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Effectiveness of Buspirone in Alleviating Anxiety Symptoms in Patients with Depressive Disorder: A Multicenter Prospective Observational Study in Korea

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Objective: We aimed to investigate the effectiveness of buspirone as an adjunctive therapy for alleviating anxiety symptoms in patients with depressive disorders who are already taking antidepressants.
Methods: This was an open-label prospective multicenter non-interventional observational study conducted over 12 weeks. We enrolled 180 patients diagnosed with depressive disorders according to DSM-5 criteria and Hamilton Anxiety Rating Scale (HAMA) scores ≥ 18. Participants were already taking selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors and were prescribed adjunctive buspirone. Efficacy was assessed using HAMA, Hamilton Depression Rating Scale (HAMD), Clinical Global Impression Scale-Improvement, Clinical Global Impression Scale-Severity, Sheehan Disability Scale (SDS), and WHO-5 Well-Being Index.
Results: The efficacy analysis included 161 patients. HAMA scores decreased significantly from 25.2 ± 6.7 at baseline to 15.4 ± 8.6 at 12 weeks ($p < 0.001$), whereas HAMD scores decreased from 19.4 ± 4.6 to 12.7 ± 5.7 ($p < 0.001$). WHO-5 and SDS scores showed significant improvements. The HAMA response rate was 39.1% and the remission rate was 13.7% at 12 weeks. Adverse drug reactions were reported in 3.7% of participants. Subgroup analyses showed no significant differences in treatment response based on buspirone dosage, baseline anxiety/depression severity, or benzodiazepine use.
Conclusion: Adjunctive buspirone therapy effectively improved anxiety symptoms in depressed patients taking antidepressants, regardless of baseline symptom severity or buspirone dosage. The treatment was well-tolerated with few adverse events. Future studies using a control group are needed.

KEY WORDS: Depression; Anxiety; Anxious depression; Buspirone.

INTRODUCTION

Depressive disorder is a common condition with a high prevalence that negatively impacts the lives of patients [1-3]. Moreover, it is known that patients with comorbid conditions have more severe and chronic symptoms and suffer significant impairments in occupational functioning, psychosocial functioning, and quality of life compared to those without comorbid conditions [4]. In de-

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pressive disorder, comorbid anxiety disorder is very common [5]. According to the National Comorbidity Survey Replication in the United States, the lifetime comorbidity rate of anxiety disorder in patients with major depressive disorder (MDD) is reported to be 59.2%, with a one-year comorbidity rate of 57.5% [6]. Failure to accurately diagnose coexisting anxiety disorders in patients with depressive disorder can affect the long-term course of the depressive disorder, leading to missed opportunities for effective treatment of anxiety disorders and potentially poor prognosis [7]. The treatment of patients with coexisting anxiety and depressive disorders largely includes pharmacotherapy, psychosocial therapy, and a combination of both [7]. In pharmacotherapy, antidepressants are generally chosen as the first-line treatment for this condition [8,9]. Antidepressants primarily include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, agomelatine, and vortioxetine [10]. Among these, SSRIs and SNRIs are effective not only for depressive disorders but also for anxiety disorders [5,11]. Therefore, these medications are preferred as first-line treatments in cases of coexisting depressive and anxiety disorders. Benzodiazepine class drugs, classified as anxiolytics, are helpful in treating anxiety disorders but are not effective for coexisting depressive disorders, and because of concerns related to abuse and dependence with long-term use, they are not suitable first-line treatments [12].

Clinical practice guidelines for anxiety disorders recommend using SSRIs, SNRIs, or buspirone as initial pharmacotherapy or in combination with benzodiazepine anxiolytics for a short duration based on clinical judgment [13,14]. Azapirone class drugs, including buspirone, have been reported to have some antidepressant effects at high doses in addition to their anxiolytic effects, making them a potential choice for coexisting anxiety and depressive disorders [15,16]. Buspirone was approved by the US Food and Drug Administration as a treatment for anxiety disorders in 1986 and is currently used in Korea. The exact mechanism of the anxiolytic effect of buspirone is not clear, but it is thought to be related to its partial agonistic action on presynaptic serotonin 1A autoreceptors, thereby reducing the firing of serotonergic neurons [17]. Buspirone does not have an antidepressant effect in severe depression but is known to have some antidepressant effect in mild depression, especially in anxious depression [18, 19]. Additionally, buspirone partially antagonizes postsynaptic serotonin 1A receptors, enhancing the activity of serotonergic antidepressants [20]. However, there is still insufficient research on the effectiveness of buspirone as a combination therapy with antidepressants in patients with depressive disorders. Therefore, this prospective observational study aims to investigate the effects of buspirone as an adjunct to antidepressants in Korean patients with coexisting anxiety and depressive disorders in a clinical setting.

