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Paroxetine versus Venlafaxine and Escitalopram in Korean Patients with Major Depressive Disorder: A Randomized, Rater-blinded, Six-week Study

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Objective: The purpose of this study was to compare the efficacy and safety of escitalopram, paroxetine and venlafaxine in Korean patients with major depressive disorder (MDD).
Methods: A total of 449 Korean MDD patients were recruited in a six-week, randomized, rater-blinded, active-controlled trial and were evenly randomized to paroxetine, venlafaxine, or escitalopram treatment.
Results: When comparing the mean difference for the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating Scale (HDRS) total scores during six weeks, paroxetine (−6.4±0.4, and −5.4±0.4, respectively) was found to be significantly superior to escitalopram (−3.7±0.5 and −3.1±0.4, respectively). Venlafaxine had a significantly lower MADRS total score (−5.4±0.4) than escitalopram. When adjusting baseline variables, the response, according to the MADRS and HDRS scores, in the paroxetine group was greater than that for the escitalopram group (odds ratio [OR]=2.43, 95% confidence interval [CI]=1.42-4.16 for MADRS; and OR=2.32, 95% CI=1.35-3.97 for HDRS) and the venlafaxine group (OR=1.94, 95% CI=1.17-3.21 for MADRS; and OR=1.71, 95% CI=1.03-2.83 for HDRS). Despite that the overall tolerability was high and similar among the three groups, a total of 268 subjects (59.7%) prematurely discontinued treatment, representing the main limitation of the present study.
Conclusion: Although a low study completion rate limits generalizability, our findings suggest that paroxetine might be superior to escitalopram in Korean MDD patients. Further studies should be conducted to draw a definite conclusion.

KEY WORDS: Paroxetine; Venlafaxine; Escitalopram; Major depressive disorder; Korean.

INTRODUCTION

Major depressive disorder (MDD) affects every country ubiquitously. However, there are remarkable differences in the prevalence rates of MDD. Previous epidemiological studies in East Asia have consistently reported a lower prevalence of MDD than have Western, and, particularly, United States (US)-based epidemiological studies.[1-4] In a cross-national comparison of MDD prevalence,[5] lifetime prevalence of MDD was found to be 1.5% in Taiwan and 2.9% in Korea, substantially lower than the 5.2-16.4% prevalence found in Western countries such as the US, Canada, France, Italy, New Zealand and Germany. Accordingly, in a recent systematic review,[4] estimates of MDD prevalence in East and Southeast Asia were much lower than other regions, even after adjusting for methodological differences.

Not only can differences in prevalence rates of depressive disorders be identified, but the profile and expression of depressive symptoms also vary among ethnic/racial groups. East Asians with depression tend to emphasize somatic complaints and conceptualize their illness as a physical rather than mental ailment,[6] while displaying a significantly lower level of positive affects compared to non-Eastern subjects.[7,8] Moreover, studies have shown that there are cross-ethnic variations in the biological aspects of MDD. Existing studies have shown that Asians tend to metabolize many psychotropic drugs slower compared to Caucasians. Thus, Asian patients tend to show a

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greater therapeutic response and experience adverse events (AE) at lower dosages than their Caucasian counterparts.[9-11] Pharmacogenetic studies have also suggested ethnic/racial differences in the polymorphisms in those genes controlling the function of neurotransmitter systems thought to be related to the pathogenesis and treatment response in MDD.[12-16]

In the aggregate, the literature has supported the idea that ethnicity/race represents some important factors in determining psychotropic responses. Consequently, a number of countries, including Asian countries, have developed their own treatment guidelines for MDD.[17-20] In Asia, however, a shortage of local evidence-based information is the primary problem in developing treatment guidelines. Most of the guidelines are based on a consensus of opinion derived from Western research data and guidelines.[21] Only a few randomized, controlled trials of MDD treatment have been conducted in Asian populations, and most studies conducted were sponsored by the pharmaceutical industry.

Herein, we conducted a randomized, rater-blinded study to compare the efficacy and safety of escitalopram, paroxetine and venlafaxine, three of the most commonly prescribed antidepressants in Korea, to provide evidence for the treatment of MDD in Korean patients.

METHODS

Participants

Men and women aged 18 to 65 years with a primary diagnosis of MDD without psychotic features, as defined by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), were eligible for enrollment. Inclusion criteria included patients who did not receive adequate antidepressant treatment, defined as $\geq$4 consecutive weeks of treatment at the recommended dosage for the particular antidepressant, and for a current major depressive episode with a minimum 17-item Hamilton Depression Rating Scale (HDRS) with a total score $\geq$14 at baseline. Those with a current or past comorbid diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, a psychotic disorder not otherwise specified, bipolar disorder, alcohol or substance dependence, dementia, an eating disorder, obsessive compulsive disorder, or other significant medical/neurological conditions, those who had been treated previously with electroconvulsive therapy for the current episode, those who were currently pregnant/breastfeeding or with an active suicidal risk were excluded. Subjects with an unclear history of antidepressant treatment prior to the study entry were also excluded.

