Original Article
https://doi.org/10.9758/cpn.2022.20.3.548 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2022;20(3):548-559

Safety and Effectiveness of Desvenlafaxine in Korean Patients with Major Depressive Disorder: A 6-month Postmarketing Surveillance Study

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Objective: Although the safety and efficacy of desvenlafaxine have been demonstrated, long-term evidence in Asians is lacking. We examined the safety and effectiveness of desvenlafaxine for up to 6 months in routine clinical practice in Korea.
Methods: This multicenter, open-label, prospective observational study was conducted from February 2014 to February 2020 as a postmarketing surveillance study of desvenlafaxine (ClinicalTrials.gov identifier: NCT02548949). Adult patients with major depressive disorder (MDD) were observed from the initiation of treatment for 8 weeks (acute treatment phase) and then up to 6 months (continuation treatment phase) in a subsample. Safety was evaluated by incidence of adverse events (AE) and adverse drug reactions. Treatment response was assessed using the Clinical Global Impression-Improvement (CGI-I) scale.
Results: We included 700 and 236 study subjects in the analysis of acute and continuation treatment phase, respectively. In acute treatment phase, AE incidence was 9.86%, with nausea being most common (2.00%). In continuation treatment phase, AE incidence was 2.97%, with tremor occurring most frequently. After acute treatment (n = 464), the treatment response rate according to the CGI-I score at week 8 was 28.9%. In long-term users (n = 213), the response rate at month 6 was 45.5%. During the study period, no clinically relevant changes in BP were found regardless of concomitant use of antihypertensive drugs.
Conclusion: This study provides evidence on the safety and effectiveness of desvenlafaxine in adults with MDD, with a low incidence of AE, consistent AE profile with previous studies, and improved response after long-term treatment.

KEY WORDS: Desvenlafaxine; Safety; Treatment outcome; Antidepressant; Major depressive disorder; Korea.

INTRODUCTION

Depression is common, with more than 264 million affected people worldwide [1]. According to a retrospective cohort study using a representative sample of one million South Koreans, the prevalence of depression has steadily increased from 2.8% in 2002 to 5.3% in 2013 [2]. The point prevalence of depression (Patient Health Questionnaire-9 score of 10 or higher) was 6.7% in approximately 5,000 subjects when analyzed using the 2014 Korea National Health and Nutrition Examination Survey [3]. Despite this low prevalence of depression, according to the Organisation for Economic Co-operation and Development (OECD) health data, the suicide rate in South Korea in 2017 was 23.0 per 100,000 persons, which is the highest rate among OECD countries [4], suggesting underdiagnosis and undertreatment of major depression in this population [5].

Desvenlafaxine succinate is a newer antidepressant categorized as a serotonin–norepinephrine reuptake inhibitor (SNRI) and is a major active metabolite of venlafaxine [6,7]. Its metabolism primarily involves the non-cytochrome P450 (CYP) enzyme uridine 5′-diphospho-glucuronosyltransferase to form its glucuronide metabolite.

Received: July 6, 2021 / **Revised:** August 11, 2021
Accepted: August 12, 2021
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It's simple metabolic pathway may allow it to avoid CYP-related alteration in response or side effect, that is the basis of the pharmacogenetics in major depressive disorder (MDD) [8], and pharmacokinetic interactions with drugs of many therapeutic classes [9]. The SNRIs have both serotonergic and noradrenergic effects which may induce nausea and sexual dysfunction (serotonergic), dry mouth, sweating, and constipation (noradrenergic) as adverse effects [10]. The side-effect profile of desvenlafaxine was found consistent with that of other SNRIs and the efficacy of desvenlafaxine has been demonstrated through short- and long-term clinical trials, but these included few Asian participants [11-13]. As an SNRI, desvenlafaxine may also result in blood pressure (BP) elevation [10,14]. However, this has not been confirmed in the Asian population, especially over a long-term period.

Evidence on the safety and efficacy of desvenlafaxine is scarce in Asians, which may lead to insufficient use for those who could benefit. Although no significant difference was documented in Asian versus white people for early improvement at week 2 [15], racial differences in the treatment effects of desvenlafaxine are possible. After the approval of desvenlafaxine in 2014, the Korean Ministry of Food and Drug Safety required a re-examination to confirm the clinical usefulness of the drug in Koreans by collecting, reviewing, identifying, and verifying its safety and effectiveness in typical clinical practice during a 6-year re-examination period.

Therefore, this study aims to observe the safety and effectiveness of desvenlafaxine in the acute (0 to 8 weeks) and continuation treatment phases (8 weeks to 6 months) in routine medical practice in Korea as postmarketing surveillance (PMS) and to identify factors that may affect the drug's safety and effectiveness.