METHODS

Study Population and Design

This was an open-label prospective multicenter non-interventional observational 12-week study that included 180 patients diagnosed with depressive disorders according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. The study was conducted at 16 university hospitals in Korea. The inclusion criteria for this study were as follows: 1) voluntarily signed informed consent forms and agreed participation; 2) adults aged 19 years and older; 3) diagnosis of a depressive disorder according to the DSM-5 criteria; 4) Hamilton Anxiety Rating Scale (HAMA) score of 18 or higher at enrollment; 5) subjects who had been prescribed SSRIs and/or SNRIs at or above the effective dosage for 4 weeks or more, and were found to require additional buspirone for the management of anxiety symptoms by the investigator (the combination of one SSRI and one SNRI was allowed, but the use of two or more SSRI or SNRI combinations, or switching between SSRIs and SNRIs was not permitted); and 6) ability to read and comprehend self-report scales. The exclusion criteria were as follows: 1) contraindicated for buspirone; 2) received azapirone class anxiolytics, including buspirone, in the past 4 weeks; 3) initiated or had changed the dosage of benzodiazepine class anxiolytics within the past week; 4) received psychostimulants or other attention-deficit/hyperactivity disorder (ADHD) medications in the past 4 weeks; 5) pregnant or breastfeeding status; 6) participation in other clinical trials within 12 weeks of the baseline; 7) risk of suicide, self-harm, or harm to others, as assessed by the investigator; and 8) considered inappropriate for the study by the investigator.

Medication

This study was designed as a non-interventional observational study, and the treatment of subjects was determined individually by the investigators in their routine clinical settings. Therefore, the study protocol did not provide consistent guidelines for specific details including the dosage of medications. The investigators made appropriate determinations taking into consideration the prescribing information of the medications and the psychiatric and medical status of the subjects. Although specific prohibited concomitant medications were not specified, the need to prescribe any of the following medications would lead to study discontinuation: 1) any antidepressant other than current medication during the study period; 2) newly prescribed antipsychotic drugs, mood stabilizers, or anticonvulsants during the study period (if the same dosage had been maintained for at least 4 weeks before the start of the study, the dosage could be continued during the study); 3) newly prescribed psychostimulants or other ADHD medications during the study; 4) newly prescribed benzodiazepines during the study (if the same dosage had been maintained for at least 1 week before the start of the study, the dosage could be continued or reduced during the study); 5) newly prescribed beta-blockers, including propranolol, during the study (if the same dosage had been maintained for at least 4 weeks before the start of the study, the dosage could be continued during the study). In addition, other concomitant medications with a low likelihood of impacting depressive symptoms could be used at the discretion of the investigators. However, all concomitant medication use was documented in the case report form.

Efficacy and Safety Assessment

Before beginning the treatment with buspirone (baseline visit, week 0), the HAMA, Hamilton Depression Rating Scale (HAMD), and the Clinical Global Impression Scale-Severity Scale (CGI-S) were applied. Evaluation for the efficacy of the buspirone combination was carried out with the HAMA, HAMD, CGI-S, and the Clinical Global Impression Scale-Improvement (CGI-I) in weeks 4, 8, and 12. To evaluate functioning and psychosocial well-being, the Sheehan Disability Scale (SDS) and 5-item World Health Organization Well-Being Index (WHO-5) were applied at baseline and week 12. The primary efficacy outcome was defined as the mean change from baseline to week 12 on the HAMA total score. Additional efficacy measures included the mean change in HAMD, CGI-S, CGI-I, SDS, and WHO-5 scores and response and remission rates on HAMA and HAMD. A response was defined as a decrease in the HAMD or HAMA total score $\geq 50\%$. Remission was defined as HAMA or HAMD total score ≤ 7. All adverse drug reactions (ADRs), serious adverse events (SAEs), and serious adverse drug reactions (SADRs) occurring after the administration of buspirone were investigated at each visit.

Statistical Analyses

The efficacy analysis set (EAS) was defined as all subjects for whom data on primary efficacy outcome measure (HAMA) were recorded at least once, and the last-observation-carried-forward (LOCF) method was applied for endpoint analysis. All subjects who received at least one dose of the study medication (buspirone) and attended at least one follow-up visit were included in the safety set. Quantitative data are expressed as mean ± standard deviation, and categorical variables are described as absolute and relative frequencies. For the analysis of quantitative outcome variables, a paired t test and repeated measure analysis of variance were used. For the analysis of categorical variables, the chi-squared test was used.

