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Efficacy and Safety of Escitalopram, Desvenlafaxine, and Vortioxetine in the Acute Treatment of Anxious Depression: A Randomized Rater-blinded 6-week Clinical Trial

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Objective: Anxious depression is associated with greater chronicity, higher severity of symptoms, more severe functional impairment, and poor response to drug treatment. However, evidence for first-choice antidepressants in patients with anxious depression is limited. This study aimed to compare the efficacy and safety of escitalopram, desvenlafaxine, and vortioxetine in the acute treatment of anxious depression.
Methods: Patients (n = 124) with major depressive disorder and high levels of anxiety were randomly assigned to an escitalopram treatment group (n = 42), desvenlafaxine treatment group (n = 40), or vortioxetine treatment group (n = 42) in a 6-week randomized rater-blinded head-to-head comparative trial. Changes in overall depressive and anxiety symptoms were assessed using the 17-item Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA), respectively.
Results: Patients demonstrated similar baseline-to-endpoint improvement in scores and similar response and remission rates for HAMD and HAMA. Analysis of the individual HAMD items revealed that desvenlafaxine significantly reduced anxiety somatic scores (p = 0.013) and hypochondriasis scores (p = 0.014) compared to escitalopram. With respect to the individual HAMA items, desvenlafaxine treatment showed significantly lower scores for respiratory symptoms (p = 0.013) than escitalopram treatment and cardiovascular symptoms (p = 0.005) than vortioxetine treatment. The treatments were well tolerated, with no significant differences.
Conclusion: Our results indicated no significant differences in the efficacy and tolerability of escitalopram, desvenlafaxine, and vortioxetine in this subtype of patients with anxious depression during the acute phase of treatment.

KEY WORDS: Depression; Anxiety; Anxious depression; Escitalopram; Desvenlafaxine; Vortioxetine.

INTRODUCTION

Symptoms of anxiety are common in patients with depressive disorders. In the clinical setting, only a few patients present with pure anxiety or depressive disorder [1,2]; moreover, 60−96% of patients with depression complain of anxiety symptoms [3]. When depression is accompanied by anxiety symptoms, the prognosis is poor, as the patients show greater chronicity, higher severity of symptoms, more severe social dysfunctions, and a poor response to drug treatment [4,5]. In addition, patients with comorbid depression and anxiety are sensitive to the side effects of therapeutic drugs and have poor compliance

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with treatment; that is, they often discontinue treatment before it is completed [5]. Previous studies have reported that comorbid anxiety is a powerful clinical factor; 30–60% of patients with depressive disorders do not respond to antidepressant treatment, and research indicates that resistance to treatment increases when accompanied by symptoms of anxiety [6,7].

Under the above clinical interest, several therapies have been proposed for the treatment of anxious depression. Regardless of whether anxiety symptoms develop concomitantly, the current guidelines available for treating depression with medication commonly recommend the "administration of antidepressants as first-line treatment" [8-10]. However, they are unable to recommend the most appropriate class of antidepressants for patients with anxious depression, mostly because of lack of evidence. Antidepressants recommended without priority are based on placebo-control studies of several classes of antidepressants or meta-analyses of these studies [11,12]. There are some indirect comparisons, but direct comparison studies are scarce. Therefore, a head-to-head study comparing the clinical outcomes of antidepressants for anxious depression is needed.

Current clinical practice for treating depressive disorders accompanied by symptoms of anxiety involves the maintenance of treatment with antidepressants that were developed primarily based on their pharmacokinetic characteristics [5,13]. However, these proposals also remain at the level of hypotheses, and evidence based on actual practice situations is lacking. Current treatment strategies for depressive disorder when anxiety is concomitant are limited; consequently, clinical treatment strategies based on the empirical theories of the clinicians have been given priority.

Previous clinical studies had limitations, such that the research hypothesis on anxiety symptoms associated with depression was often not presented in advance, and the change in anxiety symptoms was often not analyzed as a primary outcome variable [14]. In addition, although some placebo-controlled studies view relief of anxiety symptoms as a secondary outcome, these study results do not prove which class of antidepressants is superior for the relief of the symptoms of anxiety in anxious depression.

In order to provide a rationale for drug treatment strategies for anxious depression, we designed this head-to-head study to directly compare the efficacy and safety of antidepressants that have been recently developed and widely used classes of antidepressants, escitalopram, desvenlafaxine, and vortioxetine, for the acute treatment of anxious depression. Escitalopram, has been increasingly used as a selective serotonin reuptake inhibitor (SSRI) for the treatment of anxious depression in various studies [15,16]; desvenlafaxine, is a metabolite of venlafaxine, which is the recommended treatment option for anxious depression as a serotonin–norepinephrine reuptake inhibitor (SNRI) [17]; the most recently developed vortioxetine, has accumulated evidence showing effects on anxious depression [18]. This study addresses the following questions: First, which of these three antidepressants is more effective in improving depressive symptoms in patients with anxious depression? Second, which of them is more effective in improving the symptoms of anxiety in these patients? Third, which antidepressant is more effective in improving the patients' quality of life (QOL), function, somatization, and cognitive function in cases of depressive episodes with symptoms of anxiety?

METHODS

Participants

Participants aged 19–65 years were enrolled among the patients who met the criteria for major depressive disorder (MDD) without psychotic features, according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). The inclusion criteria included a baseline score ≥ 14 on the 17-item Hamilton Depression Rating Scale (HAMD) [19], a baseline score ≥ 14 on the Hamilton Anxiety Rating Scale (HAMA) [20] and absence of adequate antidepressant treatment, defined as ≥ 6 consecutive weeks of treatment at the recommended dosage for the particular antidepressant.