Treatment Protocol

This was a 6-week, prospective, randomized, rater-blinded, active-controlled trial conducted from September 2008 through to December 2013 at six university hospitals across the Republic of Korea. Eligible subjects were randomized in a 1:1:1 ratio to one of three treatment arms: paroxetine, venlafaxine, or escitalopram. 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. 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 patients were assessed at baseline, 1, 2, 3, and 6 weeks. The main outcome measure was the Montgomery-Åsberg Depression Rating Scale (MADRS) change during the 6 weeks of the study. Response was defined as a MADRS/HDRS score improvement greater than 50% of the baseline score and remission as 12 or less for the MADRS total score, and 7 or less for the HDRS total score. In addition, we used a 3-factor model for the MADRS proposed by Suzuki *et al*.[22]: factor 1, defined by three items representing dysphoria, i.e., reported sadness, pessimistic thoughts, and suicidal thoughts; factor 2, defined by four items representing retardation, i.e., lassitude, inability to feel, apparent sadness, and concentration difficulties; and factor 3, defined by three items representing vegetative symptoms, i.e., reduced sleep, reduced appetite, and inner tension. Other instruments used were the Clinical Global Impression-Severity (CGI-S) and Improvement (CGI-I), the Global Assessment of Functioning (GAF), and the Sheehan Disability Scale (SDS).[23] All assessors received the same investigators' training module and were blinded to the patients' conditions and prescribed medications.

Safety was assessed via AEs, vital signs, weight, and physical examination findings at each visit. AEs during the study period were recorded by clinical research coordinators using the Udvalg for Kliniske Undersogelser (UKU) side-effect rating scale[24] and evaluated for severity and the causal relationship to the study drug.

Statistical Analysis

Subjects who were randomized and received one or more doses of study drug and had one or more post-baseline values for the primary efficacy assessment were included in the analysis set. We compared baseline demographic and clinical characteristics data among the paroxetine, venlafaxine and escitalopram groups. We compared continuous variables such as age and scores on depressive symptom scales among the three groups using an analysis of variance (ANOVA) and categorical variables (such as sex and presence or absence of previous episodes) using the chi-square test, or Fisher's exact test when cell sizes were small.

The primary endpoint (least squares mean change in the MADRS total score from baseline) was based on a mixed model for repeated measures analysis of covariance (ANCOVA) with treatment group as the between-subject factor, and age, sex, baseline MADRS score, mean dose of antidepressant during the study (fluoxetine equivalent dose/kg/day), regional center variability, and variables that were significantly different at baseline comparison (first onset vs. recurrent depression) as covariates. Secondary variables (HDRS, CGI-S, GAF, and SDS) were analyzed in a similar manner to the primary endpoint. Response and remission rates were analyzed by multivariate logistic regression, having the same structure as the ANCOVA described above. Missing values were inputted using the last observation carried forward approach.

Serious adverse events (SAEs) 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, cases with item severity scores ≥ 2 and a level of association score of 3 in UKU were considered as experiencing drug-related AEs. AEs leading to discontinuation of the study drug or withdrawal from the study were also documented.

Statistical significance was set at $p < 0.05$ (two-tailed) for all tests. All statistical analyses were conducted using the Statistical Analysis System software package (SAS, version 9.1; SAS Institute, Inc., Cary, NC, USA).

Ethics

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice. 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 each study site.

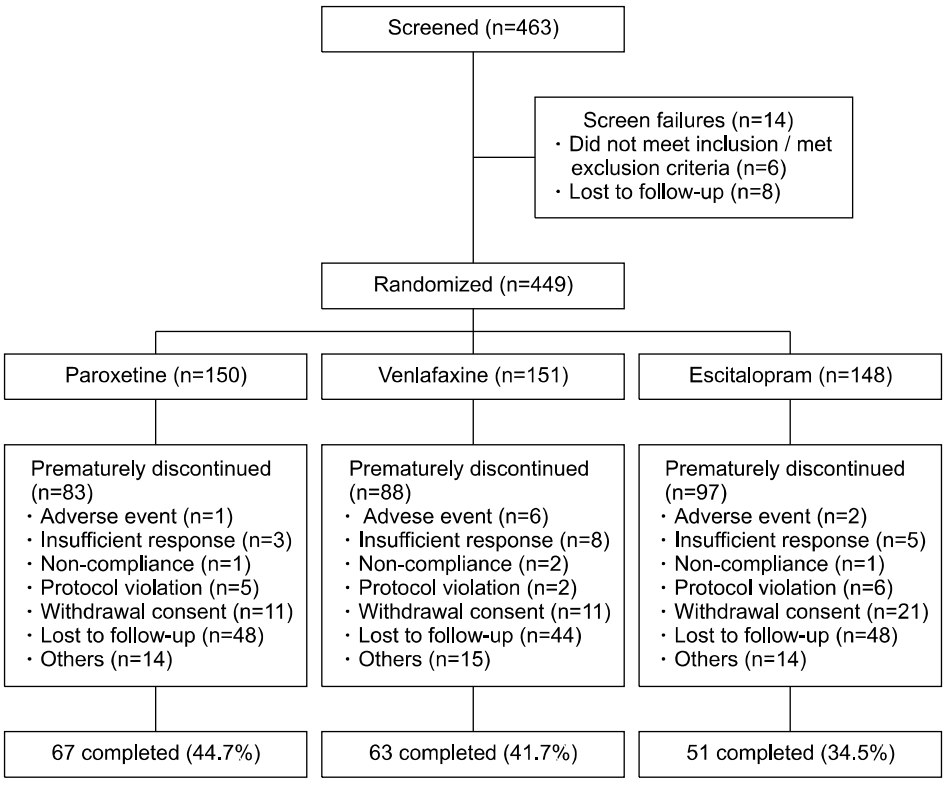

Fig. 1. Subject disposition.

