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A Double-blind, randomized, placebo-controlled, multi-center study of brofaromine in the treatment of post-traumatic stress disorder

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Abstract A large multi-center, double-blind, parallel trial to assess the efficacy of brofaromine in the treatment of post traumatic stress disorder (PTSD) failed to show a significant difference between the brofaromine and placebo treatment groups. The placebo response rate in this study was higher than that in previously published double-blind, placebo-controlled studies of PTSD.

Key words Brofaromine · MAOI · PTSD · Psychopharmacology

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Introduction

Post-traumatic stress disorder (PTSD) is a chronic and frequently disabling psychiatric disorder. Lifetime estimated prevalence rates are between 1% and 9% (Helzer et al. 1991; Breslau et al. 1991; Davidson et al. 1991. To date, no generally effective pharmacologic treatment has been identified. However, the literature is rapidly expanding to include many case reports and open trials, but few double-blind placebo-controlled studies. Of the double-blind trials, nearly all are studies of the efficacy of antidepressants [tricyclics or the monoamine oxidase inhibitors (MAOIs)], 4–8 weeks in duration, and use male combat veterans as subjects. Only four of these separate trials showed efficacy, which was slight to modest (Frank et al. 1988; Shestatzky et al. 1988; Reist et al. 1989; Davidson et al. 1991; Kosten et al. 1991). Phenelzine appeared to be more efficacious than the tricyclic imipramine (Frank et al. 1988; Kosten et al. 1991). More recently, in a multi-center European trial, PTSD patients treated with the novel MAOI brofaromine showed a significant improvement, which reached statistical significance when the cohort was limited to patients suffering from PTSD for 1 year or more (Katz et al. 1994/95). In order to evaluate further the potential efficacy of MAOIs in the treatment of PTSD, the present multicenter, double-blind, placebo-controlled trial was undertaken at sites in the US to determine the safety, tolerability, and efficacy of brofaromine. Brofaromine is a reversible selective MAO-type A inhibitor and serotonin reuptake inhibitor. Additionally, its rapid reversibility of inhibition of monoamine oxidase reduces the risk of a tyramine-induced hypertensive crisis, making it a safer alternative for PTSD patients who are prone to impulsivity and substance abuse.

Materials and methods

One hundred and forty-six outpatients of both sexes, civilians and veterans, ages 23–73, all with PTSD, were enrolled in the study. In addition to meeting DSM-III-R criteria for PTSD, patients were required to have a minimum Clinician Administered PTSD Scale (CAPS) score of 45 (Blake et al. 1990), a maximum Montgomery-Asberg Depression Scale (MADRS) score of 22 Montgomery et al. 1979 and to be symptomatic for at least 6 months. The types of trauma reported were varied (Table 1).

Women of child-bearing potential were excluded, as were those with comorbid medical or psychiatric conditions, at immediate risk of suicide, in active pursuit of compensation, receiving other forms of active treatment such as psychotherapy, or with a known sensitivity to MAOIs. Participating patients could not receive psychotropic medication except for low-dose choral hydrate, diphenhydramine, hydroxyzine, and benzodiazepines under specified conditions. All patients indicated understanding of study procedures and potential side effects, and gave written informed consent before participating in the trial. The informed consent document was approved by the appropriate institutional review board.

Placebo responders, i.e., patients who showed a 30% or more improvement in the CAPS score between the screening and baseline visits, were excluded, leaving a total of 118 patients entered into the active treatment phase of the study.

The 12-week trial, conducted at 12 centers throughout the country, utilized a randomized, double-blind, flexible dose, comparative design with two parallel groups. Eligible patients were randomized to receive either brofaromine, titrated up to 150 mg, or placebo. Safety and efficacy assessments were performed during the screening visit, at baseline, weekly at the end of weeks 1 through 4, and every other week at the end of weeks 6 through 12.

The primary efficacy variable was the change in total score of the Clinician Administered PTSD Scale (CAPS) from baseline (visit 2) to the terminal visit, defined as the last postrandomization observation point at which the patient provided efficacy data.

Secondary efficacy variables measured include change in specific symptom clusters of PTSD, as assessed in the Impact of Events Scale (IES) Horowitz et al. 1979 the Davidson Self-Rating Scale for PTSD, and the Physician's Global Evaluation.

The safety variables included physical examinations and vital signs, laboratory assessments for hematology and biochemistry, and reports of adverse events.

The analysis for the total CAPS score and the Physician's Global Evaluation were carried out at the terminal visit using the intent-to-treat patient data set. Within-treatment differences for the change in CAPS score were analyzed using one-sample t-tests. Between-treatment differences for the primary efficacy variable were analyzed using a linear, ANCOVA model, including center and treatment effects, center-by-treatment interaction, and baseline CAPS as a covariate.

The scores from the Physician's Global Evaluation at the terminal visit were analyzed using a non-parametric Rank-Sum test.

Table 1 Patient characteristics

	Brofaromine $n = 56$		Placebo $n = 58$	
	Mean	SD	Mean	SD
Age	45.0	7.2	43.0	7.1
CAPS total	83.6	17.2	83.2	18.8
IES baseline	31.9	7.9	32.1	6.9
Duration of present episode	151.3	132.9	156.0	136.4
	Male	Female	Male	Female
Gender	44	12	48	10
Type of trauma				
Sexual assault	15.5%		15.0%	
Physical assault	5.2		8.3	
Accident	10.3		6.7	
Natural disaster	–		1.7	
Combat-related	60.4		60.0	
Other	8.6		8.3	

Results

Of the 118 patients randomized to double-blind treatment, 113 (56 in the brofaromine treatment group, and 58 in the placebo group) received blinded medication at least once and had at least one post-baseline efficacy measurement, making them eligible for the intent-to-treat analysis. Safety analysis included all 118 patients. Treatment groups were well matched on demographic and baseline variables, although patients in the placebo group were somewhat younger (Table 1).

