Patients With Severe Depression May Benefit From Buspirone Augmentation of Selective Serotonin Reuptake Inhibitors: Results From a Placebo-Controlled, Randomized, Double-Blind, Placebo Wash-In Study

Björn G. Appelberg, M.D., Ph.D.; Erkka K. Syvälahti, M.D., Ph.D.; Teuvo E. Koskinen, M.D., Ph.D.; Olli-Pekka Mehtonen, M.D.; Timo T. Muhonen, M.D., Ph.D.; and Hannu H. Naukkarinen, M.D., Ph.D.

Background: Although case reports and open studies have reported augmentation with buspirone to be beneficial in the treatment of depression refractory to treatment with a selective serotonin reuptake inhibitor (SSRI), a recently published randomized, placebo-controlled, double-blind study failed to show superiority of buspirone over placebo in this respect.

Method: One hundred two outpatients who fulfilled DSM-IV criteria for a major depressive episode and who had failed to respond to a minimum of 6 weeks of treatment with either fluoxetine or citalopram were included in this double-blind, randomized, placebo-controlled study. After a single-blind placebo wash-in period of 2 weeks while continuing their SSRI, the patients were randomly assigned to adjunctive treatment with either buspirone, 10 to 30 mg b.i.d., or placebo for 6 weeks. Patients were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions scale (CGI), and visual analogue scales.

Results: After the first week of double-blind treatment, there was a significantly greater reduction in MADRS score ($p = .034$) in the buspirone group as compared with placebo. At endpoint, there was no significant difference between treatment groups as a whole, although patients with initially high MADRS scores (> 30) showed a significantly greater reduction in MADRS score ($p = .026$) in the buspirone group as compared with placebo.

Conclusion: Patients with severe depressive symptoms may benefit from augmentation with buspirone. It cannot be excluded that augmentation with buspirone may speed up the antidepressive response of patients refractory to treatment with fluoxetine or citalopram.

(J Clin Psychiatry 2001;62:448–452)

Received Dec. 13, 1999; accepted Sept. 12, 2000. *From the Department of Psychiatry, University of Helsinki, Helsinki (Dr. Appelberg); the Department of Pharmacology, University of Turku, Turku (Dr. Syvälahti); the Department of Psychiatry, University of Kuopio, Kuopio (Dr. Koskinen); the Department of Psychiatry, University of Tampere, Tampere (Dr. Mehtonen); Bristol-Myers Squibb, Helsinki (Dr. Muhonen); and the Department of Psychiatry, Helsinki University Central Hospital, Helsinki, Finland (Dr. Naukkarinen).*

Supported by a grant from Bristol-Myers Squibb, Finland.

Reprint requests to: Björn G. Appelberg, M.D., Ph.D., Department of Psychiatry, Helsinki University Central Hospital, P.O.B. 320, Lapinlahdentie, FIN-00029 HYKS, Helsinki, Finland (e-mail: Bjorn.Appelberg@huch.fi).

It has been estimated that 30% to 40% of patients with major depression do not respond to treatment with any one antidepressant and that 10% of patients do not receive optimal therapeutic benefit from antidepressants in spite of maximal dose and adequate duration of treatment.[1,2] If a patient fails to respond to treatment with an antidepressant, there are 3 main strategies that the clinician may consider: optimization of the dose, switching to another antidepressant, and augmentation of the used antidepressant. Several augmentation strategies have been used in clinical practice, including augmentation with lithium,[3–5] liothyronine (T_3),[6] tryptophan,[7] pindolol,[8–14] and buspirone.

Buspirone, a serotonin-1A (5-HT_{1A}) partial agonist used for the treatment of generalized anxiety disorder,[15] has been reported to augment the antidepressant effects of selective serotonin reuptake inhibitors (SSRIs) in several case reports and open, uncontrolled studies.[16–24] In a recently published randomized, placebo-controlled, multicenter study of 119 refractory SSRI-treated patients with major depressive disorder, the response rate of the patients treated with an SSRI plus buspirone was not greater than that of patients treated with an SSRI plus placebo.[25] In that study, however, the possible effect of buspirone as an augmenting agent may have been masked by an unusually high placebo response, i.e., 46.7% of patients in the placebo group versus 50.9% in the buspirone group responded to treatment.