RESULTS

Characteristics of the Sample

Of a total of 463 patients screened for the present study (Fig. 1), 449 met inclusion and exclusion criteria for the analysis, and were randomized and received the study drug (paroxetine, n=150; venlafaxine, n=151; escitalopram, n=148). Two hundred and sixty-eight subjects prematurely discontinued treatment, with the most common reasons being lost to follow-up (n=140), withdrawal of consent (n=43), insufficient treatment response (n=16), protocol violation (n=13), or AEs (n=9). The baseline sociodemographic and clinical characteristics of the subjects are summarized in Table 1. Mean MADRS total score of total subjects at baseline was 26.6 and the mean HDRS score was 21.3, indicating that subjects overall experienced moderately severe events. In the CGI-S, the mean score was 4.6 indicating that patients were overall moderately to markedly ill.

When comparing baseline characteristics of the three groups, there was no significant difference in socio-demographic and clinical characteristics among them (Table 1). The proportion of males and patients experiencing the first onset of depression differed among the three groups with a trend-level significance ($p<0.010$). Men constituted 28.5% (n=43) of the venlafaxine group, 21.3% (n=32) of the paroxetine group, and 18.2% (n=27) of the escitalopram group ($p=0.095$), and those experiencing first-onset depression were 70.3% (n=104) in the escitalopram group, 63.6% (n=96) in the venlafaxine group, and 57.4% (n=86) in the paroxetine group ($p=0.067$). There was no significant difference in total scores of HDRS ($p=0.584$) and MADRS ($p=0.477$), CGI-S ($p=0.224$), GAF ($p=0.546$), and SDS ($p=0.172$) scores. The MADRS factor scores (dysphoria factor, $p=0.760$; retardation factor, $p=0.324$, vegetative symptom factor, $p=0.315$) and MADRS individual item scores at baseline were not significantly

Table 1. Demographic and clinical characteristics

Characteristic		Total (n=449)	Paroxetine (n=150)	Venlafaxine (n=151)	Escitalopram (n=148)	*p* value
Male		102 (22.7)	32 (21.3)	43 (28.5)	27 (18.2)	0.095
Age (yr)	<30	83 (18.5)	26 (17.3)	32 (21.2)	25 (16.9)	0.710
	≥30, <50	152 (33.9)	56 (37.3)	47 (31.1)	49 (33.1)	
	≥50	214 (47.7)	68 (45.3)	72 (47.7)	74 (50.0)	
Married		295 (65.7)	102 (68.0)	94 (62.3)	99 (66.9)	0.537
Employed		160 (35.6)	47 (31.3)	61 (40.4)	52 (35.1)	0.237
Low family income (<2,000 USD/mo)		172 (38.3)	50 (33.3)	65 (43.0)	57 (38.5)	0.222
Level of education	Primary school	91 (20.6)	30 (20.0)	30 (19.9)	31 (21.1)	0.852
	Middle school	82 (18.6)	22 (14.7)	28 (18.5)	32 (21.8)	
	High school	155 (35.1)	54 (36.0)	53 (35.1)	48 (32.7)	
	Post-secondary	114 (25.8)	41 (27.3)	37 (24.5)	36 (24.5)	
	Not available	7 (1.6)	3 (2.0)	3 (2.0)	1 (0.7)	
Age at onset (yr)	<30	49 (10.9)	18 (12.0)	19 (12.6)	12 (8.1)	0.609
	≥30, <50	360 (80.2)	118 (78.7)	117 (77.5)	125 (84.5)	
	≥50	40 (8.9)	14 (9.3)	15 (9.9)	11 (7.4)	
First onset depression		286 (63.7)	86 (57.3)	96 (63.6)	104 (70.3)	0.067
Number of past depressive episodes		1.6±1.3	1.6±1.4	1.6±1.3	1.7±1.1	0.959
Severe depression (baseline MADRS >32)		94 (20.9)	30 (20.0)	25 (16.6)	39 (26.4)	0.108
Family history of depression		68 (15.1)	25 (16.7)	22 (14.6)	21 (14.2)	0.828
Current physical comorbidity at baseline		151 (33.6)	48 (32.0)	50 (33.1)	53 (35.8)	0.774
Benzodiazepine use at baseline		293 (65.3)	99 (66.0)	91 (60.3)	103 (69.6)	0.232
Dose of antidepressants (fluoxetine equivalent, mg/day)		22.6±10.5	19.8±9.0	20.4±11.0	27.7±9.4	<0.001*
Dose of antidepressants (fluoxetine equivalent, mg/kg/day)		0.4±0.2	0.3±0.2	0.3±0.2	0.5±0.2	<0.001*
Baseline scores	HDRS	21.3±4.7	21.0±4.8	21.6±4.5	21.3±4.9	0.584
	MADRS	26.6±7.1	26.0±6.6	26.9±6.6	26.9±8.2	0.477
	CGI-S	4.6±1.0	4.5±0.9	4.6±1.0	4.6±1.0	0.224
	GAF	59.1±7.9	58.9±7.2	59.7±8.1	58.8±8.4	0.546
	SDS	17.8±6.5	18.4±6.6	17.9±6.0	17.0±6.8	0.172