METHODS

Study Design

This was a multicenter, open-label, noncomparative, prospective, observational study in which subjects were administered desvenlafaxine as part of routine practice at 22 clinics and hospitals in Korea by accredited psychiatrists from February 2014 to February 2020 (ClinicalTrials.gov identifier: NCT02548949). The use and dosage recommendations for desvenlafaxine took place according to the approved indication and administration method. Study subjects were observed from the initiation of the administration of the study drug for 8 weeks (acute treatment phase) and then up to 6 months (continuation treatment phase) in a subsample. The number of subjects for 6 months long-term observation was planned before study initiation and prespecified in the research contract with each investigator. No visit or activity was mandated by the study protocol, but safety information was to be followed up at least once by visit, telephone, e-mail, or fax during the study.

Study Subjects

Physicians consecutively enrolled all patients who were administered desvenlafaxine for the first time and met the inclusion criteria. Patients who were 19 years of age or older, were diagnosed with major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and were administered at least one dose of desvenlafaxine for the first time were eligible for enrollment in this study. According to the prescription guidelines for desvenlafaxine, subjects with hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride, or to any included excipients; subjects who were administered desvenlafaxine concomitantly with a monoamine oxidase (MAO) inhibitor; and subjects who were within 14 days of discontinuing treatment with a MAO inhibitor were excluded.

All data, including demographic information, medical history, administration status of desvenlafaxine, BP, adverse events (AE), and effectiveness evaluation, were collected from patient charts and recorded in an electronic case report form by the investigators during the observation period. BP was recorded only when performed by the attending physician according to usual practice.

Safety and Effectiveness Evaluations

The investigators were required to assess and record information on AEs, including the specific conditions, duration, seriousness, severity (mild, moderate, or severe), causal relationship to the study drug, and outcome. An AE was defined as any untoward medical occurrence in a patient administered a medicinal product, and all AEs, excluding those whose causal relationship to the study drug were assessed as "unlikely" by the investigators, were categorized as adverse drug reactions (ADRs). A serious AE or ADR (SAE/SADR, respectively) was defined as an AE

or ADR in a patient administered a medicinal product at any dose that 1) resulted in death, 2) was life-threatening, 3) required inpatient hospitalization or prolongation of hospitalization, 4) resulted in persistent or significant disability/incapacity, 5) resulted in a congenital anomaly/birth defect, or 6) was an important medical event (i.e., the event that may jeopardize the subject or may require intervention to prevent one of the above outcomes).

For effectiveness evaluation, subjects were assessed using the Clinical Global Impression-Improvement (CGI-I) scale. They were evaluated after 8 weeks of treatment (within 2 weeks of the last administration) and after 6 months of treatment (within 2 weeks of the last administration) in the case of long-term users. Treatment response was defined as the proportion of patients who were rated "very much improved" or "much improved" by the investigators according to the CGI-I scale, as applied in previous PMS studies [16-18].

Statistical Analysis

Safety and effectiveness were analyzed separately for the acute treatment phase (weeks 0−8) and the continuation treatment phase (week 8−month 6). Descriptive summary statistics for continuous variables included the number of subjects or cases (n or N), mean, standard deviation (SD), and range. Descriptive statistics for categorical variables were given as frequencies and percentages with corresponding 95% confidence intervals (CIs). The significance of the difference in rates between subcategories regarding safety and effectiveness was statistically analyzed using the chi-square test or Fisher's exact test. To identify factors associated with AE incidence and treatment response, multiple logistic regression analysis was performed after adjusting for covariates. All test statistics were the results of two-sided tests with a significance level of 0.05. Each statistical analysis was carried out with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical Approval

The study was conducted in accordance with generally accepted research practices described in the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, the Good Epidemiological Practice guidelines issued by the International Epidemiological Association, and the Pharmaceutical Research and Manufacturers Association guidelines. The study subjects were fully informed regarding the nature and objectives of the study and possible risks associated with participation by the investigators, and written informed consent was obtained before study enrollment. The informed consent form and study protocol (including any amendments) were reviewed and approved by the Institutional Review Board/Independent Ethics Committee of each participating center (no. CNUH-2016-153, Chonnam National University Hospital).

RESULTS

Recruitment

The overall subject recruitment process is displayed in Figure 1. We enrolled 715 patients at the screening visit, of which 15 were excluded because of failure to follow-up (14 patients) or a violation of the inclusion/exclusion criteria (1 patient). Accordingly, a total of 700 study subjects were observed for at least 8 weeks and included in the safety analysis of acute treatment phase. Among them, 464 who were assessed by the CGI-I score at week 8 were subject to the effectiveness analysis for the acute phase. After excluding 464 subjects who took desvenlafaxine for less than 6 months, 236 subjects were evaluated for safety in the continuation treatment phase. The effectiveness analysis was conducted in 213 subjects who had a CGI-I score recorded at month 6.