The exclusion criteria included a current (≤ 12 months before baseline), primary diagnosis of any anxiety disorder (e.g., generalized anxiety disorder, social anxiety disorder, panic disorder, post-traumatic stress disorder); current or past comorbid diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, psychotic disorder not otherwise specified, mood-congruent or mood-incongruent psychotic features, bipolar disorder, alcohol or substance-use disorder, organic mental disorder including dementia, eating disorder, or obsessive compulsive disorder; presence of a

seizure disorder, comorbid serious medical illness including hyper- or hypothyroidism; previous treatment with electroconvulsive therapy; risk of suicide; current pregnant or lactation. Participants with an unclear history of antidepressant treatment prior to enrollment in the study were also excluded.

All patients provided a medical and psychiatric history, and physical and routine laboratory examinations were performed at the outset of the study. Written informed consent was obtained from all patients after a complete description of the study. The study protocol was approved by the institutional review or ethics committee of each study site (IRB No. 2016AS0035).

Treatment Protocol

This multicenter, 6-week, prospective, randomized, rater-blinded, parallel-group comparative trial was conducted from September 2016 to December 2018 at five university hospitals in South Korea. Eligible participants were randomized with a block randomization allocation in a 1:1:1 ratio to one of three treatment arms: escitalopram, desvenlafaxine, or vortioxetine. Drug dosages and titration schedules were based on the recommendations of the prescribing information for each product and according to the judgment of the clinicians involved in the study (escitalopram [10−20 mg/day], desvenlafaxine [50−200 mg/day], vortioxetine [10−20 mg/day]). No other psychotropic drugs were allowed during the study period, except benzodiazepines (up to 4 mg/day of lorazepam or equivalent) and hypnotics (up to 10 mg/day of zolpidem or equivalent).

Assessments

Study participants were assessed at baseline and at 2, 4, and 6 weeks. The primary efficacy variable was the change in HAMD during the 6 weeks of the study. The secondary efficacy measure was the change in the HAMA. Response was defined as an HAMD/HAMA score improvement greater than 50% of the baseline score and remission as 7 or less for the HAMD/HAMA total score [21,22].

Symptoms of depression were assessed using three clinician rating scales: the HAMD, Montgomery-Åsberg Depression Rating Scale (MADRS) [23], Clinical Global Impression Scale-Severity (CGI-S) [24]; additionally, a self-report scale was used, the Clinically Useful Depression Outcome Scale (CUDOS) [25]. Anxiety symptoms were assessed using a clinician rating scale, HAMA, and a self-report scale, the Clinically Useful Anxiety Outcome Scale (CUXOS) [26]. Somatic symptoms were assessed using a self-report scale, the Patient Health Questionnaire-15 (PHQ-15) [27]. Two other self-reported scales were administered to assess cognitive dysfunction in participants: the Perceived Deficits Questionnaire-Depression (PDQ-D) [28], and the British Columbia Cognitive Complaints Inventory (BC-CCI) [29]. Other instruments used were the Global Assessment of Functioning (GAF) [30] and the WHO Quality of Life Scale Abbreviated Version (WHOQOL-BREF) [31]. All assessors received the same investigator training module and were blinded to the patients' conditions and prescribed medications.

Safety was assessed via adverse events (AEs), vital signs, weight, and physical examination findings at each visit. AEs during the study period were recorded by the clinical research coordinators using the Systematic Assessment for Treatment Emergent Events-Specific Inquiry [32], and evaluated for severity and the causal relationship to the study drug.

Statistical Analysis

Using the chi-square test with 2 degrees of freedom, the sample size was set to discriminate the difference in the effect size (0.30 at the significance level of 0.05, and a statistical power of 80%. Considering a dropout rate of 15%, a total of 127 patients were required, and 43 patients were assigned to each group.

All participants who received one or more doses of the study drugs and had one or more post-baseline values for the primary and secondary efficacy assessments were included in the analysis set. All outcome measures were presented as differences among the three groups: escitalopram vs. desvenlafaxine vs. vortioxetine. We compared the baseline demographic and clinical characteristic data among the groups using analysis of variance (ANOVA), chi-square test, or Fisher's exact test.

The primary endpoint (mean change in the HAMD total score from baseline) was assessed using a mixed model for repeated measures analysis of covariance (ANCOVA), with treatment group as the between-subjects factor, and age, sex, baseline HAMD score, baseline HAMA score, study site, benzodiazepine or zolpidem use at baseline, and variables that were significantly different at baseline (e.g., first onset vs. recurrent depression) as covariates.