The aim of the present study was to evaluate the efficacy and safety of buspirone as an augmenting agent in major depressive disorder refractory to treatment with an SSRI. To reduce a possible placebo response, the double-blind phase of the study was preceded by a 2-week single-blind placebo wash-in period.

METHOD

Entry Criteria

Patients in open care, being treated or seeking treatment for depression, 18 years of age or older, meeting DSM-IV criteria[26] for a major depressive episode were enrolled from 13 centers in Finland. They had received fluoxetine or citalopram for at least 6 weeks without showing an antidepressant response according to the psychiatrist in charge of treatment. For at least the last 4 weeks before inclusion, their daily fluoxetine dose was at least 30 mg or their daily citalopram dose at least 40 mg.

The exclusion criteria were psychotic or bipolar depression, being regarded by the clinician in charge of treatment to be seriously suicidal, severe neurologic or somatic disease, mental disorder due to a general medical condition, substance-induced disorders, and other psychiatric disorders (except generalized anxiety disorder and specific phobias).

Study Design

The study was designed as a placebo-controlled, double-blind, randomized, flexible-dose, multicenter study with a single-blind placebo wash-in phase lasting for 2 weeks before the start of the double-blind treatment. During the single-blind placebo wash-in phase, patients were assessed at inclusion, 1 week, and 2 weeks (baseline) later. The investigators, but not the patients, were aware of the placebo wash-in period. The double-blind phase began immediately after baseline and lasted for 6 weeks. During this phase, patients were assessed at weeks 1, 2, 4, and 6 after baseline.

After inclusion, no adjustments of SSRI doses were allowed. Buspirone and placebo were administered as tablets that were identical in appearance, the starting dose of buspirone being 10 mg b.i.d. A flexible-dose regimen was used with possible downward titration and maximal upward titration of 1 tablet every third day, the maximum dose being 60 mg/day. No other psychotropic drugs were allowed, with the exception of occasional use of the hypnotics zopiclone (maximum = 15 mg/day) or zolpidem (maximum = 10 mg/day) and a benzodiazepine corresponding to a maximum of 15 diazepam equivalents per day for patients who had been taking this benzodiazepine for a minimum of 1 month prior to the study. Changes in doses were not allowed during the study period.

Patients were assessed using the Clinical Global Impressions-Severity of Illness scale (CGI-S),[27] the Montgomery Asberg Depression Rating Scale (MADRS),[28] and 3 visual analogue scales (VAS) ("irritability," "mood," and "power of initiative"). Evaluation of side effects was based on a structured safety rating, the UKU Side Effect Rating Scale,[29] recorded at each visit.

The primary response criterion was a priori defined as a change (improvement) in CGI-S score of 2 points or more. Patients fulfilling this response criterion during the placebo phase were to be excluded from the study after the single-blind phase. The primary assessment was based on the last observation carried forward (LOCF) according to the principle of intention to treat. All patients with at least 1 evaluation after baseline were included in this analysis.

Post hoc analyses were made for patients with relatively low (< 25), intermediate (25–30), and high (> 30) MADRS scores at inclusion.

Statistics

Mean values and standard deviations (SD) were calculated. For the comparison of the number of responders and nonresponders in each treatment arm, a 2-tailed chi-square test was used. For comparison of differences in percentage changes from baseline in MADRS, VAS, and UKU scores between treatment arms, Kruskal-Wallis 1-way analysis of variance (ANOVA) was used. Spearman correlations were used for correlating changes in MADRS scores with initial MADRS scores.

Ethical Considerations

The trial was carried out according to the Helsinki Declaration. Patients were recruited to the study on a voluntary basis; informed written consent was given by all patients after the nature of the study had been fully explained. The study protocol, including inclusion of patients into the study, was authorized by the Ethics Committee of the Psychiatric Clinic of the Helsinki University Central Hospital (Helsinki, Finland).

RESULTS

One hundred thirteen patients were enrolled in the study. Of these, 11 patients were excluded from the analysis for various reasons. Five patients were removed from the study during the placebo wash-in phase: 2 were removed because of protocol violation, 1 did not show up at baseline, and 2 withdrew their informed consent. No patients were removed from the study because of treatment response (change in CGI-S score ≥ 2). Six more patients (3 in the buspirone and 3 in the placebo group) were removed from the study because of protocol violation before week 1.