Values are presented as number (%), mean±standard deviation, or median (range).
USD, US dollar; HDRS, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; CGI-S, Clinical Global Impression- Severity; GAF, Global Assessment of Functioning; SDS, Sheehan Disability Scale.
*Significant differences between the three groups ($p<0.05$).

Table 2. Baseline MADRS factor and item score

Factor	Paroxetine (n=150)	Venlafaxine (n=151)	Escitalopram (n=148)	*p* value			
				1 vs. 2 vs. 3	1 vs. 2	1 vs. 3	2 vs. 3
Dysphoria factor	7.9±2.7	7.7±3.1	7.8±2.8	0.760	>0.999	>0.999	>0.999
2. Reported sadness	3.5±1.1	3.4±1.3	3.3±1.2	0.327	0.468	>0.999	0.792
9. Pessimistic thoughts	2.3±1.0	2.3±1.2	2.4±1.2	0.537	>0.999	>0.999	0.795
10. Suicidal thoughts	2.1±1.3	2.0±1.4	2.1±1.4	0.562	>0.999	>0.999	0.928
Retardation factor	10.6±3.2	10.8±3.7	10.2±3.0	0.324	0.943	>0.999	0.428
1. Apparent sadness	3.1±1.0	3.1±1.0	2.9±1.1	0.387	0.560	>0.999	0.961
6. Concentration difficulties	2.3±1.1	2.4±1.2	2.3±1.0	0.632	>0.999	>0.999	1.000
7. Lassitude	2.7±1.1	2.7±1.2	2.5±1.1	0.383	>0.999	>0.999	0.538
8. Inability to feel	2.5±1.3	2.6±1.4	2.4±1.2	0.364	0.849	>0.999	0.540
Vegetative symptom factor	8.4±2.8	8.5±3.0	8.0±2.8	0.315	0.758	>0.999	0.452
3. Inner tension	2.8±0.9	2.9±1.1	2.8±0.9	0.816	>0.999	>0.999	>0.999
4. Reduced sleep	3.2±1.6	3.4±1.6	3.0±1.6	0.088	>0.999	0.400	0.095
5. Reduced appetite	2.4±1.5	2.1±1.6	2.1±1.4	0.291	0.493	0.552	>0.999

Values are presented mean±standard deviation.
MADRS, Montgomery-Åsberg Depression Rating Scale.

Table 3. Primary and secondary endpoints

Variable	Paroxetine (n=150)	Venlafaxine (n=151)	Escitalopram (n=148)	Difference (*p* value)			*p* value
				1 vs. 2	1 vs. 3	2 vs. 3	1 vs. 2 vs. 3
Change at week 6, LS							
MADRS	−6.3±0.4	−5.3±0.4	−3.8±0.5	−1.0±0.6 (0.098)	−2.5±0.6 (<0.001**)	−1.5±0.6 (0.017)	0.001**
HDRS	−5.3±0.4	−4.3±0.4	−3.3±0.4	−1.0±0.5 (0.045)	−2.1±0.5 (<0.001**)	−1.1±0.5 (0.034)	<0.001**
CGI-S	−0.8±0.1	−0.7±0.1	−0.5±0.1	−0.2±0.1 (0.086)	−0.3±0.1 (0.001**)	−0.2±0.1 (0.098)	0.005**
Response							
MADRS	58 (38.7)	39 (25.8)	40 (27.0)	12.9 (0.023)	11.7 (0.024)	−1.2 (0.978)	0.029*
HDRS	56 (37.3)	41 (27.2)	40 (27.0)	10.1 (0.076)	10.3 (0.044)	0.2 (0.814)	0.082
Remission							
MADRS	51 (34.0)	43 (28.5)	39 (26.4)	5.5 (0.358)	7.6 (0.122)	2.1 (0.532)	0.295
HDRS	33 (22.0)	22 (14.6)	21 (14.2)	7.4 (0.112)	7.8 (0.067)	0.4 (0.813)	0.124

Values are presented as mean±standard error or number (%).
MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS, 17-item Hamilton Depression Rating Scale; CGI-S, Clinical Global Impression-Severity.
Least square (LS) mean change was adjusted for age, sex, baseline MADRS score, mean fluoxetine equivalent dose, site, HDRS item 15, and recurrence.
*Significant differences among the three groups ($p<0.05$); **significant differences between the two groups (Bonferroni correction, $p<0.017$).

different among the three groups (Table 2).