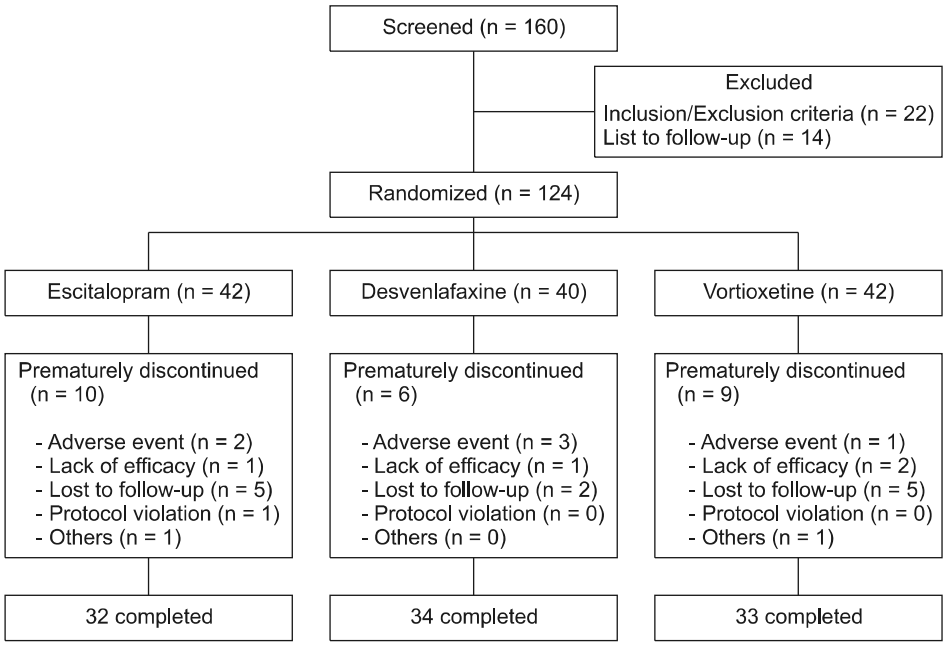

Fig. 1. Participants disposition.

The secondary endpoint (HAMA) and other variables (MADRS, CGI-S, CUDOS, CUXOS, PHQ-15, PDQ-D, BC-CCI, GAF, and WHOQOL-BREF) were analyzed in a similar manner to the primary endpoint. Response and remission rates were analyzed by multivariate logistic regression, with the same structure as the ANCOVA described above. Missing values were inputted using the last observation carried forward approach.

Serious AEs were recorded from the date the informed consent was obtained to the last follow-up contact, and other AEs were documented from the beginning of drug administration to the end of the follow-up period. In the present analysis, items that were associated with more than 5% of the participants were considered to be experiencing drug-related AEs. AEs leading to discontinuation of the study drug or withdrawal from the study were also documented.

All p values were two-tailed, and values of $p < 0.05$, were considered statistically significant. We used STATA version 15.0 (Stata Corp., College Station, TX, USA) for data analysis.

RESULTS

Baseline Characteristics

Of the 160 patients screened for the present study (Fig. 1), 124 met the inclusion and exclusion criteria for participation and were randomly assigned to receive one of the study drugs (escitalopram, n = 42; desvenlafaxine, n = 40; vortioxetine, n = 42). The baseline sociodemographic and clinical characteristics of the participants are summarized in Table 1. The mean HAMD total score of participants at baseline was 25.7, indicating that overall, participants experienced moderately severe events. For the HAMA, the mean total score was 28.3, indicating that participants had a high level of anxiety at baseline.

When comparing the baseline characteristics of the three treatment groups, there were no significant differences in sociodemographic or clinical characteristics among them. The proportion of men and participants experiencing the first onset of depression differed among the three groups, with a trend level significance ($p < 0.010$). There were no significant differences in the total HAMD ($p = 0.284$), HAMA ($p = 0.423$), MADRS ($p = 0.343$), and CGI-S ($p = 0.688$) scores. The total CUDOS ($p = 0.365$), CUXOS ($p = 0.189$), PHQ-15 ($p = 0.212$), PDQ-D ($p = 0.485$), BC-CCI ($p = 0.212$), GAF ($p = 0.196$), and WHOQOL-BREF ($p = 0.094$) scores at baseline were not significantly different among the groups (data not shown).

The mean doses of antidepressants during the study period are shown in Table 2. The mean lorazepam equivalent dose (overall $p = 0.702$) and the number of participants who used zolpidem (overall $p = 0.422$) during the study period were not statistically significantly different

Table 1. Demographic and baseline characteristics of the participants

Characteristic	Total (n = 124)	E (n = 42)	D (n = 40)	V (n = 42)	*p* value
Sex, male	28 (22.6)	11 (26.2)	9 (22.5)	8 (19.0)	0.092
Age (yr)	41.4 ± 16.1	42.2 ± 13.8	40.4 ± 17.1	38.8 ± 15.2	0.610
Married	82 (66.1)	29 (69.0)	25 (62.5)	28 (66.7)	0.537
Employed	42 (33.9)	13 (30.9)	15 (37.5)	14 (33.3)	0.237
Education level college ≥ graduate	41 (33.1)	14 (33.3)	13 (32.5)	14 (31.0)	0.852
First onset depression	77 (62.1)	24 (57.1)	25 (62.5)	28 (66.7)	0.077
Number of past depressive episodes	1.6 ± 1.3	1.6 ± 1.5	1.5 ± 1.4	1.7 ± 1.3	0.821
Family history of depression	18 (14.5)	7 (16.7)	5 (12.5)	6 (14.3)	0.728
Current physical comorbidity at baseline	32 (25.8)	10 (23.8)	10 (25.0)	12 (28.6)	0.684
Previous history of antidepressant medication	17 (13.7)	6 (14.2)	5 (12.5)	6 (14.2)	0.597
Benzodiazepine or zolpidem use at baseline	88 (55.0)	23 (54.8)	23 (57.5)	22 (52.4)	0.245
Baseline score					
HAMD	25.7 ± 8.2	26.3 ± 8.4	25.0 ± 8.0	25.1 ± 8.1	0.284
HAMA	28.3 ± 9.6	27.4 ± 8.7	28.3 ± 9.0	29.2 ± 10.2	0.423
MADRS	28.7 ± 9.1	26.9 ± 8.7	26.8 ± 8.8	28.7 ± 10.1	0.343
CGI-S	4.6 ± 1.1	4.5 ± 1.1	4.7 ± 1.1	4.7 ± 1.0	0.688

Values are presented as number (%) or mean ± standard deviation.
E, escitalopram; D, desvenlafaxine; V, vortioxetine; HAMD, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression Scale-Severity.