One hundred two patients had at least 1 evaluation after the placebo wash-in phase and were included in the final analysis. Of these, 92 completed the study. Four

Table 1. Change (mean ± SD %) in MADRS Score by MADRS Score at Inclusion During Augmentation of SSRI Treatment With Buspirone or Placebo[a]

MADRS Score at Inclusion	Week 1					LOCF				
	Buspirone		Placebo			Buspirone		Placebo		
	% Change	N	% Change	N	p Value	% Change	N	% Change	N	p Value
< 25 (low)	8.0 ± 12.7	18	7.0 ± 10.0	18	.677	21.8 ± 22.8	18	33.7 ± 20.7	15	.206
25–30 (intermediate)	13.9 ± 8.8	21	6.7 ± 9.8	18	.044	31.5 ± 18.9	21	41.7 ± 25.8	18	.120
> 30 (high)	10.3 ± 10.0	12	–0.9 ± 9.8	18	.090	37.5 ± 23.1	12	18.2 ± 17.2	18	.026
All patients	11.1 ± 11.8	51	3.6 ± 9.4	51	.034	30.5 ± 23.8	51	30.8 ± 23.5	51	.794

[a]Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor. Baseline defined as the end of the 2-week placebo wash-in; week 1 defined as the end of 1 week of SSRI + buspirone or SSRI + placebo. Change (mean ± SD %) in MADRS score was calculated as percentage of baseline MADRS score.

patients left the study after week 2 of the double-blind phase: 1 buspirone patient left because of red spots in the throat, 1 buspirone patient moved to another district, 1 placebo patient left because of a suspected angina pectoris attack, and 1 placebo patient left because her spouse threw away her study medication. Six patients discontinued after the visit at week 4: three patients (1 taking buspirone, 2 taking placebo) did not show up at the last visit (week 6), 2 patients treated with placebo (of which 1 reported lack of efficacy) stopped taking the study medication, and 1 patient (taking placebo) discontinued because of heavy misuse of alcohol.

Of the 102 patients included in final analysis, 51 patients—19 men and 32 women aged between 19 and 74 years (mean = 44 years) with a mean duration of illness of 2.5 years (range, 0.13–25 years) and a mean treatment time with SSRI of 1.2 years—were randomly assigned to receive augmentation with buspirone, while 51 patients with an identical sex ratio (19 men and 32 women) and a mean age of 44 years (range, 18–61 years) were randomly assigned to placebo. In the buspirone group, 28 patients received citalopram (mean dose = 40.0 mg/day) and 23 patients received fluoxetine (mean dose = 33.9 mg/day), while 27 patients in the placebo group received citalopram (mean dose = 40.7 mg/day) and 24 patients received fluoxetine (mean dose = 35.4 mg/day). No statistically significant differences in the inclusion or baseline parameters were observed between the treatment groups. The mean ± SD dose of buspirone was as follows: week 1, 35 ± 5 mg; week 2, 39 ± 2 mg; week 4, 48 ± 10 mg; week 6, 48 ± 10 mg (LOCF, 47 ± 11 mg).

Efficacy

A significant ($p < .001$) reduction in MADRS total scores in both groups was observed during single-blind placebo wash-in (score at inclusion compared with baseline), confirming the impact of placebo effect even in SSRI-refractory depressed patients.

After the first week of double-blind treatment, there was a statistically significant ($p = .034$) greater reduction in MADRS total score compared with end of single-blind placebo phase (baseline) in the buspirone group (11.1%; mean ± SD = 2.9 ± 3.8 MADRS points) compared with the placebo group (3.6%; 0.9 ± 3.5 MADRS points). This effect was not statistically significantly different for women versus men or for patients taking citalopram compared with patients taking fluoxetine. No other statistically significant differences between treatment groups as a whole were observed during the study. According to the a priori response criterion (a reduction of CGI-S score at inclusion ≥ 2), 17 (33%) of the 51 patients taking buspirone and 16 (31%) of the 51 placebo patients were responders.

In the buspirone group, a clear-cut positive correlation between MADRS score at inclusion and change in MADRS score from baseline to LOCF was observed ($r = 0.4$, $p = .004$), indicating that patients with initially higher MADRS scores tended to respond with greater reduction in their MADRS scores at LOCF. No such correlation was observed in the placebo group ($r = 0.019$, $p = .894$). To further analyze this correlation, patients were stratified into 3 groups: those with an initial MADRS score < 25 (low), those with an initial MADRS score of 25 to 30 (intermediate), and those with an initial MADRS score > 30 (high).