Baseline Characteristics and Treatment Pattern of Study Subjects

Socio-demographic and treatment-related characteristics are summarized in Table 1. Among the 700 study subjects, more females were included in the study (65.0%). Subjects included in the continuation treatment phase analysis were older, with 36.9% of patients being 70 years or older, but the difference in mean age between the two groups was not clinically significant. A higher proportion of mild MDD (52.6%) was documented in the continuation treatment phase group compared to the acute treatment phase group (44.2%), and more moderate MDD was found in the acute treatment phase group than in the continuation phase group (48.5% vs. 41.0%). Lower percentages of users of recent psychotropic medication and concomitant drugs were shown in long-term users (26.3%) compared to subjects included in the acute

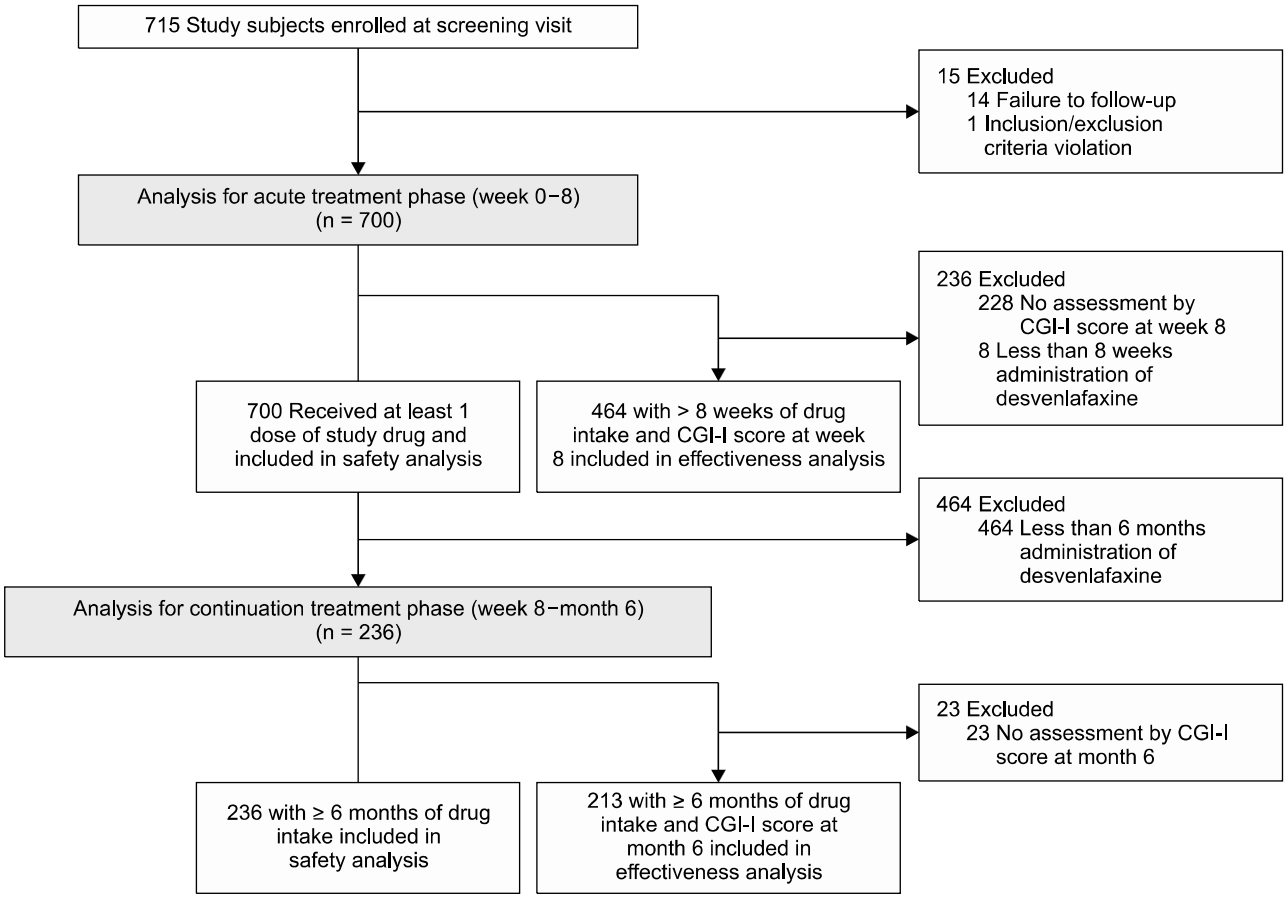

Fig. 1. Flowchart of study subjects.
CGI-I, Clinical Global Impression-Improvement.

treatment phase analysis (33.4%). A higher mean daily dosage of desvenlafaxine was administered in subjects in the continuation treatment phase analysis (63.26 ± 24.05 mg/day) compared to those in the acute treatment phase group (59.71 ± 20.38 mg/day). Among all subjects, more than 70% took a recommended daily dosage of 50 mg.