Table 2. Dose of antidepressants and benzodiazepine and number of zolpidem users at different time-points

Dose or number of users of medication	Escitalopram (n = 42)	Desvenlafaxine (n = 40)	Vortioxetine (n = 42)
Dose of antidepressants (mg/day)			
Week 0−2	6.2 ± 2.0	67.3 ± 21.2	6.1 ± 2.0
Week 2−4	11.4 ± 3.4	100.3 ± 35.2	12.3 ± 3.8
Week 4−6	14.5 ± 4.5	128.4 ± 50.4	15.9 ± 5.4
Week 6 (final visit point)	15.5 ± 5.4	138.3 ± 60.3	16.7 ± 5.8
Dose of benzodiazepine (mg/day) (lorazepam equivalent)			
Week 0−2	0.9 ± 0.5	0.8 ± 0.4	0.9 ± 0.5
Week 2−4	0.6 ± 0.3	0.5 ± 0.3	0.8 ± 0.5
Week 4−6	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.4
Number of participants who used zolpidem			
Week 0−2	3 (7.1)	2 (5.0)	2 (4.8)
Week 2−4	1 (2.4)	2 (5.0)	2 (4.8)
Week 4−6	2 (4.8)	1 (2.5)	2 (4.8)

Values are presented as mean ± standard deviation or number (%).
Dose of lorazepam (mg) equivalent: clonazepam, 0.5; diazepam, 10; alprazolam, 0.25.

among the groups at visit points (Table 2).

Acute Efficacy

In the primary efficacy analysis, there were no statistically significant differences between escitalopram, desvenlafaxine, and vortioxetine with respect to the baseline-to-endpoint improvement in the HAMD total score (p = 0.086) after adjusting for potential confounding variables. The difference among the three groups with respect to the change in the MADRS score from baseline to week 6 was also not significant (p = 0.080). In the secondary efficacy analysis, the difference among the three groups with respect to the change in the HAMA score from baseline to week 6 was not statistically significant (p = 0.114). Similarly, the other assessment variables, the CGI-S, CUDOS, CUXOS, PHQ-15, PDQ-D, BC-CCI, GAF, and WHOQOL-BREF, did not show a statistical difference among the three treatment groups. In general, the participants experienced improvement in the depressive and/or anxiety symptoms with no differences among the different treatments at any time-point throughout treatment (Table 3).

There were no significant differences among the three

Table 3. Mean changes in the overall depressive and anxiety symptom scores among the different time-points

Variable (change at week 6)	E (n = 42)	D (n = 40)	V (n = 42)	*p* value	Difference (*p* value)		
				E vs. D vs. V	E vs. D	E vs. V	D vs. V
HAMD							
Week 0−2	−7.1 ± 1.0	−8.7 ± 1.1	−6.6 ± 1.0	0.097	0.865	> 0.999	0.165
Week 2−4	−4.8 ± 0.7	−6.1 ± 0.9	−5.1 ± 1.1	0.505	0.730	> 0.999	> 0.999
Week 4−6	−3.3 ± 0.6	−3.6 ± 0.7	−1.7 ± 1.0	0.198	> 0.999	0.684	0.399
HAMA							
Week 0−2	−6.4 ± 1.1	−8.0 ± 1.5	−6.4 ± 1.2	0.254	0.364	> 0.999	0.312
Week 2−4	−5.9 ± 0.9	−6.0 ± 1.3	−5.3 ± 1.4	0.956	> 0.999	> 0.999	> 0.999
Week 4−6	−3.6 ± 0.7	4.9 ± 1.0	−1.6 ± 1.2	0.066	0.105	0.553	0.078

Values are presented as mean ± standard error.
E, escitalopram; D, desvenlafaxine; V, vortioxetine; HAMD, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.
Mean change was adjusted for age, sex, baseline HAMD score, baseline HAMA score, site, first onset of depression, and benzodiazepine or zolpidem use at baseline.

Table 4. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the treatment outcomes

Variable		Desvenlafaxine (n = 40)	Vortioxetine (n = 42)	Escitalopram (n = 42)
		OR (95% CI)	OR (95% CI)	OR (95% CI)
HAMD response	vs. Escitalopram	2.31 (0.77−6.93)	0.93 (0.31−2.80)	1
	vs. Vortioxetine	1.45 (0.78−2.45)	1	
HAMA response	vs. Escitalopram	1.67 (0.59−4.74)	0.78 (0.26−2.32)	1
	vs. Vortioxetine	1.32 (0.34−3.24)	1	
HAMD remission	vs. Escitalopram	0.91 (0.33−2.48)	1.28 (0.43−3.82)	1
	vs. Vortioxetine	1.41 (0.48−4.17)	1	
HAMA remission	vs. Escitalopram	1.00 (0.38−2.63)	0.92 (0.31−2.68)	1
	vs. Vortioxetine	0.92 (0.32−2.64)	1	

HAMD, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale.
Adjusted for age, sex, baseline HAMD score, baseline HAMA score, site, first onset depression, and benzodiazepine or zolpidem use at baseline.

groups in the unadjusted HAMD ($p = 0.094$) or HAMA ($p = 0.101$) response rates, and HAMD ($p = 0.519$) or HAMA ($p = 0.684$) remission rates. After adjusting for the potential confounding variables, no significant differences were noted between escitalopram, desvenlafaxine, and vortioxetine with respect to the response or remission rates for HAMD or HAMA (Table 4).