For subgroup analysis, the subjects were categorized as follows: low-dose group (30 mg/day or less) versus standard-dose group (more than 30 mg/day) based on the mean daily dose of buspirone; moderate anxiety group with baseline HAMA score of 18 to 24 versus severe anxiety group with baseline HAMA score of 25 or higher; mild to moderate depression group with baseline HAMD score of less than 24 versus severe depression group with a baseline HAMD score of 24 or higher. For subgroup analysis, repeated measures of analysis of covariance were used for age, sex, benzodiazepine use, baseline anxiety, and/or depression severity as covariates. All statistical tests were two-tailed with a significance level of 0.05.

Ethics

The study was conducted according to the Declaration of Helsinki and Good Clinical Practices. Written informed consent was obtained from all subjects after the subjects were given an extensive explanation of the nature and procedures of the study. The study protocol was approved by the Institutional Review or Ethics Committees at Yeouido

St. Mary's Hospital (SC20OODE0149).

RESULTS

Baseline Characteristics and Medications during the Study

In this study, a total of 180 participants were enrolled. Among these, 17 subjects did not attend subsequent visits following visit 1. Therefore, the number of participants included in the safety set was 163, whereas 161 were included in the EAS because an evaluation of the efficacy variable was not conducted for 19 subjects after the baseline visit. The baseline characteristics of the participants included in the EAS are presented in Table 1. The mean age of subjects was 39.1 ± 17.2 years, and 48.5% (n = 78) were male. The baseline scores on HAMA were 25.2 ± 6.7, indicating moderate to severe anxiety, and HAMD scores were 19.4 ± 4.6, indicating moderate depression. Among the subjects, the most prevalent diagnosis was MDD (n = 129, 80.1%), followed by persistent depressive disorder (n = 19, 11.8%) and other specified/unspecified depressive disorders (n = 12, 7.5%). Common psychiatric comorbidities included panic disorder/agoraphobia (n = 28, 17.4%) and other specified/unspecified anxiety disorders (n = 12, 7.5%). At baseline, the most frequently prescribed antidepressants were milnacipran (n = 43, 26.7%), escitalopram (n = 42, 26.1%), and paroxetine (n = 21, 13.0%). Additionally, 31 patients (19.3%) were receiving antipsychotics or mood stabilizers, with a prevalence of aripiprazole (n = 20, 12.4%) and quetiapine (n = 9, 5.6%). During the study period, 109 patients (67.7%) received benzodiazepines. The average dosage of buspirone administered throughout the entire study duration was 17.7 ± 8.6 mg/day.

Efficacy

During the 12-week study period, HAMA scores significantly decreased from a baseline of 25.2 ± 6.7 to an endpoint of 15.4 ± 8.6 ($p < 0.001$, Fig. 1A). Similarly, HAMD scores decreased from a baseline of 19.4 ± 4.6 to 12.7 ± 5.7 at 12 weeks ($p < 0.001$, Fig. 1B), and CGI-S scores also showed a significant reduction from a baseline of 4.3 ± 0.7 to 3.2 ± 1.0 points at 12 weeks ($p < 0.001$, Fig. 1C). Additionally, SDS scores decreased from a baseline of 20.3 ± 10.2 points to 15.4 ± 10.1 points at 12 weeks ($p < 0.001$, Fig. 2A), and WHO-5 scores increased from a baseline of 5.6 ± 4.4 points to 8.2 ± 5.4 points at 12 weeks ($p < 0.001$, Fig. 2B), indicating significant improvement in functioning and disability over the 12-week buspirone treatment. The CGI-I scores at week 12 indicated a minimal to much-improved status, with a score of 3.2 ± 1.0. The response and remission rates evaluated through HAMD and HAMA are presented in Figure 2. At 12 weeks, the HAMA response rate was 39.1% (n = 63), with a remission rate of 13.7% (n = 22). The HAMD response rate was 27.3% (n = 44), and the remission rate was 17.4% (n = 28) (Fig. 3).

Safety

Among 180 subjects who were included in this study, 132 (73.3%) subjects completed the 12-week study and 48 (26.7%) subjects dropped out. The reason for study incompletion was the loss of follow-up (n = 20), use of prohibited concomitant medication (n = 10), discontinuation of buspirone due to adverse events or lack of efficacy (n = 9), the decision of the investigator (n = 6), and withdrawal of consent (n = 3). During the study, ADRs occurring after the administration of investigational drugs were observed in six individuals (3.7%), totaling nine incidents. There was one incident (0.6%) of a serious adverse event, and no instances of SADRs. One suicide attempt was recorded following the administration of investigational drugs during the study period. However, the causality was assessed as 'unlikely'. ADRs leading to discontinuation of the investigational drugs occurred in four individuals (2.5%), accounting for seven cases. ADRs reported after the administration of investigational drugs during the study period included nausea in three individuals (1.8%), whereas vomiting, dizziness, somnolence, fatigue, insomnia, and pruritus were each reported in one individual (0.6%). ADRs leading to premature withdrawal from the study occurred in four individuals (2.5%) and involved seven incidents: nausea was reported by two individuals, and vomiting, dizziness, somnolence, insomnia, and pruritus were each reported by one individual.

