A Randomized, Double-Blind, Placebo-Controlled Trial of Buspirone in Combination With an SSRI in Patients With Treatment-Refractory Depression

Mikael Landén, M.D.; Göran Björling, M.D.;
Hans Ågren, M.D., Ph.D.; and Tom Fahlén, M.D., Ph.D.

Background: Case reports and open studies have reported beneficial therapeutic effects of adding buspirone to a selective serotonin reuptake inhibitor (SSRI) in the management of treatment-refractory depression. This is the first placebo-controlled study to evaluate the efficacy and safety of this combination.

Method: One hundred nineteen patients (82 women, 37 men) who fulfilled criteria for a major depressive episode according to DSM-IV and who had failed to respond to a minimum of 4 weeks (mean = 211 days) of treatment with citalopram or paroxetine were randomly assigned to 4 weeks of treatment with an SSRI plus buspirone (N = 58) or an SSRI plus placebo (N = 61). In addition, 97 patients participated in an optional open-label poststudy treatment phase with the SSRI plus buspirone for 2 weeks. The primary outcome measure was the score on the Clinical Global Impressions-Improvement (CGI-I) scale.

Results: A total of 50.9% of patients in the buspirone group and 46.7% in the placebo group responded after 4 weeks of treatment. The difference in response rate was not statistically significant. No statistically significant differences were found in the frequency of adverse events. At the follow-up of the open SSRI plus buspirone treatment, 69.4% of patients had responded.

Conclusion: Adding buspirone to an SSRI is a safe and well-tolerated drug regimen. This study failed to demonstrate any difference in efficacy between buspirone or placebo augmentation of an SSRI. It could be argued, however, that the study was inconclusive due to the unusually high placebo response.

(J Clin Psychiatry 1998;59:664–668)

Received Dec. 10, 1997; accepted March 16, 1998. From the Institute of Clinical Neuroscience, Department of Psychiatry and Neurochemistry, Göteborg University, Mölndal (Drs. Landén, Ågren, and Fahlén), and the Psychiatric Clinic, Norra Älvsborgs Län Hospital, Trollhättan (Dr. Björling), Sweden.

Supported by Bristol Myers-Squibb Sweden.

Reprint requests to: Mikael Landén, M.D., Department of Psychiatry and Neurochemistry, Göteborg University, Institute of Clinical Neuroscience, Sahlgren University Hospital/Mölndal, S-431 80 Mölndal, Sweden.

The selective serotonin reuptake inhibitors (SSRIs) provide relief for most patients suffering from major depressive disorder and have met wide acceptance as the first-line therapy for depression. In contrast to the tricyclic antidepressants, which were marred by side effects mainly because of their ability to block cholinergic receptors, SSRIs have no such affinity and have therefore a more favorable safety profile. It is estimated, however, that 30% of patients with major depression do not respond to any one antidepressant treatment[1] and that 10% of patients do not achieve optimal therapeutic effect of antidepressants in spite of adequate duration of treatment and maximal dose. These patients show substantial suffering and poor psychosocial functioning, and they represent a major socioeconomic problem.

If a patient fails to respond, there are 3 main strategies for the clinician to consider: optimization (e.g., a higher dose), augmentation therapy, and switching strategies. Various augmentation techniques for clinical practice have been described, e.g., adding lithium,[2–4] triiodothyronine (T_3),[5] tryptophan,[6] or buspirone to an antidepressant drug.

Buspirone is an azapirone derivative and a 5-hydroxytryptamine ($5\text{-}HT_{1A}$) partial agonist, currently used in medicine to treat generalized anxiety disorder.[7] Controlled studies suggest that buspirone also has antidepressant properties.[8–11] Moreover, results of several trials indicate that buspirone may be a useful agent for augmentation of other psychotropic medications in various disorders, e.g., schizophrenia, panic disorder, obsessive-compulsive disorder, and depression (cf. Harvey and Balon[12]). The usefulness of adding buspirone to an SSRI in treating depression was suggested in a report of 3 patients with depression unresponsive to fluoxetine who improved markedly on dual therapy.[13] In a minor open study with 7 patients refractory to treatment with fluoxetine alone, 6 responded when buspirone was added.[14] In a larger open study with 25 depressed patients who had failed to respond to either fluvoxamine or fluoxetine, 17 showed a complete or marked response upon receiving buspirone in addition to the SSRI for 3 weeks.[15] Finally, buspirone has recently been suggested to be an effective augmenting agent in severe treatment-refractory depression.[16]