Analysis of the individual HAMD items revealed statistically significant differences among the three treatments with respect to suicide ($p = 0.045$), anxiety-somatic ($p = 0.013$), somatic-gastro ($p = 0.018$), and hypochondriasis ($p = 0.007$) scores. Desvenlafaxine significantly reduced somatic ($p = 0.013$) and hypochondriasis ($p = 0.014$) scores compared to escitalopram, which were significant after applying the Bonferroni correction for multiple comparisons (Table 5). Analysis of the individual HAMA items revealed statistically significant differences among the three treatments with respect to fear ($p = 0.048$), cardiovascular symptoms ($p = 0.007$), and respiratory symptoms ($p = 0.013$). After Bonferroni correction, desvenlafaxine had greatly reduced scores for respiratory symptoms ($p = 0.013$) compared to escitalopram, and for cardiovascular symptoms ($p = 0.005$) compared to vortioxetine (Table 6).

Discontinuations and Adverse Events

Twenty-five participants prematurely discontinued treatment, with the most common reasons being lost to follow-up (n = 12), AEs (n = 6), insufficient treatment response (n = 4), or protocol violation (n = 1). The dropout rate was 23.8% (n = 10) in the escitalopram group, 15.0% (n = 6) in the desvenlafaxine group, and 21.4% (n = 9) in the vortioxetine group. Desvenlafaxine showed a significantly lower dropout rate than escitalopram ($\chi^2 = 2.457$, df = 2, $p = 0.022$), and a statistically marginally lower dropout rate than vortioxetine ($\chi^2 = 1.877$, df = 2, $p = 0.054$). The desvenlafaxine group had the highest number

Table 5. Mean changes in the individual HAMD item scores from the baseline to the endpoint

HAMD item (change at week 6)	E (n = 42)	D (n = 40)	V (n = 42)	*p* value	Difference (*p* value)		
				E vs. D vs. V	E vs. D	E vs. V	D vs. V
1. Depressed mood	−0.9 ± 0.2	−1.3 ± 0.2	−1.2 ± 0.2	0.110	0.221	0.306	0.863
2. Feeling of guilt	−0.9 ± 0.2	−1.3 ± 0.2	−0.9 ± 0.2	0.186	0.408	> 0.999	0.317
3. Suicide	−1.1 ± 0.2	−1.2 ± 0.2	−0.8 ± 0.2	0.045*	0.122	> 0.999	0.088
4. Insomnia, initial	−0.9 ± 0.2	−1.2 ± 0.1	−0.7 ± 0.2	0.075	0.416	0.967	0.071
5. Insomnia, middle	−0.8 ± 0.2	−1.0 ± 0.1	−0.8 ± 0.2	0.124	0.254	> 0.999	0.223
6. Insomnia, delayed	−0.8 ± 0.2	−0.9 ± 0.1	−0.6 ± 0.2	0.088	0.368	0.659	0.098
7. Work & interests	−1.2 ± 0.2	−1.4 ± 0.2	−1.2 ± 0.3	0.271	0.422	> 0.999	0.639
8. Retardation	−0.8 ± 0.1	−1.0 ± 0.2	−0.9 ± 0.2	0.460	0.759	> 0.999	> 0.999
9. Agitation	−1.0 ± 0.1	−1.3 ± 0.1	−1.0 ± 0.1	0.108	0.206	> 0.999	0.232
10. Anxiety psychic	−1.0 ± 0.2	−1.1 ± 0.2	−1.1 ± 0.2	0.708	> 0.999	> 0.999	> 0.999
11. Anxiety somatic	−0.9 ± 0.2	−1.5 ± 0.2	−1.1 ± 0.2	0.013*	0.013**	> 0.999	0.146
12. Somatic (gastro)	−0.7 ± 0.1	−1.0 ± 0.1	−0.6 ± 0.2	0.018*	0.049	> 0.999	0.047
13. Somatic (general)	−0.7 ± 0.1	−0.8 ± 0.2	−0.5 ± 0.2	0.573	> 0.999	> 0.999	0.885
14. Genital symptoms	−0.6 ± 0.1	−0.8 ± 0.1	−0.6 ± 0.1	0.300	0.591	> 0.999	0.541
15. Hypochondriasis	−0.9 ± 0.2	−1.5 ± 0.2	−1.0 ± 0.2	0.007*	0.014**	> 0.999	0.038
16. Loss of weight	−0.6 ± 0.1	−0.9 ± 0.1	−0.5 ± 0.2	0.114	0.286	> 0.999	0.188
17. Insight	−0.6 ± 0.1	−0.6 ± 0.1	−0.3 ± 0.1	0.469	> 0.999	0.817	0.824

Values are presented as mean ± standard error.
E, Escitalopram; D, desvenlafaxine; V, vortioxetine; HAMD, 17-item Hamilton Depression Rating Scale.
Mean change was adjusted for age, sex, baseline HAMD score, baseline HAMA score, site, first onset depression, and benzodiazepine or zolpidem use at baseline.
*Significant differences among the three groups ($p < 0.05$); **significant differences between two groups (Bonferroni correction, $p < 0.017$).