When comparing mean fluoxetine equivalent dose[25] per weight of each group during the study period, a significant difference was found. The mean fluoxetine equivalent dose was 0.3±0.2 mg/kg/day in the paroxetine group, 0.3±0.2 mg/kg/day in the venlafaxine group, and 0.5±0.2 mg/kg/day in the escitalopram group ($p<0.001$). The mean lorazepam equivalent dose during the study period was not significantly different among the groups; 1.1±0.6 mg/day in the paroxetine group, 1.2±1.0 mg/day in the escitalopram group, and 1.1±0.7 mg/day in venlafaxine group ($p=0.802$).

Efficacy

In the primary efficacy analysis, paroxetine and venlafaxine were found to be significantly superior to escitalopram (Table 3). The mean difference was −2.7 (standard error [SE]±0.6; $p<0.001$) between paroxetine and escitalopram, and −1.7±0.6 ($p=0.010$) between venlafaxine and escitalopram for the MADRS total score at week 6. The difference between paroxetine and venlafaxine in MADRS change from baseline to week 6 (−1.0±0.6; $p=0.106$) was not significant. For the HDRS total score, the difference between paroxetine and escitalopram (−2.3±0.5; $p<0.001$) was significant, but the difference between paroxetine and venlafaxine (−1.1±0.5; $p=0.036$), and venlafaxine and escitalopram (−1.2±0.5; $p=0.022$) did not reach significance at week 6 after the Bonferroni correction for multiple comparisons ($p<0.017$).

Table 4. Adjusted odds ratio (OR) and 95% confidence interval (CI) of treatment outcomes

Variable	Paroxetine (n=150)			Venlafaxine (n=151)			Escitalopram (n=148)
		OR (95% CI)	*p* value		OR (95% CI)	*p* value	OR (95% CI)
MADRS response	vs. escitalopram	2.43 (1.42-4.16)	0.001*	vs. escitalopram	1.26 (0.73-2.19)	0.413	1
	vs. venlafaxine	1.94 (1.17-3.21)	0.010*	vs. paroxetine	1		
HDRS response	vs. escitalopram	2.32 (1.35-3.97)	0.002*	vs. escitalopram	1.36 (0.78-2.35)	0.275	1
	vs. venlafaxine	1.71 (1.03-2.83)	0.038*	vs. paroxetine	1		
MADRS remission	vs. escitalopram	1.96 (1.12-3.45)	0.019*	vs. escitalopram	1.34 (0.76-2.36)	0.309	1
(≤12)	vs. venlafaxine	1.45 (0.87-2.46)	0.149	vs. paroxetine	1		
HDRS remission	vs. escitalopram	2.40 (1.24-4.63)	0.009*	vs. escitalopram	1.23 (0.61-2.45)	0.562	1
(≤7)	vs. venlafaxine	1.95 (1.05-3.63)	0.034*	vs. paroxetine	1		

MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS, 17-item Hamilton Depression Rating Scale.
Adjusted for age, sex, baseline MADRS score, mean fluoxetine equivalent dose, site, and recurrence.
*$p<0.05$.

Table 5. Adjusted least squares mean changes in MADRS factor and item score during 6 weeks

	Paroxetine	Venlafaxine	Escitalopram	*p* value			
				1 vs. 2 vs. 3	1 vs. 2	1 vs. 3	2 vs. 3
Dysphoria factor	−2.1±0.2	−1.9±0.2	−1.2±0.2	<0.001*	0.247	<0.001*	0.002*
2. Reported sadness	−0.8±0.1	−0.7±0.1	−0.5±0.1	0.002*	0.294	0.001*	0.025
9. Pessimistic thoughts	−0.6±0.1	−0.6±0.1	−0.4±0.1	0.01*	0.655	0.011*	0.034
10. Suicidal thoughts	−0.7±0.1	−0.6±0.1	−0.3±0.1	<0.001*	0.334	<0.001*	0.003*
Retardation factor	−2.1±0.2	−1.8±0.2	−1.2±0.2	0.001*	0.224	0.002*	0.043
1. Apparent sadness	−0.7±0.1	−0.6±0.1	−0.4±0.1	<0.001*	0.413	0.001*	0.007*
6. Concentration difficulties	−0.4±0.1	−0.4±0.1	−0.2±0.1	0.031*	0.462	0.028	0.129
7. Lassitude	−0.5±0.1	−0.4±0.1	−0.2±0.1	0.585	0.616	0.401	0.712
8. Inability to feel	−0.5±0.1	−0.4±0.1	−0.3±0.1	0.015*	0.160	0.011*	0.211
Vegetative symptom factor	−2.1±0.2	−1.7±0.2	−1.2±0.2	<0.001*	0.040	<0.001*	0.042
3. Inner tension	−0.6±0.1	−0.5±0.1	−0.4±0.1	0.027*	0.671	0.061	0.138
4. Reduced sleep	−1.1±0.1	−0.8±0.1	−0.6±0.1	<0.001*	0.017	<0.001*	0.141
5. Reduced appetite	−0.5±0.1	−0.4±0.1	−0.2±0.1	0.013*	0.221	0.012*	0.167

Values are presented as mean±standard error.
MADRS, Montgomery-Åsberg Depression Rating Scale
Adjusted for age, sex, baseline MADRS score, mean fluoxetine equivalent dose, site, and recurrence.
*Significant difference between the three groups ($p<0.05$); **significant difference between the two groups (significance was adjusted by Bonferroni correction, $p<0.017$).