These results indicate that buspirone augmentation may be a useful strategy in patients who do not respond to an adequate dosage of an SSRI. Controlled studies of buspirone augmentation are lacking, however. The present study is, to our knowledge, the first to investigate in a double-blind controlled fashion the efficacy and safety of adding buspirone to an SSRI for patients who are refractory to the SSRI (in this study, citalopram or paroxetine) alone.

METHOD

Entry Criteria

Patients 18 years of age or older were enrolled from 12 centers in Sweden and 1 in Norway. All patients met criteria for a major depressive episode—accounted for by either a major depressive disorder or a bipolar affective illness—according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV).[17] They had received citalopram or paroxetine for a minimum of 4 weeks, the last 2 weeks of which they received a lowest daily dose of 30 mg of paroxetine or 40 mg of citalopram. Refractoriness was defined as a Clinical Global Impressions-Improvement rating[18] of "worse"/"no improvement" compared with the baseline rating or "minimal improvement" if no further improvement had occurred in the last 2 weeks. The exclusion criteria were pregnancy or use of an unreliable contraceptive method, epilepsy, severe somatic disease, mental disorder due to a general medical condition, substance-induced disorders, high risk of suicide, and other psychiatric disorders (except generalized anxiety disorder or specific phobias). All patients gave informed consent orally and in writing to participate in the study.

Study Design

This was a placebo-controlled, double-blind, flexible-dose, multicenter study. At baseline, patients were assigned in a double-blind and random fashion to 4 weeks of treatment with buspirone plus an SSRI or placebo plus an SSRI. Buspirone and placebo were administered as tablets that were identical in appearance. Those with active drug contained 10 mg of buspirone hydrochloride. The patients were instructed to take the assigned buspirone or placebo every morning and every afternoon. A flexible-dose regimen was used with upward maximal titration of 10 mg of buspirone or 1 tablet of placebo every third day. The investigators had the option of increasing the dose to buspirone, 60 mg/day (or the corresponding amount of placebo), provided that adverse effects did not preclude such increase. The investigators dispensed the medication at each visit, and unused tablets were collected. The SSRI doses were fixed throughout the study. No other psychotropic drugs were allowed, with the exception of occasional use of the hypnotic zopiclone and a moderate daily dose of a benzodiazepine for patients who had been taking this benzodiazepine for a minimum of 1 month prior to the study. Change of dosages was not allowed, however.

After the end of the study, all patients were invited to participate in an optional open-label poststudy treatment phase that consisted of a trial of the SSRI plus buspirone for 2 weeks. Those who accepted were evaluated in the same way as at week 4 of the blinded phase.

Assessments

Assessments were made at baseline and on day 7, day 14, day 21 (± 3 days), and day 28 (± 5 days). At baseline and at each subsequent visit, each patient was evaluated using the CGI scales[18] (Severity of Illness [CGI-S] and Global Improvement [CGI-I]), the Montgomery-Asberg Depression Rating Scale (MADRS),[19] and 4 visual analogue scales (VAS) ("irritability," "mood," "power of initiative," and "ability to feel excited and interested"). The Global Assessment of Functioning (GAF) scale of the DSM-IV[17] was administered at baseline and at endpoint. Patients were considered responders if they were rated as "much improved" or "very much improved" on the CGI after 4 weeks. All other CGI scores indicated nonresponse. The VAS, MADRS, and GAF were used to assess the severity of depression and to obtain secondary efficacy measures.

The safety evaluations were based both on spontaneously reported adverse events and on structured safety ratings[20] recorded at each visit. The adverse events were classified on a 4-point scale on which 0 = no, 1 = mild, 2 = moderate, and 3 = severe symptoms.