Table 6. Mean changes in the individual HAMA item scores from the baseline to the endpoint

HAM-A item (change at week 6)	E (n = 42)	D (n = 40)	V (n = 42)	*p* value	Difference (*p* value)		
				E vs. D vs. V	E vs. D	E vs. V	D vs. V
1. Anxious mood	−0.9 ± 0.2	−1.3 ± 0.2	−1.2 ± 0.2	0.156	0.247	0.425	0.784
2. Tension	−1.2 ± 0.2	−1.6 ± 0.2	−1.2 ± 0.2	0.312	0.459	> 0.999	0.803
3. Fears	−0.6 ± 0.1	−1.2 ± 0.2	−0.9 ± 0.2	0.048*	0.045	> 0.999	0.464
4. Insomnia	−1.6 ± 0.2	−1.7 ± 0.2	−1.4 ± 0.3	0.098	0.530	0.317	0.145
5. Intellectual	−1.0 ± 0.2	−1.2 ± 0.3	−0.9 ± 0.3	0.187	0.244	0.912	0.225
6. Depressed mood	−0.7 ± 0.2	−0.9 ± 0.1	−0.7 ± 0.2	0.279	0.405	> 0.999	0.641
7. Somatic (muscular)	−1.2 ± 0.2	−1.5 ± 0.2	−1.2 ± 0.3	0.271	0.422	> 0.999	0.639
8. Somatic (sensory)	−0.8 ± 0.1	−1.1 ± 0.2	−0.9 ± 0.1	0.460	0.759	> 0.999	> 0.999
9. Cardiovascular symptoms	−1.2 ± 0.1	−1.6 ± 0.1	−0.7 ± 0.1	0.007*	0.280	0.291	0.005**
10. Respiratory symptoms	−0.9 ± 0.2	−1.5 ± 0.2	−1.1 ± 0.2	0.013*	0.013**	> 0.999	0.146
11. Gastrointestinal symptoms	−1.1 ± 0.2	−1.4 ± 0.2	−1.1 ± 0.2	0.204	0.339	> 0.999	0.456
12. Genitourinary symptoms	−1.3 ± 0.2	−1.4 ± 0.2	−0.9 ± 0.2	0.116	> 0.999	0.341	0.131
13. Autonomic symptoms	−1.2 ± 0.2	−1.3 ± 0.3	−0.8 ± 0.2	0.301	> 0.999	0.715	0.398
14. Behavior at interview	−1.2 ± 0.2	−1.7 ± 0.2	−1.3 ± 0.2	0.084	0.114	> 0.999	0.301

Values are presented as mean ± standard error.
E, escitalopram; D, desvenlafaxine; V, vortioxetine; HAMA, Hamilton Anxiety Rating Scale.
Mean change was adjusted for age, sex, baseline HAMD score, baseline HAMA score, site, first onset depression, and benzodiazepine or zolpidem use at baseline.
*Significant differences among the three groups ($p < 0.05$); **significant differences between two groups (Bonferroni correction, $p < 0.017$).

of discontinuations due to AEs (n = 3), but the least number was lost to follow-up (n = 2).

A total of 47 participants (37.9%) reported a total of 176 AEs. The proportions of participants who reported at least one AE during the study period were 37.1%, 40.2%, and 35.8% in the escitalopram, desvenlafaxine, and vortioxetine groups, respectively ($\chi^2 = 0.922$, df = 2, $p = 0.313$). The most frequently reported AEs, in the order of fre-

Table 7. Adverse events experienced by ≥ 5% of the participants in the treatment groups

Adverse event	Total (n = 124)	Escitalopram (n = 42)	Desvenlafaxine (n = 40)	Vortioxetine (n = 42)
Fatigue	23 (18.5)	8 (19.0)*	7 (19.4)	8 (19.0)
Anxiety/agitation	20 (16.1)	8 (19.0)*	6 (16.7)	6 (14.3)
Insomnia	21 (16.9)	7 (16.7)	6 (16.7)	8 (19.0)
Dry mouth	21 (16.9)	7 (16.7)	6 (16.7)	8 (19.0)
Somnolence	17 (13.7)	6 (14.3)	6 (16.7)	5 (11.9)
Headache	15 (12.1)	5 (11.9)	5 (13.9)	5 (11.9)
Constipation	13 (10.5)	5 (11.9)	4 (11.1)	4 (9.5)
Palpitation or tachycardia	12 (9.7)	3 (7.1)	7 (19.4)*	2 (4.8)
Memory impairment	8 (6.5)	3 (7.1)	2 (5.6)	3 (7.1)
Nausea/vomiting	9 (7.3)	2 (4.8)	3 (8.3)*	4 (9.5)*
Weight loss/decreased appetite	6 (4.8)	2 (4.8)	2 (5.6)	2 (4.8)
Increased sweating	6 (4.2)	2 (4.8)	3 (8.3)*	1 (2.4)
Dizziness	5 (4.0)	2 (4.8)	2 (5.6)	1 (2.4)
Total	176	60	59	57

Values are presented as number (%).
*Discontinuation due to adverse events.

quency—reported in at least 5% of the participants in the treatment groups—were fatigue, anxiety/agitation, insomnia, dry mouth, somnolence, headache, constipation, palpitation/tachycardia, memory impairment, nausea/vomiting, weight loss, increased sweating, and dizziness (Table 7). Six participants had AEs leading to study discontinuation: 2 (4.8%), 3 (7.5%), and 1 (2.4%) participant in the escitalopram, desvenlafaxine, and vortioxetine groups, respectively. The AEs leading to treatment discontinuation were fatigue (n = 1) and agitation (n = 1) in the escitalopram group, palpitation (n = 1), nausea (n = 1), and sweating (n = 1) in the desvenlafaxine group, and vomiting (n = 1) in the vortioxetine group.