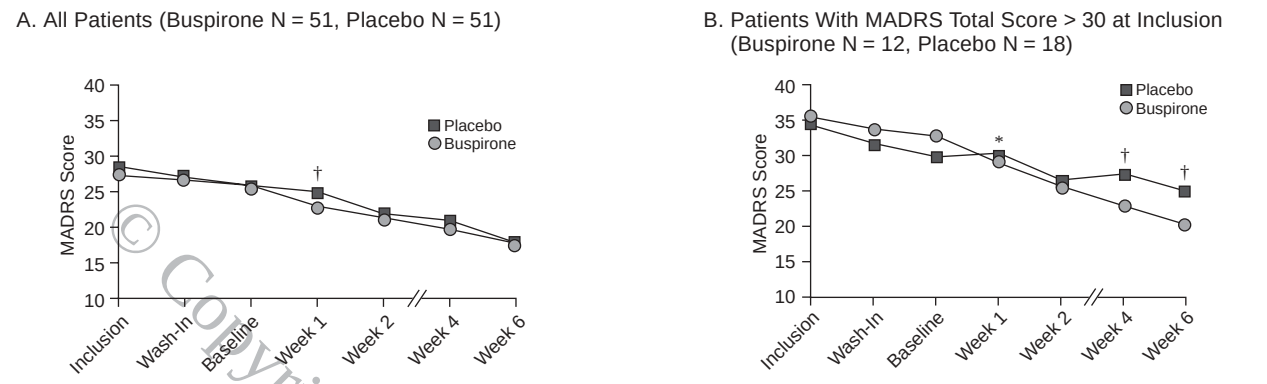
In this analysis, patients with an initially high MADRS score responded with a significantly greater reduction in MADRS score at LOCF in the buspirone group compared with the placebo group (Table 1).

MADRS scores throughout the study for all patients and for patients with an initially high MADRS score (> 30) are shown in Figure 1. Except for week 2, the reduction in MADRS score tended to be or was significantly greater in the buspirone group compared with the placebo group for patients with an initially high MADRS score.

Safety

Overall, 16 patients, 6 in the buspirone group and 10 in the placebo group, discontinued the study after the beginning of the double-blind phase. No serious adverse events were observed. No statistically significant differences were observed in UKU scores between treatment groups throughout the study.

Figure 1. Mean MADRS Total Score for SSRI-Refractory Patients at Inclusion, After 1 (wash-in) and 2 Weeks of Placebo Wash-in (baseline), and After Weeks 1, 2, 4, and 6 of Augmentation With Either Buspirone or Placebo[a]



[a]Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.
*p < .1. †p < .05.

DISCUSSION

No significant differences in side effects or dropout rates were observed between patients taking buspirone or patients taking placebo. Thus, buspirone seems to be a safe adjunctive to citalopram or fluoxetine in patients with refractory depression. In fact, more patients (10 vs. 6) in the placebo group discontinued the study prematurely. Although no patient was regarded as a responder during the placebo wash-in period according to the a priori criteria, a clear-cut decrease in MADRS total score was seen in the single-blind phase of this study. This decrease was probably a placebo response, even if one cannot exclude a late response to the SSRI treatment in spite of the fairly long pretreatment period (a minimum of 6 weeks, and an average of about 1 year before the beginning of the placebo wash-in).

Patients taking buspirone had a greater reduction in MADRS score after the first week of treatment compared with patients taking placebo, which indicates that buspirone may speed up the antidepressant response of patients taking SSRIs. The present study was, however, not designed to detect an early treatment response, and therefore it is also not possible to estimate the magnitude of this speed-up. No difference in antidepressant response was observed at LOCF between treatment groups according to the a priori efficacy parameter (CGI-S score) or the other efficacy parameters (MADRS and VAS scores). The magnitude of response in the placebo augmentation group was a 30.8% decrease in MADRS score in spite of the initial 2-week placebo period, reflecting the importance of unspecific, placebo-like effects in this kind of patient sample and possibly also a gradual SSRI-induced time-dependent decline in depressive symptoms. The study by Landén et al.[25] reported an even higher placebo response, with a reduction in MADRS score of 40%. In the present study, patients were seen by the investigator every second week during the last month of the study, which may have reduced the placebo response relative to the study by Landén et al.,[25] in which patients were seen every week throughout the study.