Statistics

The appropriate sample size was calculated with the β value (power) set to 80% and the α value (level of significance chosen for rejection of the null hypothesis) to .05 using a 2-tailed test. The computation assumed that the difference in response rate would be 30% (specifically, 30% in the SSRI + placebo group vs. 60% in the SSRI + buspirone group). This necessitated a lowest target study sample size of 86 subjects with 43 per treatment group. These assumptions would enable us to report the difference in response rate with a precision (95% confidence level) of approximately ± 20%. Specifically, an observed difference of 30% would be reported with a 95% confidence interval (CI) of 10% to 50%.

For between-group comparisons of categorical variables (response vs. nonresponse), the 2-tailed chi-square test was employed.

The primary assessment was based on last observation carried forward (LOCF), according to the principle of intention-to-treat. All randomized patients with at least 1 evaluation after baseline were included in this analysis.

Ethical Considerations

The trial was carried out according to the Helsinki Declaration. The Ethics Committee of the Faculty of

Table 1. Baseline Clinical and Demographic Characteristics

Variable	SSRI + Buspirone (N = 58)	SSRI + Placebo (N = 61)
Female/male, N	39/19	43/18
Mean (range) age, y	44.9 (21–82)	48.2 (21–76)
Median (range) duration of current episode, d	243 (49–1857)	304 (42–6209)
Median (range) duration of SSRI treatment, d	140 (28–845)	141 (29–982)

Medicine at Göteborg University approved the study protocol.

RESULTS

One hundred nineteen patients were enrolled in the study between March 1995 and May 1996. Two patients (1 in the buspirone group and 1 in the placebo group) failed to have at least 1 evaluation after baseline and were therefore excluded from the efficacy analysis. Thus, 117 patients were included in the intent-to-treat analysis. Table 1 lists patients' baseline clinical and demographic data. The severity of depression was moderate to severe; the median CGI-S score was 5 (range, 3–6), the median MADRS score was 28 (range, 12–48), and the median GAF score was 51 (range, 30–75). Seventy-seven patients had been treated with citalopram (mean ± SD dosage = 46.1 ± 9.6 mg/day) and 42 with paroxetine (mean dosage = 39.8 ± 9.5 mg/day). The mean daily dose of buspirone at endpoint was 4.9 (SD = 1.0) tablets of 10 mg in the buspirone group and 5.1 (SD = 1.1) tablets in the placebo group.

Three (5%) of the patients in the buspirone group discontinued treatment: 1 woman proved to be pregnant, 1 suffered from the side effects listed below plus coordination disability, and 1 required an additional psychopharmacologic drug not allowed in the study. Four (7%) patients in the placebo group withdrew: 1 because of a change for the worse of the depression that required inpatient care, 1 because of nausea, 1 because of a relapse into alcohol abuse, and 1 because of urticaria.

After 1 week of treatment, 21 patients (37%) in the buspirone group and 22 (37%) in the placebo group reported adverse events, and after 4 weeks of treatment, 12 patients (21%) in the buspirone group and 10 (17%) in the placebo group reported adverse events. Chi-square analysis revealed no significant differences in side effects between the 2 groups. On the structured safety rating form, the most frequently reported adverse events during medication treatment were sedation (48% for buspirone-treated subjects vs. 58% for placebo-treated subjects), headache (38% vs. 44%), changes in dreaming (33% vs. 27%), and sweating (32% vs. 22%). None of the differences in frequency of side effects between the groups reached statistical significance.

Table 2 summarizes the outcome measures after 4 weeks of double-blind treatment. Of 57 previous nonresponders given an SSRI plus buspirone, 29 (50.9%) responded ("much improved" or "very much improved" on the CGI). Of 60 previous nonresponders given an SSRI plus placebo, 28 (46.7%) responded. This difference in response between the groups was shown not to be significant, by both the intent-to-treat analysis and the completer analysis. No statistically significant differences in response were found in the secondary measures (MADRS, GAF, and VAS). Figure 1 illustrates the reductions in the MADRS total score over time in both groups.