AE Incidence

The overall AE incidence in all study subjects regardless of observation period was 11.4% (80/700, 112 cases). Incidences of mild, moderate, and severe AE were 78.6% (88 cases), 19.6% (22 cases), and 1.8% (2 cases), respectively. Three serious AEs were reported, including tremor, chest pain, and aggravated angina pectoris. However, all were assessed by the investigators as unlikely to be caused by the study drug. Moreover, AEs related to suicide or death were not reported from the study subjects. The overall discontinuation rate due to AE (including temporary and permanent discontinuations and delayed administration) was 10.6% (74/700). Figure 2 describes the AE occurrence over time as documented by AE reported date. Most AEs occurred during week 1−2 after first administration, and specifically, nausea was not reported after week 5.

In the acute treatment phase, AE incidence was low at 9.86%. During this period, gastrointestinal system AEs had the highest percentage of all AEs, of which nausea was the most common (2.00%). The next most common AEs were headache (1.29%), somnolence (1.14%), and insomnia (0.96%) (Table 2, Supplementary Table 1 [available online]). In the continuation treatment phase, the total AE incidence was 2.97%, and tremor occurred most frequently at 0.85% (Table 2, Supplementary Table 2 [available online]).

Independent variables that showed significant association with AE incidence (Supplementary Table 3; available

Table 1. Baseline characteristics and treatment pattern of study subjects

Characteristics	Acute treatment phase (n = 700)	Continuation treatment phase (n = 236)
Sex		
Male	245 (35.00)	83 (35.17)
Female	455 (65.00)	153 (64.83)
Age (yr)		
Mean ± SD	58.23 ± 17.67	60.31 ± 16.02
< 30	73 (10.43)	15 (6.36)
30−49	123 (17.57)	43 (18.22)
50−69	282 (40.29)	91 (38.56)
≥ 70	222 (31.71)	87 (36.86)
Elderly (≥ 65 yr)	292 (41.71)	111 (47.03)
Duration of the disease[a]		
Mean ± SD (d)	709.41 ± 1,220.50	741.15 ± 1,458.39
< 4 months	306 (48.43)	114 (51.58)
≥ 4 months	327 (51.66)	107 (48.42)
Severity of the disease[b]		
Mild	307 (44.17)	123 (52.56)
Moderate	337 (48.49)	96 (41.03)
Severe	51 (7.34)	15 (6.41)
Recent history of psychotropic medication uses within 30 days	234 (33.43)	62 (26.27)
Concomitant medication	586 (83.71)	178 (75.42)
Current medical history	420 (60.00)	135 (57.20)
Past medical history	78 (11.14)	28 (11.86)
Renal disorders	7 (1.00)	2 (0.85)
Hepatic disorders	17 (2.43)	3 (1.27)
Allergy history	23 (3.29)	8 (3.39)
Total administration period[c]		
Mean ± SD (d)	123.16 ± 97.87	213.37 ± 96.93
< 4 weeks	98 (14.61)	0 (0.00)
4−8 weeks	57 (8.49)	0 (0.00)
8−12 weeks	130 (19.37)	0 (0.00)
≥ 12 weeks	386 (57.53)	236 (100.00)
Total administration dosage[d]		
Mean ± SD (mg)	7,732.91 ± 7,212.31	13,569.49 ± 8,064.44
Mean daily administration dosage[e]		
Mean ± SD (mg/d)	59.71 ± 20.38	63.26 ± 24.05
50 mg/d	529 (75.90)	168 (71.19)
> 50 and < 100 mg/d	127 (18.22)	50 (21.19)
> 100 and ≤ 200 mg/d	41 (5.88)	18 (7.63)

Values are presented as number (%).
SD, standard deviation.
[a]Sixty-seven subjects from the acute treatment phase and 15 subjects from the continuation treatment phase had an unknown duration of the disease and were excluded from the calculations. [b]Five subjects from the acute treatment phase and two subjects from the continuation treatment phase had an unknown severity of the disease and were excluded from the calculation. [c]Twenty-nine subjects from the acute treatment phase had an unknown total administration period and were excluded from the calculation. [d]Thirty subjects from the acute treatment phase had an unknown total administration dosage and were excluded from the calculation. [e]Three subjects from the acute treatment phase had an unknown daily administration dosage and were excluded from the calculation.

online) were included in a logistic regression analysis. The analysis of AE incidence in the acute treatment phase revealed that subjects who were younger, were female, had a current medical history, or had shorter administration period were more likely to report an AE (odds ratio, OR [95% CI]: 0.98 [0.96−0.99] for higher age, 0.50 [0.26−0.98] for males, 2.32 [1.17−4.60] for having a current medical history, and 0.98 [0.97−0.98] for a longer administration period; Table 3). In the continuation treatment phase, subjects who had recent history of psy-