Both the brofaromine and placebo groups showed significant reductions in symptoms as measured by the CAPS (the brofaromine group had a reduction in CAPS score from 82.16 to 54.86, and the placebo group had a reduction from 79.66 to 54.98, with a within-group P-value for both groups of 0.001). However, no significant difference was demonstrated in the between-groups analysis (Fig. 1). Using specific clusters of PTSD symptoms of the CAPS, the Physician's Global Evaluation, the Davidson Self-Rating PTSD Scale, and the IES, no between-group difference of secondary variables was found.

Of the 35 patients who discontinued the study prematurely, ten brofaromine and six placebo patients did so because of adverse experiences with the medication. One patient in the brofaromine study was discontinued because of abnormal laboratory values.

Fig. 1 Between treatment comparison of brofaromine and placebo. $F = 0.36$, $df = 1$, $P = 0.549$

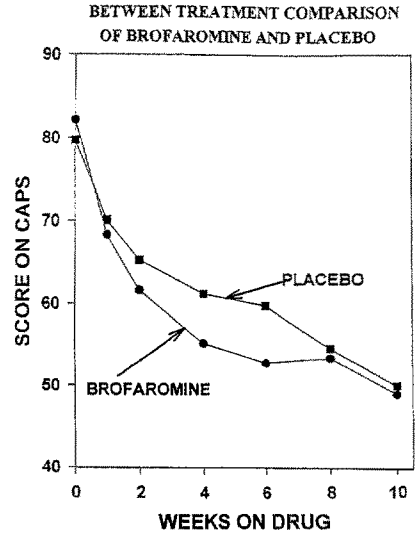

Table 2 Comparison of placebo response rate across studies

Drug	Number of subjects	Study length	IES baseline	Percent improvement on drug	Percent improvement on placebo
Comparative change in IES score					
Desipramine[a]	$n = 18$	4 weeks	55.2	2.5%	<1.0%
Phenelzine[b]	$n = 60$	8 weeks	30.6	44.0%	5.0%
Imipramine[b]	$n = 60$	8 weeks	36.5	25.0%	5.0%
Amitryptyline[c]	$n = 46$	8 weeks	31.8	21.0%	6.0%
Alprazolam[d]	$n = 10$	5 weeks	28.1	12.0%	4.0%
Phenelzine5[e]	$n = 13$	4 weeks	34.0	3.0%	16.0%
Brofaromine[f]	$n = 113$	10 weeks	31.9	26.0%	26.0%
Comparative change in CAPS score					
	Number of subjects	Study length	CAPS baseline	Percent improvement on drug	Percent improvement on placebo
Brofaromine[f]	$n = 113$	10 weeks	82.2	33.0%	31.0%
Brofaromine[g]	$n = 45$	14 weeks	80.6	48.0%	29.0%
Fluoxetine[h]					
Civilians	$n = 23$	5 weeks	80.0	44.0%	17.0%
Veterans	$n = 24$	5 weeks	93	15.0%	2.0%

[a]Reist et al.1989, [b]Kosten et al. 1991, [c]Davidson et al. 1990, [d]Braun et al. 1990, [e]Shetatsky et al.1988, [f]Current study, [g]Katz et al. 1994/95
[h]Van der Kolk et al. 1994

Discussion

In a double-blind, placebo-controlled, multi-center trial of brofaromine or placebo in 113 patients with PTSD, no differences in outcome were found. The maximum improvement in the total CAPS score during the study was 33% in patients taking brofaromine and 31% in patients taking placebo. The 31% placebo response rate measured on the CAPS is comparable to the 29% placebo response rate in the European brofaromine study, and both are higher than the 2–17% placebo response rate found in the recent fluoxetine study of PTSD (Van der Kolk et al. 1994; Katz et al. 1994/95). The 26% placebo response rate measured on the IES in the current study is also higher than the 0–16% placebo response rates measured on the IES in earlier studies (Braun et al. 1990; Frank et al. 1988; Shestatzky et al. 1988; Reist et al. 1989; Davidson et al. 1990; Kosten et al. 1991), (Table 2). In the studies which can be compared, the disparity is difficult to interpret, but the higher placebo response in the brofaromine trials, which are longer than others, may reflect therapeutic patient-rater interactions inherent in repeated administration of the CAPS, which is a structured interview. Comparatively, change on efficacy measures such as the IES and CAPS at 8–10 weeks was modest for all drugs (Table 2).

Brofaromine, which is a short-acting, selective inhibitor of Type A monoamine oxidase, a deaminator of serotonin and norepinephrine, shows excellent antidepressant efficacy, presumably through increased availability of norepinephrine and serotonin. Animal studies show drug-induced, dose-dependent increases of brain catecholamines (Moller et al. 1991). The inability to show drug-placebo outcome differences in this study, and the modest and incomplete treatment of PTSD symptoms by drugs with a similar mechanism of action suggests the need to reassess the neuropharmacology of PTSD. It indicates, as has been suggested by some neuroendocrine researchers, that while PTSD patients feel depressed, the underlying pathophysiology of PTSD is distinct. Other neurotransmitter alterations or adaptations, in addition to those affecting the catecholamines, may be crucial to the neuropharmacology, as may be the timing of treatment. Expanded neurobiological research into the CNS mechanisms underlying PTSD will be critical in the development of more effective pharmacologic interventions.

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