It was suggested that subgroups of the studied cohort might have responded more favorably. Therefore, post hoc comparisons were made on the basis of sex, severity of depression, duration of the current depressive episode, duration of SSRI treatment, and dose of buspirone or placebo. However, no subgroup with statistically significant favorable response was found. Table 3 shows the response rates stratified by duration of treatment with the SSRI. No obvious trend in the investigation sites was discernible in the site-effect analysis. Table 4 shows the response rate for each center respectively.

At the follow-up of the open buspirone treatment, 69.1% of patients had responded. No difference in response rate was found between patients previously treated with placebo and those previously treated with buspirone.

Dose and Plasma Levels

The mean plasma level of citalopram increased during the study, whether the patients were taking buspirone (baseline, 312 ng/mL; endpoint, 327 ng/mL) or placebo (baseline, 281 ng/mL; endpoint, 299 ng/mL). Similarly, an increase in mean plasma levels of paroxetine occurred in both the buspirone (baseline, 197 ng/mL; endpoint, 223 ng/mL) and the placebo (baseline, 228 ng/mL; endpoint, 281 ng/mL) group. Nine patients had no or very low plasma levels of the SSRI.

With one exception, all patients who were given buspirone during the blind phase had detectable plasma levels of buspirone or its major metabolite, 1-pyrimidinylpiperazine. One patient who was given placebo during the blind phase had a detectable level of buspirone in plasma. The reason for this is unclear.

Given the increase in the plasma level of the SSRI, it seems probable that increased compliance to the SSRI during the course of the study could account for the high placebo response. A subgroup analysis was performed, from which all subjects with more than a 25% increase in the plasma SSRI level at endpoint compared with baseline were excluded. In this subgroup, 52.4% responded to buspirone augmentation of the SSRI (N = 42) compared with 40.9% in the placebo group (N = 44). This difference was not statistically significant.

Table 2. Intent-to-Treat Analysis of 117 Subjects: Outcome After 4 Weeks of Double-Blind Treatment and at Follow-Up With Open-Label Buspirone Treatment*

Variable	Baseline (N = 117) Buspirone (N = 57)	Baseline (N = 117) Placebo (N = 60)	p Value	Week 4 (N = 117) Buspirone	Week 4 (N = 117) Placebo	p Value	Follow-Up (Week 6) (N = 97) Buspirone Open
Response rate on CGI-I, N responders (%)[a]	…	…		29 (50.9%)	28 (46.7%)	NS	67 (69.1%)
CGI-S score, mean (range)	4.4 (3–6)	4.6 (3–6)	NS	3.0 (1–5)	3.25 (1–6)	NS	2.6 (1–5)
MADRS score, mean (range)	26.7 (12–41)	28.0 (13–48)	NS	15.4 (0–36)	16.7 (2–46)	NS	11.4 (0–36)
GAF score, mean ± SD	53 ± 11.0	54 ± 11.7	NS	65 ± 16.3	61 ± 16.7	NS	…
VAS score, mean ± SD							
Power of initiative	25 ± 22.0	24 ± 20.3	NS	45 ± 32.0	49 ± 31.7	NS	62 ± 29.1
Ability to feel excited and interested	28 ± 22.2	30 ± 23.1	NS	50 ± 31.7	46 ± 31.1	NS	72 ± 29.5
Mood	29 ± 20.1	31 ± 22.0	NS	51 ± 32.3	50 ± 31.6	NS	62 ± 29.4
Irritability	57 ± 32.7	54 ± 32.7	NS	39 ± 31.1	42 ± 34.0	NS	31 ± 29.2

*Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = CGI-Severity of Illness scale, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, VAS = Visual Analogue Scales. Symbol: ... = not applicable.
[a]Patients rated "very much improved" or "much improved" after 4 weeks were considered responders.