Interestingly, buspirone seemed to be better than placebo for patients with initial MADRS scores over 30 throughout the double-blind phase of the study and at LOCF (with the exception of 2 weeks after the beginning of the double-blind phase). This difference may indicate that patients who benefit from augmentation with buspirone are those with relatively severe depression. One could argue that a tendency for patients with initially higher MADRS scores to exhibit relatively larger changes in MADRS scores simply reflects a regression toward the mean. However, this phenomenon was seen in the buspirone group only; in the placebo group, no significant correlation between initial MADRS score and change in MADRS score was observed. In fact, the largest percentage response in the placebo group was seen in patients with an initially intermediate MADRS score, followed by patients with an initially low MADRS score.

It is concluded that adjunctive buspirone may be a useful treatment option for patients with severe depressive symptoms suffering from SSRI-refractory major depressive disorder and that although buspirone was not different from placebo in efficacy in a larger group of outpatients in the long run, one cannot exclude a faster onset of recovery from depressive symptoms due to adjunctive buspirone. Further studies that focus on speed of onset of treatment response and severely ill depressive patients and possibly include hospitalized patients are, however, needed to verify these conclusions.

Drug names: buspirone (BuSpar), citalopram (Celexa), diazepam (Valium and others), fluoxetine (Prozac), liothyronine (Cytomel, Triostat), zolpidem (Ambien).

REFERENCES

1. Roose SP, Glassman AH, Walsh BT, et al. Tricyclic nonresponders: phenomenology and treatment. Am J Psychiatry 1986;143:345–348
2. Frank E, Karp JF, Rush AJ. Efficacy of treatments for major depression. Psychopharmacol Bull 1993;29:457–475
3. 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
4. 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
5. 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
6. 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
7. Young SN. Use of tryptophan in combination with other antidepressant treatments: a review. J Psychiatry Neurosci 1991;16:241–246
8. Artigas F, Perez V, Alvarez E. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. Arch Gen Psychiatry 1994;51:248–251
9. Blier P, Bergeron R. Effectiveness of pindolol with selected antidepressant drugs in the treatment of major depression. J Clin Psychopharmacol 1995; 15:217–222
10. Maes M, Vandoolaeghe E, Desnyder R. Efficacy of treatment with trazodone in combination with pindolol and fluoxetine in major depression. J Affect Disord 1996:17:201–210
11. Tome MB, Isaac MT, Harte R, et al. Paroxetine and pindolol: a randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. Int Clin Psychopharmacol 1997;12:81–89
12. Perez V, Gilaberte I, Faries D, et al. Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. Lancet 1997;349:1594–1597
13. Berman RM, Darnell AM, Miller HL, et al. Effects of pindolol in hastening response to fluoxetine in the treatment of major depression: a double-blind, placebo-controlled trial. Am J Psychiatry 1997;154:37–43
14. Maes M, Libbrecht I, van Hunsel F, et al. Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. J Clin Psychopharmacol 1999;19:177–182
15. Rickels K. Buspirone in clinical practice. J Clin Psychiatry 1990; 51(9, suppl):51–54
16. Rickels K, Amsterdam JD, Clary C, et al. Buspirone in major depression: a controlled study. J Clin Psychiatry 1991;52:34–38
17. 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
18. Fabre LF. Buspirone in the management of major depression: a placebo-controlled comparison. J Clin Psychiatry 1990;51(9, suppl):55–61
19. Rickels K, Amsterdam J, Clary C, et al. Buspirone in depressed outpatients: a controlled study. Psychopharmacol Bull 1990;26:163–167
20. Harvey KV, Balon R. Augmentation with buspirone: a review. Ann Clin Psychiatry 1995;7:143–147
21. Bakish D. Fluoxetine potentiation by buspirone: three case histories. Can J Psychiatry 1991;36:749–750
22. Jacobsen FM. Possible augmentation of antidepressant response by buspirone. J Clin Psychiatry 1991;52:217–220
23. Joffe RT, Schuller DR. An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. J Clin Psychiatry 1993; 54:269–271
24. 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
25. Landén M, Björling G, Agren H, et al. A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J Clin Psychiatry 1998;59: 664–668
26. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
27. 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
28. Montgomery SA, Asberg M. A new depression rating scale designed to be sensitive to change. Br J Psychiatry 1979;134:381–389
29. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale. Acta Psychiatr Scand 1987;76(suppl 334):1–100