Pindolol Augmentation of Treatment-Resistant Depressed Patients

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Background: Recent uncontrolled reports describe a dramatic and rapid improvement of depressive symptoms in patients treated with the combination of pindolol and serotonin selective reuptake inhibitors or monoamine oxidase inhibitors. The present study attempts to replicate those findings.

***Method*:** Ten outpatients with current DSM-III-R major depressive disorder who had failed to obtain or maintain an appropriate response to an adequate trial of antidepressant drug were included in a randomized double-blind, placebo-controlled, crossover study. Subjects received pindolol 2.5 mg p.o. t.i.d. or placebo for 2 weeks in addition to their current antidepressant. Clinical monitoring, vital signs, and behavioral ratings were performed weekly for the duration of the study.

Results: Pindolol was well tolerated by all patients. None of the subjects experienced significant symptom worsening during the addition of either placebo or active drug. At the end of the 2-week trial, there was no statistically significant difference between pindolol augmentation and placebo. Two patients had a categorical response during placebo treatment. No categorical responses were observed during pindolol augmentation.

***Conclusion*:** This study failed to replicate the rapid and dramatic response to pindolol augmentation in treatment-resistant depressed patients.

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Depression continues to be an extremely debilitating disease. This is in part due to the relatively high frequency of treatment resistance and partial treatment response. Because of these concerns, attempts to improve the adequacy of available treatments are broadly welcome.

A recent report by Artigas et al.[1] describes a dramatic and rapid (within 3–7 days) improvement of depressive symptoms in patients treated with the combination of pindolol and serotonin selective reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs). Pindolol is a β-adrenoceptor and 5-HT_{1A} receptor antagonist with high ability to penetrate the central nervous system. Presynaptic 5-HT_{1A} somatodendritic and nerve terminal receptors of the midbrain raphe nuclei serve as inhibitory autoreceptors, reducing 5-HT neuronal firing, synthesis, and terminal release.[2] Selective blockade of 5-HT_{1A} receptors increases 5-HT concentrations in the hippocampus of rats receiving an SSRI.[3] Artigas[4] hypothesized that blocking the negative feedback inhibition through 5-HT_{1A} autoreceptors would lead to a greater and less delayed therapeutic response in the presence of a 5-HT reuptake inhibitor by further enhancing 5-HT release. On the basis of this hypothesis, Artigas's group conducted an open trial utilizing pindolol in addition to SSRIs and MAOIs.[1] It resulted in a dramatic and rapid antidepressant response. Blier and Bergeron (1995) replicated these findings in a second open trial.[5] Although these trials were not placebo-controlled, the results are striking and support further, placebo-controlled trials.

The present study attempts to replicate the rapid and dramatic improvement observed in subjects with treatment-resistant depression when pindolol is added to the standard antidepressant regimen under double-blind, placebo-controlled conditions.

METHOD

Subjects

Ten subjects (6 men and 4 women) aged 23 to 68 years (mean ± SD = 43 ± 13 years) with a current diagnosis of major depressive disorder (MDD) based on the Structured Clinical Interview for DSM-III-R (SCID)[6]

Table 1. Subject Characteristics*†

Subject	Age (y)	Sex	Axis I Duration (Wk)	History of Substance Abuse	Current Axis II Disorder	Current Treatment/Dose	HAM-D Score: Pindolol Wk 0	Pindolol Wk 2	Placebo Wk 0	Placebo Wk 2
1	46	Male	9	Alcohol and marijuana abuse	None	Fluoxetine 40 mg/d	20	16	16	8[a]
2	43	Male	16	Alcohol dependence	PD NOS	Fluoxetine 40 mg/d	24	29	29	19
3	37	Female	4	Alcohol and marijuana abuse	None	Fluoxetine 40 mg/d	32	20	20	24
4	43	Female	156	None	PD NOS	Bupropion 450 mg/d	22	17	17	17
5	46	Male	200	Alcohol abuse	PD NOS	Fluoxetine 40 mg/d	30	23	23	26
6	23	Female	43	None	None	Desipramine 300 mg/d	28	26	32	28
7	56	Male	64	None	Unknown	Fluoxetine 40 mg/d	16	12	18	16
8	68	Female	88	None	None	Fluoxetine 20 mg/d	19	21	18	19
9	41	Male	52	None	PD NOS	Fluoxetine 20 mg/d	8	7	21	8[a]
10	29	Male	47	Unknown	Unknown	Fluoxetine 9 mg/d	13	8	18	13

*Abbreviations: HAM-D = Hamilton Rating Scale for Depression; PD NOS = personality disorder not otherwise specified.
†All subjects had an Axis I diagnosis of major depressive disorder. Subjects 1 through 5 received pindolol augmentation prior to crossover, and subjects 6 to 10 received placebo prior to crossover.
[a]Subjects considered categorically responsive (total HAM-D score decreased by ≥ 50% and had a final HAM-D score ≤ 10).