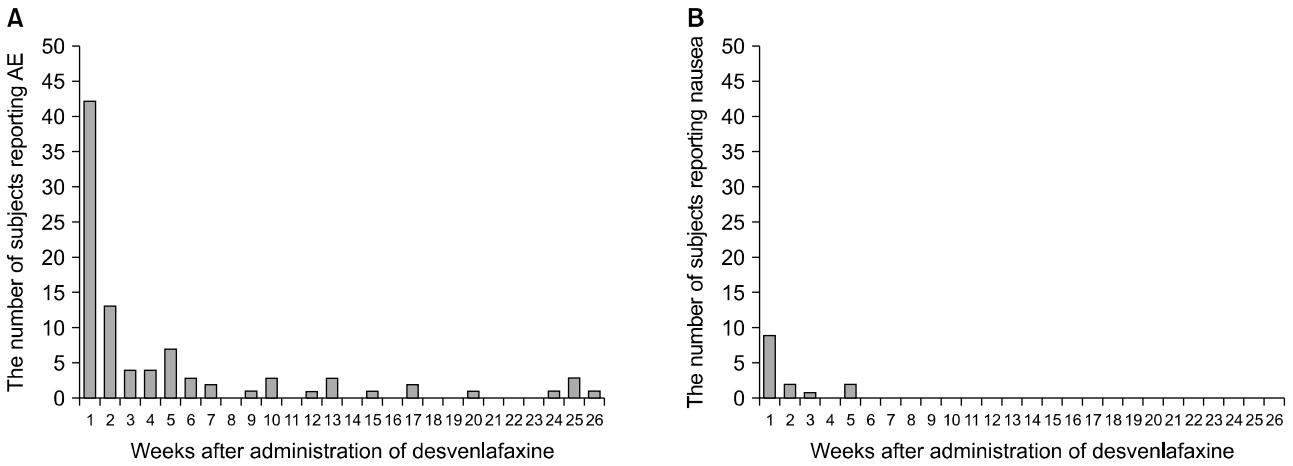

Fig. 2. Occurrence of adverse events over time. (A) All adverse events. (B) Nausea.
AE, adverse event.

Table 2. Adverse event (AE) and adverse drug reaction (ADR) incidences in the acute and continuation treatment phases

System organ class	AE		ADR	
	Number (%)	Case	Number (%)	Case
Acute treatment phase (n = 700)				
Gastrointestinal system disorders	29 (4.14)	33	24 (3.43)	26
Psychiatric disorders	20 (2.86)	20	15 (2.14)	15
Central & peripheral nervous system disorders	15 (2.14)	15	13 (1.86)	13
Body as a whole—general disorders	10 (1.43)	10	6 (0.86)	6
Heart rate and rhythm disorders	2 (0.29)	2	2 (0.29)	2
Skin and appendage disorders	2 (0.29)	2	1 (0.14)	1
Resistance mechanism disorders	2 (0.29)	2	0 (0.00)	0
Hearing and vestibular disorders	1 (0.14)	1	1 (0.14)	1
Urinary system disorders	1 (0.14)	1	1 (0.14)	1
Myo-, endo-, pericardial & valve disorders	1 (0.14)	1	0 (0.00)	0
Cardiovascular disorders, general	1 (0.14)	1	1 (0.14)	1
Musculoskeletal system disorders	1 (0.14)	1	0 (0.00)	0
Total	69 (9.86)	89	56 (8.00)	66
Continuation treatment phase (n = 236)				
Gastrointestinal system disorders	2 (0.85)	2	1 (0.42)	1
Central & peripheral nervous system disorders	2 (0.85)	5	1 (0.42)	4
Psychiatric disorders	1 (0.42)	1	0 (0.00)	0
Skin and appendage disorders	1 (0.42)	1	0 (0.00)	0
Resistance mechanism disorders	1 (0.42)	1	1 (0.42)	1
Hearing and vestibular disorders	1 (0.42)	1	0 (0.00)	0
Musculoskeletal system disorders	1 (0.42)	1	1 (0.42)	1
Total	7 (2.97)	12	3 (1.27)	7

chotropic medication use had a higher AE incidence (OR [95% CI]: 24.55 [2.65—227.74]).

Treatment Response Rate

The treatment response rate according to the CGI-I score at week 8 was 28.9% (134/464). In the continuation phase group, the response rate at month 6 was 45.5% (97/213). The overall response rate was lower than that reported in previous randomized controlled studies of desvenlafaxine, but it increased with longer desvenlafaxine treatment. Furthermore, none of the study subjects was evaluated as "worse" or "very much worse" on the CGI-I scale at their last visit.