Figure 1. Intent-to-Treat Analysis: Comparison Between the Effect of the SSRI + Placebo and the Effect of the SSRI + Buspirone During the Course of Treatment, as Measured Using the MADRS

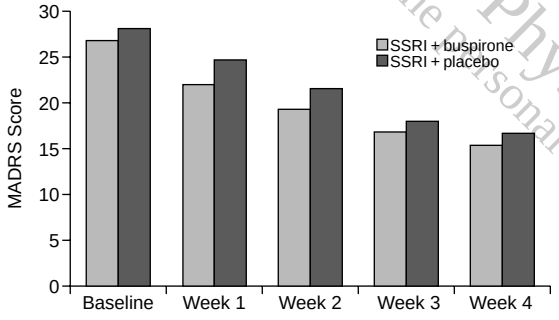

Table 3. Response Rates[a] Stratified by Duration of Treatment With the SSRI

Days of SSRI Treatment	Buspirone N	Buspirone %	Placebo N	Placebo %	p Value
< 42	1/3	33	2/6	33	NS
42–89	6/17	35	8/16	50	NS
90–179	9/16	56	5/15	33	NS
180–364	7/12	58	7/11	64	NS
> 365	6/10	60	6/13	46	NS

[a]Patients rated "very much improved" or "much improved" on the CGI after 4 weeks were considered responders.

Finally, no correlation was found in the total cohort or in the 2 groups between clinical improvement—as determined by percentage decrease in MADRS score—and the percentage increase in plasma level of the SSRI.

DISCUSSION

One of the objectives of the present study was to evaluate the safety profile of buspirone-augmented SSRI treatment. Buspirone has a favorable side effect profile when used as monotherapy. The combination of an SSRI and buspirone was well tolerated. No statistically significant differences were found between the placebo- and buspirone-treated groups, nor were there any serious adverse events that were attributable to the medication given. Thus, data from the present study suggest that adding buspirone to an SSRI (citalopram or paroxetine) is a safe and well-tolerated drug regimen.

This was a controlled trial comparing an SSRI plus buspirone and an SSRI plus placebo in 117 inpatients and outpatients who were refractory to treatment with SSRIs. About half of the patients responded favorably, irrespective of given buspirone or placebo. The lack of difference between the 2 groups as well as the high placebo response was surprising.

There are several conceivable reasons for the high placebo response. First, the plasma concentrations of the SSRI increased significantly during the course of the study. An increase in plasma level may be due to pharmacokinetic interaction or increased compliance. Since the plasma concentrations of citalopram and paroxetine were no higher in the group treated with an SSRI and buspirone than in that treated with an SSRI and placebo, increased compliance with reference to the SSRI would be a possible explanation. Whether this increased compliance resulted in higher response rate is, however, uncertain. A subgroup analysis was conducted with subjects whose SSRI plasma levels increased 25% or less from baseline to endpoint. A slight increase, however, not reaching statistical significance, in between-group difference was then found in favor of the buspirone-plus-SSRI group. No correlation between the decrease in MADRS score and increase in plasma level was found.

Second, the high response could have been due to spontaneous remission. This is unlikely, however, be-

Table 4. Response Rate in the Different Centers of the Study

Center	Buspirone/ Placebo, N	Placebo, %	Buspirone, %
1	1/1	0	0
2	2/3	33	50
3	3/3	67	33
4	4/4	0	100
5	7/9	56	43
6	6/5	40	33
7	2/3	0	100
8	5/6	83	20
9	9/9	44	33
10	5/5	40	80
11	5/6	50	20
12	6/6	67	83
13	2/2	50	50

cause the patients had been depressed for a relatively long time (median = 264 days) and had recently failed to improve on antidepressant medication (median duration of treatment = 141 days).

Third, it is possible that a minimum of 4 weeks of treatment with an SSRI before entering the study was too short a course of treatment. It may be argued that not all the patients could be expected to respond to an SSRI within 4 weeks, especially since a daily dose of at least 30 mg of paroxetine and 40 mg of citalopram was compulsory only in the last 2 weeks. Some patients may not have obtained full effect of their SSRI treatment until the double-blind phase with buspirone or placebo had commenced, which may have resulted in a blunted buspirone/placebo difference. On the other hand, no difference was found in a subgroup analysis based on the duration of the current episode of depression and the duration of SSRI treatment (see Table 3).