and a 25-item Hamilton Rating Scale for Depression (HAM-D)[7] score ≥ 18 (mean ± SD = 29 ± 6) were included in the study. Subjects failing to obtain or maintain a therapeutic response (final HAM-D score ≤ 17 and less than 50% of initial score) during outpatient research studies in which antidepressants were used for ≥ 8 weeks (mean ± SD = 18 ± 11 weeks) were invited to participate. Of those agreeing to participate, 8 subjects were receiving fluoxetine (mean ± SD = 31 ± 13 mg/day), 1 received desipramine (300 mg/day), and 1 bupropion (450 mg/day). The number of previous treatment failures is determined by the Thase and Rush stages of depression.[8] This scale ranges from Stage 0, for individuals who have had no adequate trial of antidepressant medication, to Stage 5, for individuals who have failed different antidepressant trials, including two or more augmentation strategies and ECT. Subjects ranged from Stages 0 to 3 (mean ± SD = 1.25 ± 0.89).

The duration of the current episode of depression varied broadly. Two of the fluoxetine-treated subjects had a chronic course of illness, and 2 had relapsed during fluoxetine treatment after improvement early during the course of treatment. Five of the 8 fluoxetine-treated patients and the 1 treated with bupropion had no prior treatment failures with other drugs. Subjects with bipolar disorder, serious medical illnesses compromising the safety of the study, and depression secondary to general medical illness or substance abuse were excluded from the study. Four of the patients had a past history of psychoactive substance use disorders, and 4 had personality disorder NOS based on SCID-II interviews (see Table 1).

Procedure

After obtaining informed consent, patients were randomly assigned under double-blind conditions to receive pindolol 2.5 mg by mouth three times a day or placebo for 2 weeks, and then were crossed over to the alternate condition for 2 additional weeks.

Measurements

Clinical monitoring, vital signs, and behavioral ratings were obtained weekly for the duration of the study. Behavioral ratings included the HAM-D, Hamilton Rating Scale for Anxiety (HAM-A),[9] and Inventory for Depressive Symptomatology (IDS).[10]

Analysis

Main effect of drug (pindolol vs. placebo), time (baseline, Week 1, Week 2), and drug × time interaction were assessed with repeated measures analysis of variance (ANOVA). Results were considered significant when $p \leq .05$. Patients were considered responders if they had a total decrease in HAM-D score ≥ 50% with a final HAM-D score ≤ 10.

RESULTS

None of the subjects experienced significant adverse effects or worsening of depression during the addition of pindolol or placebo. Table 1 displays the weekly HAM-D scores during baseline and pindolol or placebo augmentation. HAM-D scores were minimally but significantly reduced at the end of 2 weeks, but pindolol did not differ from placebo in reducing HAM-D scores (main effect of time: $F = 5.2$, $p = .01$; main effect of drug: $F = 0.02$, $p = .88$; drug × time interaction: $F = 0.33$, $p = .72$). Only 2 patients showed categorical improvement, and both were taking placebo. One of these 2 patients had pindolol augmentation prior to crossover, and the other had placebo first. Similarly negative results were obtained using the IDS (a self-rated depression inventory)[10] and the HAM-A.[9]

DISCUSSION

This study failed to demonstrate a rapid and dramatic response to pindolol augmentation of ongoing antidepres-

sant treatment in patients who had not responded to antidepressant monotherapy.

Treatment-resistant depressed patients are a highly heterogeneous population. Factors contributing to heterogeneity are differences in chronicity of illness, the particular stage of treatment resistance,[8] psychosocial stress, substance abuse history, and variations in personality characteristics. These variables (not described in prior studies)—along with methodological differences, such as the primary antidepressant being utilized; factors affecting pharmacokinetics, such as body weight, metabolic rate, and protein levels (not accounted for); and the duration of pindolol exposure—also could explain why our results differ from results of prior studies.[1,5]

The population selected for this study came from our outpatient psychopharmacology research clinic. The female:male ratio observed in our subject sample is inverse to the classic 2:1. The mean stage of refractoriness was 1.25 ± 0.89, which is minimal.

Although a crossover design may not be the best option to study the effects of a drug over extended periods of time, the rapid (within 1–2 weeks) and robust effects on depressive symptoms seen in prior studies[1,5] should have been replicated with the present design.

In spite of possible differences due to different patient characteristics, the lack of significant therapeutic effects seen in our study suggests that pindolol augmentation is unlikely to be better than placebo in causing a rapid and dramatic improvement of depression in most patients who have had a poor antidepressant response. Due to the limited scope of this study, no comments can be made about the efficacy of pindolol augmentation in other diagnostic groups, at different dosages, or with different lengths of exposure.

Drug names: bupropion (Wellbutrin), desipramine (Norpramin and others), fluoxetine (Prozac), pindolol (Visken).

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