Subgroup Analysis

Among the 161 subjects in the EAS, 147 were categorized into the low-dose group, with a mean daily dose of buspirone at 30 mg/day or below, and 14 were classified into the high-dose group, exceeding 30 mg/day. In both groups, the HAMA total score and HAMD total score at 12

Table 1. Baseline demographic and clinical characteristics of included subjects (total n = 161)

Variables		Value
Age (yr)		39.1 ± 17.2
Male		78 (48.5)
Education[a]	Elementary school	13 (8.1)
	Middle school	9 (5.6)
	High school	90 (55.9)
	College degree or higher	48 (29.8)
Diagnosis	Major depressive disorder	129 (80.1)
	Persistent depressive disorder	19 (11.8)
	Other specified depressive disorder/unspecified depressive disorder	12 (7.5)
	Disruptive mood dysregulation disorder	1 (0.6)
Psychiatric comorbidity	Social anxiety disorder	6 (3.7)
	Panic disorder/agoraphobia	28 (17.4)
	Generalized anxiety disorder	3 (1.9)
	Other specified anxiety disorder/unspecified anxiety disorder	12 (7.5)
	Obsessive-compulsive and related disorders	3 (1.9)
	Posttraumatic stress disorder	8 (5.0)
	Dissociative disorders	1 (0.6)
	Somatic symptom and related disorders	6 (3.7)
	ADHD	4 (2.5)
	Avoidant personality disorder	1 (0.6)
Physical comorbidity	Dyslipidemia	33 (20.5)
	Hypertension	14 (8.7)
	Diabetes mellitus	5 (3.1)
	Gastrointestinal disorders	31 (19.3)
	Musculoskeletal and connective tissue disorders	11 (6.8)
	Hepatobiliary disorders	5 (3.1)
	Neoplasms (benign, malignant and unspecified)	5 (3.1)
	Respiratory, thoracic and mediastinal disorders	4 (2.5)
	Cardiac disorders	4 (2.5)
	Anemia	3 (1.9)
	Hypothyroidism	1 (0.6)
Antidepressants	Milnacipran	43 (26.7)
	Escitalopram	42 (26.1)
	Paroxetine	21 (13.0)
	Sertraline	15 (9.3)
	Fluoxetine	16 (9.9)
	Desvenlafaxine	11 (6.8)
	Duloxetine	9 (5.6)
	Venlafaxine	5 (3.1)
Antipsychotics	Aripiprazole	20 (12.4)
	Quetiapine	9 (5.6)
	Olanzapine	1 (0.6)
Mood stabilizers	Lithium	1 (0.6)
Baseline scores	HAMA	25.2 ± 6.7
	HAMD	19.4 ± 4.6
	CGI-S	4.3 ± 0.7
	SDS	20.3 ± 10.2
	WHO-5	5.6 ± 4.4

Values are presented as number (%) or mean ± standard deviation.
ADHD, attention-deficit hyperactivity disorder; CGI-S, Clinical Global Impression Scale-Severeity; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; SDS, Sheehan Disability Scale; WHO-5, 5-item World Health Organization Well-Being Index.
[a]Data for 1 subject was missing.