Independent variables that showed significant associa-

Table 3. Logistic regression analysis results for factors associated with adverse event incidence

Variable	Acute treatment phase (n = 700)				Continuation treatment phase (n = 236)			
	β	SE	OR (95% CI)	*p* value	β	SE	OR (95% CI)	*p* value
Age, one year increase	−0.02	0.01	0.98 (0.96−0.99)	0.0094	0.02	0.03	1.02 (0.97−1.08)	0.4399
Sex, female vs. male	−0.69	0.34	0.50 (0.26−0.98)	0.0429	−1.33	0.98	0.26 (0.04−1.80)	0.1735
Severity of the disease								
Mild	−0.24	0.60	0.79 (0.24−2.56)	0.6950	−2.88	1.60	0.06 (< 0.01−1.29)	0.0714
Moderate	0.37	0.58	1.45 (0.47−4.47)	0.5188	−0.66	1.05	0.52 (0.07−4.07)	0.5314
Severe			Ref.				Ref.	
Current medical history, no vs. yes	0.84	0.35	2.32 (1.17−4.60)	0.0165	1.53	1.31	4.62 (0.35−60.85)	0.2441
Recent history of psychotropic medication uses within 30 days, no vs. yes			NA		3.20	1.14	24.55 (2.65−227.74)	0.0049
Total administration period, one day increase	−0.02	0.00	0.98 (0.97−0.98)	< 0.0001			NA	
Mean daily administration dosage, one mg/day increase			NA		0.02	0.01	1.02 (0.99−1.04)	0.2209

SE, standard error; OR, odds ratio; CI, confidence interval; NA, not applicable; Ref., reference.

Table 4. Logistic regression analysis results for factors associated with treatment response rate assessed by the CGI-I scale[a]

Variable	Acute treatment phase (n = 464)				Continuation treatment phase (n = 213)			
	β	SE	OR (95% CI)	*p* value	β	SE	OR (95% CI)	*p* value
Age, one year increase	0.01	0.01	1.01 (1.00−1.03)	0.0849	0.02	0.01	1.02 (1.00−1.04)	0.0192
Sex, female vs. male	−0.37	0.27	0.69 (0.41−1.16)	0.1600	0.20	0.33	1.22 (0.65−2.32)	0.5343
Duration of the disease, one day increase	−0.00	0.00	1.00 (1.00−1.00)	0.1056	−0.00	0.00	1.00 (1.00−1.00)	0.4346
Severity of the disease							NA	
Mild	−1.20	0.50	0.30 (0.11−0.80)	0.0162				
Moderate	−0.88	0.50	0.41 (0.16−1.10)	0.0770				
Severe			Ref.					
Current medical history, no vs. yes	−0.32	0.29	0.72 (0.41−1.28)	0.2680	−1.06	0.41	0.35 (0.16−0.77)	0.0097
Recent history of psychotropic medication uses within 30 days, no vs. yes	−0.37	0.29	0.69 (0.39−1.22)	0.2026			NA	
Mean daily administration dosage, one mg/day increase	−0.00	0.01	1.00 (0.98−1.01)	0.4833			NA	
Concomitant medication, no vs. yes	−1.58	0.36	0.21 (0.10−0.42)	< 0.0001	−0.01	0.46	0.99 (0.40−2.45)	0.9903

CGI-I, Clinical Global Impression-Improvement; SE, standard error; OR, odds ratio; CI, confidence interval; NA, not applicable; Ref., reference.
[a]Treatment response was defined as the proportion of patients who were rated "very much improved" or "much improved" by the investigators according to the CGI-I scale.

tion with the treatment response rate (Supplementary Table 4; available online) were included in the logistic regression model. In the acute treatment phase, subjects who had mild MDD or concomitant medication use were less likely to respond to desvenlafaxine treatment (OR [95% CI]: 0.30 [0.11−0.80] for mild MDD and 0.21 [0.10−0.42] for taking concomitant medication; Table 4). In the continuation treatment phase, older subjects were more likely to respond to desvenlafaxine treatment (OR [95% CI]: 1.02 [1.00−1.04]), whereas having a current medical history was significantly associated with a lower response rate (OR [95% CI]: 0.35 [0.16−0.77]; Table 4).

Blood Pressure

BP was measured at follow-up visits in some of the subjects as usual practice, and the mean BP change was evaluated as shown in Table 5. Mean systolic BP decreased significantly from baseline in the overall population (−2.98 ± 11.42 mmHg, $p = 0.0006$) and in those who had BP measured at week 8−month 6 (−2.72 ± 10.85 mmHg, $p = 0.0040$). In both populations, subjects who did not take

Table 5. Change in mean blood pressure by concomitant administration of antihypertensive drugs