The unadjusted MADRS response rate was significantly different among the three treatment groups (Table 3); MADRS response at week 6 was achieved in 38.7% (n=58), 25.8% (n=39), and 27.0% (n=40) of subjects in the paroxetine, venlafaxine, and escitalopram groups, respectively (χ^2=7.065, degree of freedom [*df*]=2, *p*=0.029). There was no significant difference among the three groups in unadjusted HDRS response rate (χ^2=4.995, *df*=2, *p*=0.082) and MADRS remission (χ^2=2.445, *df*=2, *p*=0.295) and HDRS remission (χ^2=4.172, *df*=2, *p*=0.124) rates (Table 3). After adjusting for potential confounding variables, the paroxetine group showed a significantly higher response rate for MADRS (odds ratio [OR]=2.43, 95% confidence interval [CI]=1.42-4.16, *p*=0.001) and HDRS (OR=2.32, 95% CI=1.35-3.97, *p*=0.002) than the escitalopram group (Table 4). Even when compared to the venlafaxine group, the paroxetine group showed a significantly higher response rate for MADRS (OR=1.94, 95% CI=1.17-3.21, *p*=0.010) and HDRS (OR=1.71, 95% CI=1.03-2.83, *p*=0.038). The remission rate was also significantly higher in the paroxetine group than the escitalopram (OR=2.40, 95% CI=1.24-4.63, *p*=0.009) and venlafaxine (OR=1.95, 95% CI=1.05-3.63, *p*=0.034) groups for HDRS. The MADRS remission rate was significantly higher in the paroxetine group when compared with the escitalopram group (OR=1.96, 95% CI=1.12-3.45, *p*=0.019), but was not significantly different between the paroxetine group and the venlafaxine group (OR=1.45, 95% CI=0.149, *p*=0.149; Table 4).

The changes in MADRS factor scores (Table 5) were similar to the changes in the MADRS total score. Paroxetine had greatly reduced scores for all three factors compared to escitalopram with significance (dysphoria factor; $p<0.001$, retardation factor; *p*=0.002, vegetative

Table 6. Adverse events experienced by ≥5% of subjects

Adverse event	Full sample (n=449)	Paroxetine (n=150)	Venlafaxine (n=151)	Escitalopram (n=148)
Any adverse event	204 (45.4)	72 (48.0)	65 (43.0)	67 (45.3)
Cognitive impairment	103 (22.9)	37 (24.7)	29 (19.2)	37 (25.0)
Dysphoric mood	102 (22.7)	34 (22.7)	30 (19.9)	38 (25.7)
Fatigue	98 (21.8)	34 (22.7)	28 (18.5)	36 (24.3)
Anxiety	89 (19.8)	32 (21.3)	23 (15.2)	34 (23.0)
Insomnia	88 (19.6)	32 (21.3)	27 (17.9)	29 (19.6)
Dry mouth	83 (18.5)	28 (18.7)	30 (19.9)	25 (16.9)
Sedation	76 (16.9)	26 (17.3)	21 (13.9)	29 (19.6)
Headache	63 (14.0)	22 (14.7)	22 (14.6)	19 (12.8)
Constipation	51 (11.4)	19 (12.7)	19 (12.6)	13 (8.8)
Sexual dysfunction	34 (7.6)	10 (6.7)	12 (7.9)	12 (8.1)
Palpitation or tachycardia	31 (6.9)	9 (6.0)	12 (7.9)	10 (6.8)
Increased dream activity	31 (6.9)	8 (5.3)	9 (6.0)	14 (9.5)
Weight loss/decreased appetite	30 (6.7)	11 (7.3)	10 (6.6)	9 (6.1)
Increased sweating	26 (5.8)	9 (6.0)	7 (4.6)	10 (6.8)
Dizziness/orthostatic dizziness	25 (5.6)	6 (4.0)	9 (6.0)	10 (6.8)
Nausea/vomiting	22 (4.9)	7 (4.7)	5 (3.3)	10 (6.8)
Weight gain/increased appetite	21 (4.7)	7 (4.7)	6 (4.0)	8 (5.4)

Values are presented as number (%).

symptom factor; $p < 0.001$), and venlafaxine had a lower dysphoria factor score than escitalopram (p=0.002).