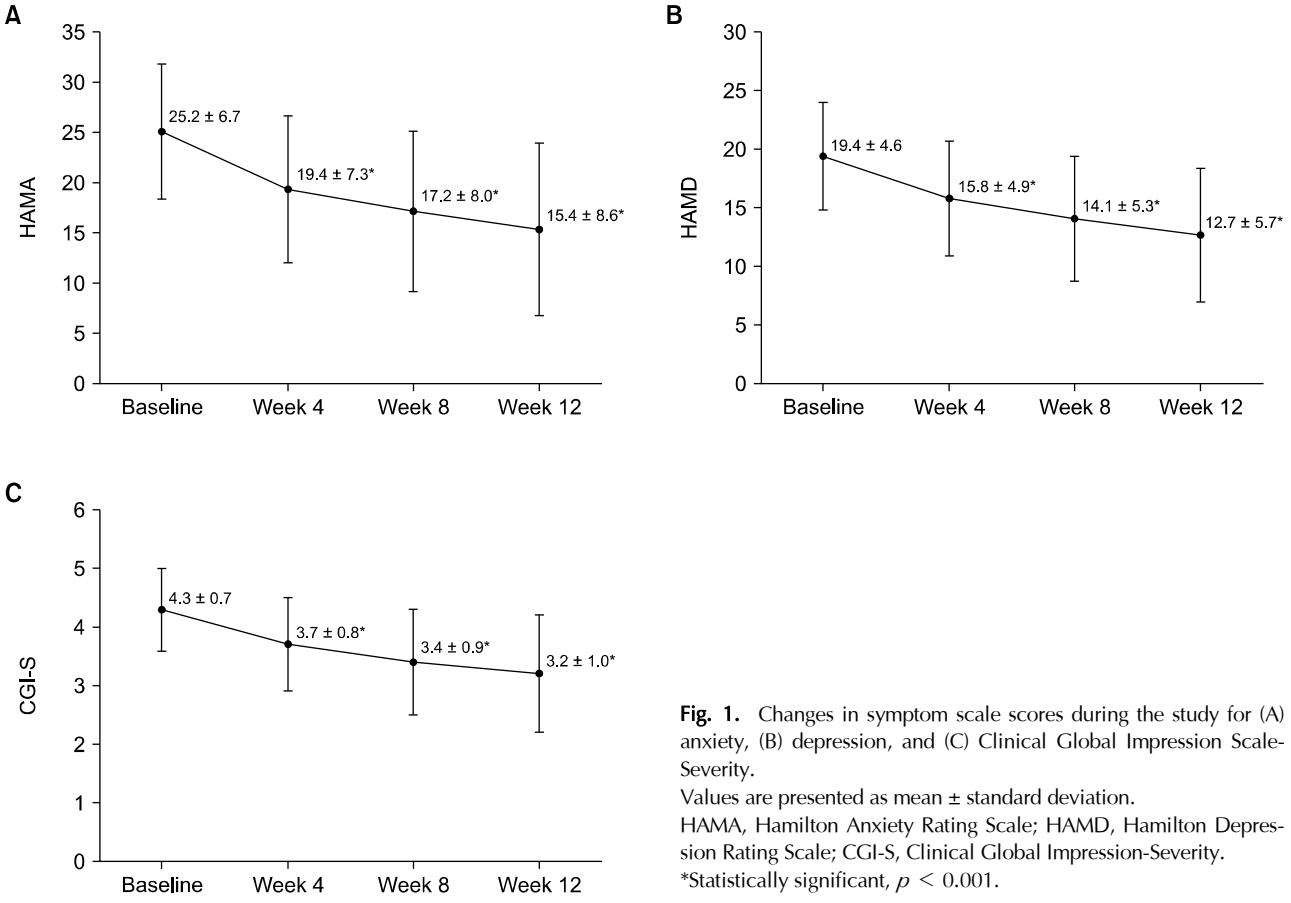

Fig. 1. Changes in symptom scale scores during the study for (A) anxiety, (B) depression, and (C) Clinical Global Impression Scale-Severity.
Values are presented as mean ± standard deviation.
HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; CGI-S, Clinical Global Impression-Severity.
*Statistically significant, $p < 0.001$.