DISCUSSION

This study was a head-to-head comparative trial designed to assess the efficacy and safety of three antidepressants (escitalopram vs. desvenlafaxine vs. vortioxetine) during the 6-week acute treatment of patients with comorbid depression and anxiety. All drugs showed similar therapeutic efficacy in the treatment response and remission rate, decrease in the total score on each scale, and symptom improvement over time, for both anxiety and depressive symptoms. The efficacy was also similar in terms of improving somatic symptoms, function, QOL, and cognitive functioning. In the individual analysis of depressive and anxiety symptoms, desvenlafaxine was found to be superior to the other drugs for certain symptom categories. In terms of side effects and safety, all groups showed similar types, distributions, and frequencies of side effects; however, desvenlafaxine had a significantly lower dropout rate.

To date, studies using antidepressants for the acute treatment of depressive disorders have accumulated supporting evidence through placebo-controlled studies; however, only a few direct head-to-head studies have been conducted. Comparison of the efficacy and acceptability of different antidepressants has depended on indirect comparisons provided by meta-analyses [14,33,34]. In particular, comparative trials have shown limited evidence regarding the efficacy of newly developed antidepressants [14]. Recently developed antidepressants are frequently used in clinical practice as they are purported to have the same effects as existing antidepressants with fewer side effects. However, direct evidence regarding their superiority with respect to safety and efficacy has rarely been provided in actual treatment guidelines [35]. The design of this clinical study was significant in this regard. As this study was intentionally conducted among patients with subtypes of depression that were accompanied by high levels of anxiety, recommendations can be made regarding the use of these new antidepressants in patients with depressive disorders accompanied by anxiety.

In this study, escitalopram, desvenlafaxine, and vortioxetine showed sufficient therapeutic effects for MDD. Each individual drug has demonstrated efficacy in previous studies and all have shown similar therapeutic ef-

fects in several indirect comparisons. In a network meta-analysis (522 double-blind studies, 116,477 participants) comparing the efficacy and acceptability of 21 antidepressants during acute treatment of MDD, escitalopram, desvenlafaxine, and vortioxetine all showed effective treatment response rates and acceptability [14]. In the indirect head-to-head comparison in this meta-analysis, the three antidepressants did not differ statistically with respect to treatment response and dropout rates. In an indirect comparative study, escitalopram and vortioxetine were comparable in terms of efficacy and acceptability based on the results of three placebo-controlled studies using escitalopram and vortioxetine [36]. A recent study provided an indirect comparison between vortioxetine and other antidepressants. This study compared conventional SSRIs (escitalopram and sertraline) with SNRIs (venlafaxine, desvenlafaxine, and duloxetine) for treatment efficacy and acceptability 2 months after the baseline. Vortioxetine showed comparable treatment efficacy with escitalopram and desvenlafaxine; its side effects were similar to those of escitalopram but were significantly fewer than those of desvenlafaxine [33].

Several direct comparison studies between escitalopram and desvenlafaxine have been conducted. Vortioxetine has been scarcely compared to escitalopram or desvenlafaxine directly in the treatment of depressive disorders, due to desvenlafaxine being relatively new antidepressant, and vortioxetine being the more recently developed. Escitalopram and desvenlafaxine showed equivalent therapeutic effects and acceptability during the 6-week double-blind randomized treatment of 60 patients with MDD [37]. In an 8-week randomized double-blind study conducted in 607 MDD patients, escitalopram and desvenlafaxine showed equivalent treatment response rates, improvement in symptoms, and incidence and type of side effects [38]. When the study was extended by 6 months for 123 patients who had an inadequate treatment response during the 8-week acute phase of the aforementioned study, escitalopram and desvenlafaxine showed equivalent results in terms of treatment effects and acceptability [39]. After changing antidepressants from citalopram, paroxetine, and sertraline to escitalopram and vortioxetine to solve sexual dysfunction, MDD patients showed equivalent effects with respect to the maintenance of treatment effects and side effects, except for significantly lowered incidence of sexual dysfunction in the vortioxetine group [40].

Compared with patients with non-anxious depression, those with anxious depression show different responses to drug treatment [5]. Therefore, it is necessary that studies take this into account and include patients with depressive disorders accompanied by anxiety. Several clinical trials that used anxiety and depressive symptoms as primary efficacy endpoints for this patient group have been conducted. Only one head-to-head randomized controlled trial conducted in 86 patients with depressive disorders with high levels of anxiety reported that escitalopram and desvenlafaxine showed similar response rates in the HAMD ($p = 0.599$) and HAMA ($p = 0.610$), but analyses of side effects were not reported [41]. Escitalopram and desvenlafaxine are known to be relatively effective medications for the treatment of depressive disorders accompanied by anxiety based on placebo-controlled studies and meta-analyses [17,42]. Based on the similar efficacy in anxiety and depression observed in controlled studies on SSRIs and venlafaxine [43], it can be assumed that desvenlafaxine, an active metabolite of venlafaxine, can be used effectively in this patient group as well. Although vortioxetine (an antagonist of 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors, a partial agonist of 5-HT_{1B} receptors, and an agonist of 5-HT_{1A} receptors) shows different pharmacological properties compared with conventional SSRIs and SNRIs, placebo-controlled studies have reported that the symptoms of depressive disorder patients with anxiety could be effectively reduced [18].