Time of BP measurement	Study subject number	Systolic blood pressure				Diastolic blood pressure			
		Mean ± SD (mmHg)				Mean ± SD (mmHg)			
		Baseline	After intake	Mean difference	p value*	Baseline	After intake	Mean difference	p value*
Overall[a]	160	123.86 ± 14.05	120.88 ± 12.10	−2.98 ± 11.42	0.0006	74.03 ± 10.18	72.62 ± 8.82	−1.41 ± 9.32	0.1786
Without antihypertensive drugs	133	124.16 ± 13.70	121.50 ± 11.78	−2.66 ± 10.91	0.0037	74.02 ± 10.09	72.51 ± 8.47	−1.51 ± 9.23	0.1925
With antihypertensive drugs	27	122.37 ± 15.89	117.85 ± 13.39	−4.52 ± 13.81	0.1010	74.07 ± 10.84	73.15 ± 10.57	−0.93 ± 9.92	0.6318
BP measured before week 8	38	124.68 ± 14.96	121.00 ± 12.64	−3.68 ± 13.37	0.0764	75.16 ± 10.59	74.87 ± 8.06	−0.29 ± 12.91	0.6466
Without antihypertensive drugs	29	125.17 ± 13.59	121.86 ± 13.23	−3.31 ± 12.57	0.2610	75.38 ± 10.42	74.38 ± 7.48	−1.00 ± 12.50	0.6699
With antihypertensive drugs	9	123.11 ± 19.60	118.22 ± 10.73	−4.89 ± 16.50	0.4001	74.44 ± 11.77	76.44 ± 10.08	2.00 ± 14.70	0.6938
BP measured at week 8−month 6[b]	120	123.94 ± 13.85	121.23 ± 12.14	−2.72 ± 10.85	0.0040	73.85 ± 10.11	72.08 ± 9.03	−1.77 ± 7.98	0.0264
Without antihypertensive drugs	102	124.28 ± 13.81	121.85 ± 11.57	−2.43 ± 10.51	0.0101	73.84 ± 10.06	72.19 ± 8.76	−1.66 ± 8.24	0.0264
With antihypertensive drugs	18	122.00 ± 14.31	117.67 ± 14.83	−4.33 ± 12.78	0.1684	73.89 ± 10.69	71.50 ± 10.70	−2.39 ± 6.49	0.1369

BP, blood pressure; SD, standard deviation.
[a]Overall BP denotes BP in all subjects whose BP was measured before and after administration regardless of measurement time. [b]Three subjects had BP measurement after 6 months and were excluded from the calculation. One subject had BP measurements at both before week 8 and week 8−month 6 and was included in the calculation for both groups.
*p value for mean BP change from baseline (i.e., before administration of desvenlafaxine).

antihypertensive drugs also showed a decrease in mean systolic BP, which was statistically significant (−2.66 ± 10.91 mmHg [p = 0.0037] and −2.43 ± 10.51 mmHg [p = 0.0101], respectively). All other mean systolic BP changes were not significant. At all periods, no significant differences in mean systolic BP change were observed between subjects who were concomitantly administered antihypertensive medication and those who were not ($p > 0.05$ for all). The mean diastolic BP decreased significantly from baseline in those who had BP measured at week 8−month 6 (−1.77 ± 7.98 mmHg, p = 0.0264). Subjects who did not take antihypertensive drugs in the same group also showed a significant decrease in mean diastolic BP (−1.66 ± 8.24 mmHg, p = 0.0264). All other mean diastolic BP changes were not significant. At all periods, differences in mean diastolic BP change were not significant between antihypertensive users and nonusers ($p > 0.05$ for all).

DISCUSSION

From this observational study of desvenlafaxine, the AE incidences in the acute treatment phase and the continuation treatment phase were low at 9.86% and 2.97%, respectively. In addition, there were no particular safety issues related to desvenlafaxine that were previously unknown. Moreover, the treatment response rates according to the CGI-I score ranged from approximately 29−46% during 6 months of administration. To our knowledge, this PMS study is the largest study on desvenlafaxine in the Asian population. The results may have clinical significance as we analyzed the acute and continuation treatment phases separately. Influence on BP is an important aspect of safety for SNRIs, and we evaluated the long-term safety of desvenlafaxine on BP in the general population of Korea.

In this study, the overall safety profile was consistent with previous reports on desvenlafaxine [19,20], including the results from a low-dose randomized controlled study in which 50% of subjects were Japanese [21]. The incidence of AEs in our study was lower than that from pooled results of double-blind, randomized controlled trials [19,20]. This may result from the underreporting of AEs due to noninterventional study design and some of the safety information being collected by remote methods like telephone calls, although we were not able to confirm how many cases were evaluated this way. Moreover,

many subjects (approximately 76%) took 50 mg/day of desvenlafaxine in this study, which may have led to better tolerability. Most of the AEs were mild to moderate, and no AEs related to suicide or death were reported. Nausea was the most frequent AE in the acute treatment phase, followed by headache, somnolence, and insomnia. In the continuation treatment phase, tremor was the most common AE, occurring in less than 1% of patients.