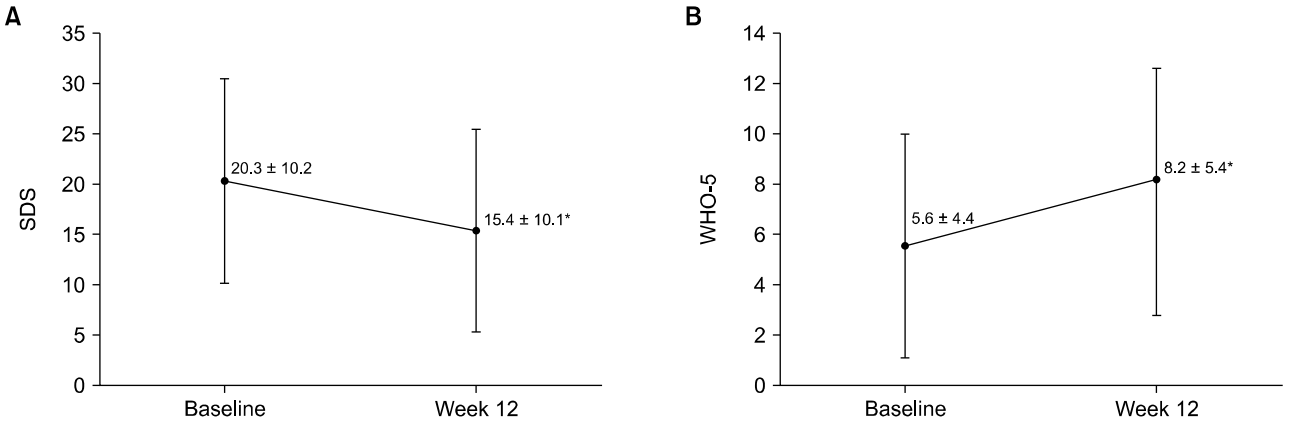

Fig. 2. Changes in (A) WHO-5 and (B) SDS scores during the study.
Values are presented as mean ± standard deviation.
SDS, Sheehan Disability Scale; WHO-5, 5-item World Health Organization Well-Being Index.
*Statistically significant, $p < 0.001$.

weeks significantly decreased compared to baseline, with no significant differences observed between the two groups (Table 2). During the study period, 109 individuals were included in the benzodiazepine-use group, and 52 individuals were included in the non-use group. Similar to the low and high-dose groups, both groups exhibited a significant reduction in HAMA and HAMD total scores at 12 weeks compared to baseline, with no significant differ-

ences between the two groups. The moderate anxiety group, comprising 99 individuals with a baseline HAMA total score of 24 or below, and the severe anxiety group, consisting of 62 individuals with a baseline HAMA total score 25 or higher, both demonstrated a significant reduction in HAMA and HAMD total scores at 12 weeks, irrespective of baseline anxiety severity. No significant differences were observed between the two groups (Table 2). In terms of baseline HAMD total score, the mild to moderate depression group included 135 individuals with a score below 24, whereas the severe depression group comprised 26 individuals with a score of 24 or above. Both groups showed a significant reduction in HAMA and HAMD total scores during the 12-week study period, with no significant differences in the extent of reduction between the two groups (Table 2).

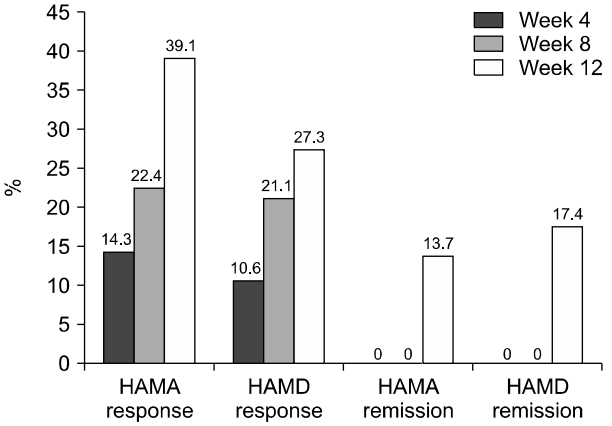

Fig. 3. Response and remission rate during the study.
HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale.

DISCUSSION

In this study, subjects with anxious depression exhibited significant reductions in anxiety and depression scores. Additionally, WHO-5 scores increased, which reflected improved well-being and SDS scores and suggested better functioning and reduced disability. The study reported a HAMA response rate of approximately 39% and a HAMD response of around 27%. In terms of safety, 73% of participants completed the study, and ADRs were observed in a small percentage of participants. Subgroup analyses revealed that augmentation of SSRI or SNRI treatment with buspirone improved depression and anxiety symptoms in patients with severe depression or anxiety at baseline to the same extent as those with moderate depression or anxiety. Interestingly, the dosage of buspirone did not affect the improvement in depression and anxiety symptoms.

The improvement in depressive symptoms observed with buspirone augmentation in our study is consistent with the findings of previous studies. Earlier studies that examined the effectiveness of buspirone in treating depression suggested that buspirone offers significant benefits as both a primary and adjunctive treatment for depression, with its antidepressant effects shown to be in-

Table 2. Changes in HAMA and HAMD total score during the study based on subgroup analysis