The changes in GAF score during the 6 weeks in the paroxetine group and venlafaxine group were greater than in the escitalopram group, but the differences were not statistically significant. The mean difference was 2.1±1.0 (p=0.029) for paroxetine vs. escitalopram, and 1.9±1.0 (p=0.042) for venlafaxine vs. escitalopram. The SDS score decreased from 18.6±6.4 at baseline to 15.6±7.6 at week 6 in the paroxetine group, from 18.0±6.1 to 15.6±7.1 in the venlafaxine group, and from 17.1±6.8 to 15.5±7.2 in the escitalopram group, and was therefore not significantly different among the three groups (p=0.776).

Safety

The dropout rate was 55.3% (n=83) in the paroxetine group, 58.3% (n=88) in the venlafaxine group, and 65.5% (n=97) in the escitalopram group, and was therefore not significantly different among the three treatment groups (χ^2=3.414, df=2, p=0.181). A total of 204 patients (45.4%) reported 1093 cases of AEs. The percentage of subjects who reported at least one AE during the study period was 48.0%, 43.0%, and 45.3% in the paroxetine, venlafaxine, and escitalopram groups, respectively (χ^2=0.747, df=2, p=0.688). The most frequently reported AEs—which were reported in at least 5% of the subjects in any of the treatment groups—were cognitive impairment, dysphoric mood, fatigue, anxiety, insomnia, dry mouth, sedation, headache, constipation, sexual dysfunction, palpitation/tachycardia, increased dream activity, weight loss/decreased appetite, increased sweating, dizziness/orthostatic dizziness, nausea/vomiting, and weight gain/increased appetite (Table 6). In all treatment groups, the majority of AEs reported were considered to be of mild or moderate severity; 728 cases (66.6%) were mild and 321 cases (29.4%) were moderate. Only 44 cases (4.0%) were rated as severe. There were 4 subjects who reported a SAE; 2 cases of hospitalization due to aggravation of depressive symptoms (both of them treated with venlafaxine), and 1 case of suicide attempt in the escitalopram group.

Nine subjects had AEs leading to study discontinuation: 1 (0.7%), 6 (4.0%), and 2 (1.4%) subjects in the paroxetine, venlafaxine, and escitalopram group, respectively. AEs leading to treatment discontinuation were sexual dysfunction (n=1) in the paroxetine group, headache (n=2), fatigue (n=2), dizziness (n=1), and blurred vision (n=1) in the venlafaxine group, and insomnia (n=1), and suicide attempt (n=1) in the escitalopram group.

DISCUSSION

In the present study, paroxetine was found to be superior to escitalopram for the treatment of MDD patients. For several secondary efficacy measures, paroxetine was more effective than venlafaxine in the treatment of MDD. Paroxetine was shown to be superior to venlafaxine and escitalopram according to the response rates measured using MADRS and HDRS scores, and the remission rate measured using the HDRS score when adjusted for baseline variables. This significant superiority of paroxetine

over escitalopram was also observed in changes from baseline to week 6 according to the adjusted MADRS, HDRS total scores as well as the CGI-S score. Venlafaxine was also superior to escitalopram in the adjusted MADRS total score change.

This result is not coincident with results from previous studies which reported an inferior or comparable antidepressant efficacy of paroxetine compared to escitalopram or venlafaxine. Cipriani *et al*.[26] reported that escitalopram and venlafaxine were more efficacious than paroxetine. In their meta-analysis which included 117 randomized, controlled trials, the OR for response was 1.35 for escitalopram and 1.27 for venlafaxine. In a recent Cochrane meta-analysis which included a total of 115 randomized, controlled trials, there was no significant difference in antidepressant efficacy when comparing paroxetine to escitalopram or venlafaxine.[27]

The discrepancy between the results from the present study and previous studies could be attributed to a few contributing factors. First of all, inter-ethnic differences in pharmacogenetics could affect antidepressant responsiveness.[28] Variations in gene allele frequencies can contribute to differences in antidepressant responses in different ethnic groups.[29] Over 90% of all drug metabolism could be accounted for by cytochrome P450 (CYP) enzymes, and 1A2, 2D6, 2C9, 2C19, and 3A4 account for 60% of metabolism.[30] Escitalopram is metabolized by CYP3A4, CYP2C19 and, to a lesser extent, by CYP2D6,[31,32] and paroxetine is mainly metabolized by CYP2D6, while CYP3A4 also contributes to the metabolism of paroxetine.[33] As for venlafaxine, CYP2D6 is the major metabolizing enzyme, and its metabolism is partly mediated by CYP3A4 and CYP2C19.[34]

A marked inter-ethnic difference in the allelic frequencies of CYP genes has been reported, and variants in these genes have been hypothesized to predict variations in antidepressant metabolism, therapeutic responses, and risk of adverse effects.[35,36] Most differences between East Asians and Caucasians have been particularly shown in the enzymatic activity of CYP2D6 and the CYP2C subfamily.[15] Kirchheiner *et al*.[37] reported that genetic polymorphisms in CYP2D6 or CYP2C19 would require at least a doubling of the dose of extensive metabolizers (EMs) in comparison to poor metabolizers (PMs). Meanwhile, the CYP3A4 exhibits few genetic polymorphisms.