In an analysis of individual items of HAMD and HAMA, desvenlafaxine showed superiority over other drugs in terms of treatment effects for physical anxiety, health anxiety, and cardiovascular and respiratory symptoms. This finding indicates that desvenlafaxine is a better treatment option for patients with depression who have either physical or anxiety symptoms. SNRI-based antidepressants are assumed to block the reuptake of norepinephrine and have superior analgesic effects compared to those of single neurotransmitter inhibitors such as SSRIs, as confirmed by the treatment effects for somatization symptoms of depressed patients in several studies [44]. This finding is supported by the results of a placebo-controlled study, which showed that desvenlafaxine is effective in depressed patients with somatic symptoms or postmenopausal women with vasomotor symptoms [45]. The fact that somatic symptoms can affect the selection of anti-

depressants suggests that clinicians should not neglect the assessment of somatic symptoms in patients with depressive disorder accompanied by anxiety.

Previous studies have shown that during the acute phase of MDD treatment with escitalopram, desvenlafaxine, or vortioxetine, the side effects were comparable [46]. In the present study, the side effects that occurred after the administration of the three drugs were similar. Desvenlafaxine had the lowest dropout rate for the acceptability of this study. These inconsistencies may arise from the fact that previous studies were conducted on patients with depressive disorder without consideration of any possible anxiety symptoms, while this study was intentionally conducted solely on patients with anxious depression. It is also possible that the dropout rate remained low for other reasons not included in the analysis of this study (e.g., subjective satisfaction with drug administration, drug prices, and other factors that increase drug compliance).

If all three groups show similar therapeutic effects, side effects, and acceptability in the acute phase of antidepressant treatment for patients with depression accompanied by anxiety symptoms, the economics of treatment may be a factor in drug selection. In this study, since escitalopram and desvenlafaxine appear to have the same effect and stability, taking into consideration any economic benefits, the drug with the lowest cost may be superior in drug selection. However, since desvenlafaxine has an advantage over escitalopram and vortioxetine on some individual items of depression and anxiety, desvenlafaxine may be selected as the superior treatment.

The considerations for interpreting the results and the limitations of this study are as follows: The diagnosis of all participants was not made based on structured diagnostic interviews such as the Structured Clinical Interview for DSM-5 or Mini-International Neuropsychiatric Interview. This was an open-label, rater-blind study, and not a double-blind study. The dose of antidepressant administered at each period was determined based on the clinician's discretion (flexible dose) rather than accurately controlled (controlled fixed dose). However, this more accurately reflects the real-life clinical setting in which antidepressants are used. There is a possibility of error considering the sample size, although it was sufficient for statistical analysis. However, due to the small sample size, small differences in treatment efficacy or acceptability may not have been verified. Hence, a large-scale, prospective, randomized, double-blind study should be conducted to confirm the results of this study. Lastly, because this study allowed anxiolytics, the efficacy of anxiolytics may have been reflected in efficacy. However, the use of anxiolytics was adjusted in the analysis as a confounding factor, and there was no difference in the use of anxiolytics in each group.

The advantages of this study are as follows: First, the study compared recently developed antidepressants, which have rarely been used in previous studies. Second, the study included patients with depression accompanied by a high level of anxiety. Since these patient groups are known to differ significantly from those with general depressive disorder, studies such as the one here are critically important. Third, both depression and anxiety symptoms were reported during the primary efficacy assessment and were used as the primary outcome. Fourth, the secondary efficacy assessment compared the treatment effects by measuring all areas of psychiatric symptomatology, including somatic symptoms, cognitive functioning, function, and QOL.

This study evaluated the treatment response and side effects of three groups of drugs (escitalopram, desvenlafaxine, and vortioxetine) in a head-to-head trial in patients with depression accompanied by anxiety symptoms during the 6 weeks of the acute phase of treatment. Because escitalopram, desvenlafaxine, and vortioxetine showed similar efficacy and acceptability, all of these drugs may be suggested as a primary treatment option in patients with depressive disorder accompanied by anxiety symptoms. However, in terms of individual performance, desvenlafaxine demonstrated superiority over the other two drugs in terms of improving somatic symptoms, and the administration of desvenlafaxine may be a more reasonable choice for patients with marked somatic symptoms. However, if somatic symptoms are not pertinent, economic factors should be considered. The results of this study must be verified using a large-scale, randomized, double-blind study.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Changsu Han, Sang Won Jeon. Data acquisition: Changsu Han, Cheolmin Shin, Sang Won Jeon, Chi-Un Pae, Narei Hong, Hyun Kook Lim, Seung-Hoon Lee. Formal analysis: Sang Won Jeon, Hyonggin An. Writing—original draft: Cheolmin Shin, Sang Won Jeon. Supervision: Changsu Han, Ashwin A. Patkar. Writing—review & editing: Prakash S. Masand, Ashwin A. Patkar. All authors contributed significantly to the study, and have approved the final manuscript.

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