Subgroups	Category	Scale	Baseline (n^a = 161)	Week 4 (n^a = 152)	Week 8 (n^a = 155)	Week 12 (n^a = 161)	p value[b]
Buspirone dose	Low dose (≤ 30 mg/day)	HAMA	25.3 ± 6.9	19.8 ± 7.7	17.2 ± 8.3	15.1 ± 8.8	0.118
	Standard dose (> 30 mg/day)		24.1 ± 3.2	19.9 ± 4.8	20.0 ± 4.1	18.2 ± 5.6	
	Low dose (≤ 30 mg/day)	HAMD	19.6 ± 4.6	16.1 ± 5.0	14.2 ± 5.5	12.5 ± 5.7	0.203
	Standard dose (> 30 mg/day)		17.6 ± 4.3	15.3 ± 3.2	14.7 ± 3.8	14.5 ± 4.6	
Baseline HAMA	Moderate anxiety (HAMA ≤ 24)	HAMA	21.1 ± 2.0	16.4 ± 4.8	13.9 ± 5.4	11.9 ± 6.0	0.856
	Severe anxiety (HAMA ≥ 25)		31.8 ± 6.3	25.2 ± 7.8	23.2 ± 8.4	20.8 ± 9.4	
	Moderate anxiety (HAMA ≤ 24)	HAMD	17.7 ± 3.9	14.7 ± 4.3	12.5 ± 4.6	10.8 ± 4.9	0.107
	Severe anxiety (HAMA ≥ 25)		22.2 ± 4.1	18.0 ± 5.0	16.9 ± 5.4	15.7 ± 5.5	
Baseline HAMD	Mild to moderate depression (HAMD < 24)	HAMA	23.8 ± 5.2	18.7 ± 6.6	16.3 ± 7.3	14.0 ± 7.5	0.751
	Severe depression (HAMD ≥ 24)		32.4 ± 8.7	25.2 ± 9.2	23.9 ± 9.1	22.3 ± 10.9	
	Mild to moderate depression (HAMD < 24)	HAMD	18.0 ± 3.6	15.1 ± 4.4	13.3 ± 5.0	11.9 ± 5.4	0.152
	Severe depression (HAMD ≥ 24)		26.4 ± 2.3	20.6 ± 4.6	18.8 ± 5.0	16.8 ± 5.0	

HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale.
[a]Number of participants included in analysis adjusted with last-observation-carried-forward (LOCF) method.
[b]p value based on between-group repeated measure of analysis of covariance.

dependent of its anxiolytic effects [21]. Subsequent studies have further explored the efficacy of buspirone in untreated patients with depression. In a placebo-controlled study by Landén *et al.* [22], patients with major depressive episodes unresponsive to SSRI treatment were randomly assigned to either buspirone or placebo augmentation for 4 weeks. The study found no statistically significant difference in response rates between the buspirone and placebo groups. However, an optional open-label phase showed a 69.4% response rate to buspirone augmentation, indicating potential efficacy in some patients despite a high placebo response rate. In a double-blind, placebo-controlled study by Appelberg *et al.* [23], patients with major depressive episodes unresponsive to fluoxetine or citalopram were treated with either buspirone or a placebo. Results indicated a significantly greater reduction in depressive symptoms in the buspirone group compared to placebo after the first week, especially in patients with initially high MADRS scores. The sequenced treatment alternatives to relieve depression (STAR*D) trial [24] also found that buspirone augmentation for an average of 9.2 weeks in patients with MDD who did not achieve remission after approximately 12 weeks of SSRI (citalopram) treatment resulted in about a 30% remission rate (HAMD score $\leq$ 7) and a 17.1% reduction in the symptom scores as measured by the Quick Inventory of Depressive Symptomatology. Additionally, in another double-blind placebo-controlled clinical trial by Fava *et al.* [25], a combination of low-dose buspirone and melatonin significantly improved depressive symptoms compared to placebo or buspirone monotherapy, highlighting its potential as an effective treatment strategy for MDD. Collectively, this evidence suggests that buspirone augmentation can effectively improve depressive symptoms.

The anxiolytic efficacy of buspirone in generalized anxiety disorder is well established [26] and has high tolerability [27]. However, previous studies have also shown that buspirone can treat comorbid depression associated with anxiety disorders along with improvement in anxiety symptoms. In a 6-week double-blind trial evaluated by HAMD and HAMA [28], buspirone improved depressive and anxiety symptoms in patients with generalized anxiety disorder comorbid mild depression. In a previous meta-analysis [29], compared to placebo, buspirone showed an improvement in the symptoms of anxiety and depression. Moreover, physicians measured a global improvement, regardless of the severity of comorbid depression in generalized anxiety disorder. This evidence suggests that buspirone is helpful in the treatment of comorbid depressive symptoms as well as primary anxiety symptoms in anxiety disorders. In this study, buspirone was also effective in treating comorbid anxiety in patients with a primary diagnosis of depression. To the best of our knowledge, this is the first study to identify the anxiolytic effects of buspirone on anxious depression. Our findings suggest the potential use of buspirone in depression with anxiety symptoms, in addition to its established use for generalized anxiety disorder.