CYP2D6 polymorphism is the most extensively studied oxidation polymorphism in humans. In general, CYP2D6 PMs (who are lacking functional enzymes due to defective or deleted genes) reach higher peak serum concentrations and have lower clearances and longer half-lives as compared with CYP2D6 EMs (who are carrying two functional genes). Hence, PMs may have greater susceptibility to adverse effects[38] and exhibit lower treatment responses than EMs.[39-41] Moreover, the frequency of the phenotype of CYP2D6 PMs differs among ethnic groups. Less than 1% of Asians, 5% to 10% of Caucasians are PMs of CYP2D6.[42] Because CYP2D6 is the major enzyme involved in the metabolism of paroxetine and venlafaxine, but is not so extensively involved in the metabolism of escitalopram, the antidepressant efficacy of paroxetine and venlafaxine could be underestimated in studies which include predominantly Caucasians, who have a higher risk of being a PM of paroxetine and venlafaxine than Asians.

Moreover, in a recent cross-ethnic study that investigated the association between serotonin transporter promoter polymorphism (5-HTTLPR) and escitalopram efficacy in depression,[43] the response rate for escitalopram treatment was 64% in Caucasian subjects and 47% in Koreans. Among those with the l/l, but not l/s or s/s genotypes, Caucasian subjects showed higher response and remission rates compared with Koreans. They reported the frequency of the favorable l allele in Caucasian as 51% and 24% in Koreans, and suggested that it may be expected that Koreans would be less likely to respond to escitalopram due to a lower proportion of l alleles in the population, although there have been inconsistent results.[44-47]

Ethnic differences in depressive symptomatology might also contribute to the discrepancy between results from the present study and other studies, which are mainly from Western countries. It has been known that Asians report more somatic and less affective symptoms of depression,[48-51] and high levels of somatic symptoms respond less well to antidepressant treatment.[52-54] The association between genetic polymorphisms and somatic symptoms was suggested by Klengel *et al*.[55] who reported an association between serotonin 2A receptor gene (HTR2A) polymorphism (G/G genotype in rs9534505) and somatization in MDD patients. Moreover, a recent meta-analysis[56] confirmed that patients with s/s genotype of 5-HTTLPR experience a slower improvement of somatic anxiety symptoms. The frequency of both of G/G genotype in HTR2A polymorphism and s/s genotype in 5-HTTLPR is higher in Asian populations than in Caucasians.[43,57,58] Asians may show a different or poorer response to antidepressant treatment when compared to Caucasians.

Another issue that should be considered is the dose of antidepressants. Dose equivalence is critically important

for comparative clinical trials and their meta-analyses, and setting comparable dosages is necessary to facilitate a proper interpretation of results.[59] However, in previous studies which reported superiority of escitalopram or a lack of difference in efficacy between antidepressants, categorical dosing classification was used to compare the doses of different antidepressants.[26,27] In the present study, we used results from the most recent study to calculate dose equivalents of antidepressants,[25] and this might contribute to the inconsistency of the results.

There are a number of limitations that should be considered when interpreting the results from the present study. The most important limitation was the low study completion rate. Only 40% of subjects completed this six-week study. The dropout rates for previous studies which compared paroxetine with venlafaxine or escitalopram ranged from 10% to 26%,[26] indicating this study had an approximately 14% to 30% higher dropout rate. The most common reason for dropout in this study was lost to follow-up (31.2%, n=140). The dropout rate due to insufficient efficacy (3.6%, n=16) or AEs (2.0%, n=9) was very low, and this might suggest that the difference in efficacy and safety reported in this study was not a result of the high dropout rate. According to the results from STAR*D, attrition during antidepressant treatment is related to a number of patient characteristics, including non-white race, lower income, less education and negative attitudes about psychiatric medication.[60,61] In this study, the high proportion of low income status (38.3%), and low educational level (39.2% below high school) patients might have lowered the study completion rate. Moreover, it is noteworthy that Korean patients have a more negative attitude towards depression than their counterparts in Western countries,[62] and this could decrease the completion rate.

The lack of a placebo arm was another limitation in this study. Hence, it was unable to detect the placebo response rate and to exclude the possibility of an improvement in depressive symptoms as part of the natural course of the disease. The absence of assessing inter-rater reliability was another limitation of the present study. In addition, a structured diagnostic interview was not carried out, which might allow for a more detailed diagnosis of psychiatric comorbidities and subtypes of depression. Finally, although the study sample could not be homogenous in terms of type of depression and bipolarity, the issues of bipolarity was not addressed.

The results of this randomized, rater-blinded, six-week, prospective, head-to-head comparison study suggested that paroxetine was more efficacious than escitalopram in overall treatment effects in Korean MDD patients. Paroxetine was found to be superior to venlafaxine in terms of the change in MADRS during six weeks, the response rates for MADRS and HDRS, and the remission rate for HDRS. Venlafaxine had a lower MADRS total score than escitalopram, but a difference could not be identified for the other efficacy measures. Overall tolerability was similar among the three groups. Further studies with a larger cohort are needed to draw definite conclusions on the differences in efficacy among different antidepressants in Asian MDD patients.

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