Fourth, as has been pointed out recently, the investigational sites in a multicenter study are crucial for the discriminative power of a placebo-controlled trial. "Nondiscriminative centers" may blunt a real effect of the drug.[21] We performed a post hoc analysis of the 13 centers without recognizing any trend in discriminating versus nondiscriminating centers (Table 4).

Last, participants in the study were subjected to psychological counseling that provided the following benefits: strengthened expectation of improvement, opportunities to verbalize distress, and positive interest from the clinicians (cf. Brown[22] and Frank[23]). This psychological effect might mask a potential augmenting effect of buspirone. The possible benefits of this counseling were unanticipated and were not controlled for.

CONCLUSION

This study failed to prove any difference in efficacy between buspirone-augmented SSRI treatment and placebo-augmented SSRI treatment. However, it could be argued that the study was inconclusive because of the unusually high placebo response, which may be due to methodological shortcomings. Further studies are needed to reliably establish whether buspirone is effective as an augmenting agent in the treatment of depression with SSRIs. Improved clinical management during a clinical trial could help to explain the surprisingly high placebo effect.

Drug names: buspirone (BuSpar), citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil).

REFERENCES

1. Roose SP, Glassman AH, Walsh BT, et al. Tricyclic nonresponders: phenomenology and treatment. Am J Psychiatry 1986;143:345–348
2. Katona CL, Abou Saleh MT, Harrison DA, et al. Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. Br J Psychiatry 1995;166:80–86. Correction 1995;166:544
3. Fava M, Rosenbaum JF, McGrath PJ, et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry 1994;151:1372–1374
4. Joffe RT, Singer W, Levitt AJ, et al. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. Arch Gen Psychiatry 1993;50:387–393
5. Aronson R, Offman HJ, Joffe RT, et al. Triiodothyronine augmentation in the treatment of refractory depression: a meta-analysis. Arch Gen Psychiatry 1996;53:842–848
6. Young SN. Use of tryptophan in combination with other antidepressant treatments: a review. J Psychiatry Neurosci 1991;16:241–246
7. Rickels K. Buspirone in clinical practice. J Clin Psychiatry 1990;51(9, suppl):51–54
8. Rickels K, Amsterdam JD, Clary C, et al. Buspirone in major depression: a controlled study. J Clin Psychiatry 1991;52:34–38
9. Robinson DS, Rickels K, Feighner J, et al. Clinical effects of the 5-HT_{1A} partial agonists in depression: a composite analysis of buspirone in the treatment of depression. J Clin Psychopharmacol 1990;10(3, suppl): 67S–76S
10. Fabre LF. Buspirone in the management of major depression: a placebo-controlled comparison. J Clin Psychiatry 1990;51(9, suppl):55–61
11. Rickels K, Amsterdam J, Clary C, et al. Buspirone in depressed outpatients: a controlled study. Psychopharmacol Bull 1990;26:163–167
12. Harvey KV, Balon R. Augmentation with buspirone: a review. Ann Clin Psychiatry 1995;7:143–147
13. Bakish D. Fluoxetine potentiation by buspirone: three case histories. Can J Psychiatry 1991;36:749–750
14. Jacobsen FM. Possible augmentation of antidepressant response by buspirone. J Clin Psychiatry 1991;52:217–220
15. Joffe RT, Schuller DR. An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. J Clin Psychiatry 1993; 54:269–271
16. Bouwer C, Stein DJ. Buspirone is an effective augmenting agent of serotonin selective re-uptake inhibitors in severe treatment-refractory depression. S Afr Med J 1997;87:534–537,540
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
18. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
19. Montgomery SA, Asberg M. A new depression rating scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
20. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale. Acta Psychiatr Scand 1987;76(suppl 334):1–100
21. Niklson IA, Reimitz PE, Sennef C. Factors that influence the outcome of placebo-controlled antidepressant clinical trials. Psychopharmacol Bull 1997;33:41–51
22. Brown WA. Placebo as a treatment for depression. Neuropsychopharmacology 1994;10:265–269
23. Frank E. Placebo as treatment for depression [commentary]. Neuropsychopharmacology 1994;10:275–277