

than 4 of their 23 patients in the fluoxetine plus pindolol group had in fact an atypical depression. It is yet unknown if the pindolol combination is effective in this subtype of depression characterized mainly by hyperphagia and hypersomnia. A second confounding factor is that half of the patients in that study had a history of substance abuse or dependence. Such patients are generally more difficult to treat, and it is not mentioned in the latter article whether a drug screen test was carried out before allowing entrance into the trial. Nevertheless, it is interesting to note that 3 of 20 patients demonstrated a clinical deterioration upon discontinuation of double-blind pindolol at the end of this 6-week trial, thus providing evidence that pindolol had exerted an effect at least in some patients.

Taken together, these results indicate that pindolol is effective in some patients to accelerate the antidepressant response. However, the main question is whether there are any factors that predict a favorable response. It is noteworthy that in the trial carried out by the British group,[27] the patients who were referred mainly from primary care settings had an extremely rapid response when given pindolol (mean time to 50% improvement = 8 days with pindolol versus 42 days with placebo addition). In fact, this group of patients accounted entirely for the decrease in the time to onset of action of paroxetine, as the other group of patients, referred mostly from psychiatrists, failed to show any acceleration of the antidepressant response to the SSRI. Similarly, in the negative double-blind trial,[29] there were fewer patients without a history of prior treatment in the pindolol group than in the placebo group. Clearly, further research is needed to identify predictors of response.

A greater efficacy was documented in two of the five double-blind trials carried out in nonresistant patients (Table 2). For instance, the response rate in the SSRI plus placebo group was 59%, whereas in the fluoxetine plus pindolol group it was 75%, with remission rates (a HAM-D score ≤ 8) of 45% and 60%, respectively, at the end of a 6-week trial.[26] The latter results constitute evidence of a greater efficacy of the pindolol augmentation strategy. In the trial carried out by Tome et al.[27] it is interesting to note that, although the rate of response in the patients who received pindolol was identical to that in the patients who received placebo after 6 weeks, the percentage of patients maintaining an improvement of 50% after 6 months on paroxetine prolongation was much greater in those who had received pindolol in the acute trial (80% versus 53%.)[31] In the controlled trial using mainly resistant patients (26 of the 33 cases), a response rate of 73% was obtained with trazodone (a weak 5-HT reuptake blocker with sedative properties) plus pindolol, a response rate of 75% with fluoxetine plus trazodone, and a response rate of 20% with trazodone plus placebo.[31] One may speculate that depressed patients who are rapidly and markedly improved by the addition of the 5-HT_{1A} antagonist pindolol may have failed to respond to their antidepressant drug regimen because their 5-HT_{1A} autoreceptors did not desensitize, thus precluding a recovery of the fir-

ing activity of 5-HT neurons. It will be interesting to test this hypothesis when a probe for the 5-HT_{1A} autoreceptor in humans becomes available.

PRACTICAL CONSIDERATIONS WHEN USING PINDOLOL AS AN ADJUNCT TREATMENT

Pindolol is formally contraindicated in patients with a history of asthma, as it could trigger a bronchospasm that would be difficult to treat with adrenergic agents because pindolol blocks both β_1 and β_2 adrenoceptors. Similarly, it would be hazardous to use pindolol in patients with severe allergies, as adrenergic agents would again be of little use in the clinical management of the allergic reaction. Pindolol should be used with caution, or not at all, in cardiac conduction impairments. Finally, in diabetic patients, pindolol and all other β-blockers are relatively contraindicated because they can mask the symptoms of hypoglycemia.

When prescribing pindolol, the use of the original drug (Visken) is highly recommended. We have indeed observed cases of patients responding well to Visken and later relapsing when their prescription was renewed with a generic formulation. This phenomenon is certainly attributable to a lesser bioavailability of these preparations. Such observations raise the issue of the optimal dose of pindolol to potentiate the antidepressant response. Thus far, almost all published studies were carried out with the 2.5-mg t.i.d. regimen. Blood levels of pindolol are currently being examined in relation to clinical response.[26] Until such results are available and confirmed by another group, the standard 2.5 mg thrice-daily regimen should be used, as pindolol has an elimination half-life of only a few hours and we have seldom observed a favorable outcome by raising the dose. Nevertheless, in nonresponding cases and in patients of high body weight when a decrease in pulse or blood pressure does not occur, the dose may be increased. In elderly patients or in patients with a low blood pressure or pulse, a lower regimen may be used (i.e., 2.5 mg b.i.d.).

In general, pindolol is well tolerated and rarely leads to treatment discontinuation. Probably due to its partial β-adrenergic agonistic properties, sometimes referred to as intrinsic sympathomimetic activity, pindolol seldom produces symptomatic decreases in pulse and blood pressure. Paradoxically, all the cases of pindolol cessation we have observed were due to increased irritability, anxiety, or insomnia. We have observed a few cases of increased sweating in nonmenopausal women.

When using pindolol as an augmenting agent in resistant patients, if there is no response after a 2-week trial, this strategy should be discontinued, as we have seen no clear responses with prolongation beyond this treatment period. In fact, in most responsive patients, a significant improvement is generally obtained within a week. If pindolol produces an improvement, then it should be continued until remission is achieved. This is based on the results of a trial showing a more rapid onset of action but not a greater efficacy when pindolol was concurrently given for only 1 week in a 4-week study[31] and on those of a 6-week trial by the group of Tome et al.[27] Although in the latter two trials no clinical deterioration was noted upon abrupt discontinuation of pindolol while continuing the SSRI, Berman et al.[29] mention three cases of deterioration upon double-blind discontinuation. We and others have also, on occasions, observed a rapid deterioration corresponding with the time to achieve elimination of pindolol when this agent was stopped due to cardiovascular or respiratory side effects.[21] Consequently, we have been tapering down the pindolol regimen to 2.5 mg b.i.d. for 1 to 2 weeks, then 2.5 mg once a day for the same period and then stopping it. Obviously, in severe or highly resistant cases, one should consider prescribing pindolol on a continuous basis with the antidepressant drug.

CONCLUSION

In summary, there are now controlled studies indicating that pindolol addition exerts both a rapid onset of action and perhaps a greater efficacy in major depression. It is too early, however, to give a response rate that can be expected with this strategy. Furthermore, there are no placebo-controlled trials comparing the effectiveness of this approach with that of other treatments, such as lithium, T_3, or electroconvulsive shocks. Nevertheless, given that there are so few contraindications for using pindolol and that it is generally well tolerated, endowed with a rapid onset of action, and inexpensive, it may be proposed as a valuable possibility in treatment algorithms for depression. Hopefully, further research may provide us with information that will help predict response not only to pindolol addition, but also to other augmentation strategies.

Drug names: buspirone (BuSpar), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), metoprolol (Lopressor), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), pindolol (Visken), sertraline (Zoloft), trimipramine (Surmontil).

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DISCLOSURE OF OFF-LABEL USAGE

The following agent mentioned in this article is *not* indicated for treatment of major depression: the 5-HT_{1A} agonist buspirone, either alone or in conjunction with pindolol.

The following agent mentioned in this article is *not* indicated to potentiate certain antidepressant drugs: pindolol.