Of the participants in this study, about half were taking milnacipran (n = 43, 26.7%) and escitalopram (n = 42, 26.1%). In global treatment guidelines, SSRIs are the recommended first-line medication for the treatment of MDD [9,30], and this is also the case in Korea [10]. Milnacipran, an SNRI, was the medication used most commonly for depression in this study. This was probably because patients had co-occurring anxiety symptoms at the onset of their illness, which led physicians to choose an SNRI, or patients were switched to an SNRI because their initial SSRI monotherapy did not improve their anxiety. Approximately 19% of patients were also taking an augmentation drug for depression, such as antipsychotics and mood stabilizers, indicating that they were less responsive to initial treatment with SSRIs.

Another unique aspect of this study is the relatively low dose of buspirone (17.7 $\pm$ 8.6 mg/day) used throughout when compared to previous studies of buspirone augmentation with SSRIs, which have used doses as low as 20 mg/day and as high as 60 mg/day [22-24,29]. The dose in our study is also considered low given that the recommended starting dose of buspirone is 15 mg/day [21]. One possible explanation is that our study is open-label and low doses of medication may have been used as an adjunctive medication along with antidepressants. In other words, the presence of antidepressants already being taken might have made it difficult to add a relatively high dose of buspirone. Accordingly, the use of lower doses may have resulted in a lower rate of adverse events in this study.

In subgroup analysis, patients did not differ in their response to buspirone adjunctive therapy based on the severity of depressive and anxiety symptoms. Furthermore, there was no difference in response to treatment based on

the dose of buspirone. This is consistent with previous meta-analyses that have shown buspirone to be effective regardless of the degree of comorbid depression or anxiety in generalized anxiety disorder. This may be because anxiety and depression are thought to be on a continuum and to be highly comorbid, so when one improves, the other improves in parallel [31,32]. In this study, the improvement in anxiety and depressive symptoms could be attributed to the augmentation of buspirone in patients taking SSRIs or SNRIs, which may have enhanced the therapeutic effects of the antidepressant and buspirone.

The limitations of this study are as follows. First, this is an open-label observational study, meaning there is no control group. This makes it difficult to know whether buspirone use improved anxiety symptoms associated with depression independent of antidepressants. In addition, in this study, we did not compare the anxiolytic effects of buspirone between groups using SSRI or SNRI monotherapy or a combination of both medications. Second, the low dose of the drug used suggests that the improvement in anxiety may not be due to the actual pharmacologic mechanism of buspirone. Third, we did not check the past drug use of the patient and resistance to treatment. While these are important factors in determining patient prognosis and treatment effectiveness, this study did not include these criteria in patient selection and analysis. Finally, the number of participants was not large, around 180, which limits the generalizability of the results. In addition, the LOCF method used to correct for missing values in this study may introduce bias into the results of the analysis. This may also have affected the interpretation of the study results. Nevertheless, the study has value in that it included patients using a variety of medications, including SSRIs and SNRIs, over a 12-week period at multiple sites.

In conclusion, our study found that adjunctive therapy with buspirone effectively treated anxiety symptoms in patients with depression taking antidepressants. In addition, it has significantly improved the quality of life for patients. These benefits were seen regardless of the severity of depression or anxiety, and the incidence of adverse effects was low throughout the trial. Future research will require larger studies with controlled groups, including comparisons of buspirone's anxiolytic effects in patients taking SSRIs versus SNRIs. Additionally, further investigation of the pharmacologic interactions between antidepressants and buspirone is needed to verify the effectiveness and safety of combination therapy.

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■ Conflicts of Interest

Won-Myong Bahk is a member of the Editorial Board of Clinical Psychopharmacology and Neuroscience, Chi-Un Pae is an editor-in-chief of Clinical Psychopharmacology and Neuroscience, Young-Eun Jung and Young Sup Woo are the associate editors of Clinical Psychopharmacology and Neuroscience. These authors were not involved in the journal's review of, or decisions related to, this manuscript. No other potential conflicts of interest pertinent to this article were reported.

■ Author Contributions

Conceptualization: Young Sup Woo, Won-Myong Bahk. Investigation: Young Sup Woo, Won-Seok Choi, Jong-Hyun Jeong, Jonghun Lee, Do-Hoon Kim, Jong-Chul Yang, Se-Hoon Shim, Seung-Gul Kang, Young-Eun Jung, Won Kim, Chi-Un Pae, Won-Myong Bahk. Formal analysis: Young Sup Woo. Data curation: Young Sup Woo, Won-Myong Bahk. Supervision: Won-Myong Bahk. Funding: Won-Myong Bahk. Writing–original draft: Young Sup Woo, Won-Seok Choi. Writing–review & editing: Won-Myong Bahk.

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