In this study, several factors were associated with higher AE incidence in the acute treatment phase. Females were more likely to report AE than males, and as noted in the literature, different pharmacokinetic profiles and clinical characteristics may lead to different AE profiles between genders [22,23]. Young adult patients, specifically those who were younger than 30 years old, showed the highest AE incidence among all age groups, and older subjects experienced significantly less frequent AEs compared to younger patients. In clinical practice, physicians tend to use low doses of a medication and try not to escalate the dose in elderly patients, and this may have contributed to the relatively low AE occurrence in the older age group in the acute treatment phase. In this study, older subjects took a significantly smaller daily amount of desvenlafaxine during the study compared to younger subjects (Supplementary Table 5; available online). Another significant factor was the total administration period, and subjects with a longer administration period in the acute treatment phase were less likely to experience an AE. It could be reasoned that subjects who experienced fewer AEs have better adhered to the treatment than subjects with more frequent AEs. However, this result may suggest that desvenlafaxine has long-term tolerability in Asians, in line with the results from a previous open-label study in Japan [24]. In the continuation treatment phase, a recent history of psychotropic medication use was a factor associated with high AE incidence. It is possible that many patients with this history concomitantly took other psychiatric drugs with desvenlafaxine, which may lead to high likelihood of AE occurrence.

In a pooled analysis of short-term studies on desvenlafaxine, there were significant increases in supine systolic BP and supine diastolic BP in the pooled desvenlafaxine 50- and 100-mg groups compared with those in the placebo group [14]. By contrast, long-term safety regarding BP change was documented in a double-blind, placebo-controlled, randomized withdrawal study with 50 mg/d of desvenlafaxine, where there was no significant BP change at the final evaluation when compared to the placebo [25]. In our PMS study of Korean MDD patients, a significant or clinically relevant increase in BP was not observed regardless of coadministration of antihypertensive drugs, and to the contrary, a significant decrease in systolic BP was observed in patients who had a BP check-up. These results suggest the possibility of ethnic differences and relative vascular safety in Asian people, although further research is needed to confirm this.

The overall response rate was lower than that reported in previous randomized controlled studies of desvenlafaxine (~40−70%) [11,26,27]. The relatively lower response rate in the current study may be attributed to the observational, noninterventional study design, since optimal experimental conditions of randomized controlled trials enrolling selective patients may lead to greater response than in observational studies for general patient group [28]. However, this study may better reflect the real-world situation. The response rate increased to 45.5% for those with the 6-month desvenlafaxine treatment in this study, showing the benefits and necessity of long-term antidepressant therapy.

In the acute treatment phase, subjects with mild baseline depression had a lower response rate compared to subjects with moderate or severe depression. Severe MDD patients showed the highest response rate after 8 weeks (Supplementary Table 4; available online). It could be that patients with milder symptoms were not prescribed intense treatment at the acute phase resulting in an insufficient response. Meanwhile, baseline depression severity was not associated with treatment response in the continuation treatment phase analysis. Moreover, subjects who were concomitantly taking other drugs were less likely to improve with desvenlafaxine treatment. Among all subjects using concomitant medication, 60.8% were taking antidepressants. Subjects with resistant depression who are expected to have a low improvement rate may have received combination therapy [29,30]. In the analysis of the response rate for the continuation treatment phase, older subjects were more likely to respond to desvenlafaxine treatment. As older subjects experienced fewer AEs compared to younger patients, they may have been more compliant with the therapy [31], which led to a higher treatment response rate. Medical comorbidities, which were also associated with a lower response rate,

may have negatively affected the clinical outcomes of depression [32].

This study has several limitations. First, AEs may have been underreported because of the noninterventional study design. Second, because this was a noninterventional study, data could not be collected from all study subjects, resulting in a small sample size that may be underpowered to detect the significance of certain results. Third, AE incidence could have been underestimated in the acute phase observation and overestimated in long-term users because of inherent limitations in the calculation method. Lastly, only the CGI-I scale, which has limited specificity, was used for effectiveness evaluation, instead of other validated depression scales.

In this PMS study on the safety and effectiveness of desvenlafaxine in adult patients with MDD, desvenlafaxine showed a low incidence of AEs, with a consistent AE profile with previous studies. The overall response rate at week 8 was approximately 29%, which increased to approximately 46% after 6 months of administration. Because this is the first PMS study reporting 6 months of follow-up results in Asians, this study adds significant evidence of desvenlafaxine use in a real-world setting, especially in the Asian population.

■ Funding

This study was sponsored by Pfizer.

■ Acknowledgments

All investigators who participated in this study are listed in below (name [organization]). Organizations are presented in alphabetical order.

Young Myo Jae (Bong Seng Memorial Hospital), Kang Soo Lee (CHA Bundang Medical Center-CHA University), Sun Mi Kim (Chung-Ang University Hospital), Sie Kyeong Kim (Chungbuk National University Hospital), Ik Seung Chee (Chungnam National University Hospital), Jeong Lan Kim (Chungnam National University Hospital), Jae-Min Kim (Chonnam National University Hospital), Sang Hoon Kim (Chosun University Hospital), Do Hoon Kim (Hallym University Chuncheon Sacred Heart Hospital), Ji Wook Kim (Hallym University Dongtan Sacred Heart Hospital), Duk In Jon (Hallym University Sacred Heart Hospital), Sungwon Roh (Hanyang University Seoul Hospital), Kang Joon Lee (Inje University Ilsan Paik Hospital), Byung Joo Ham (Korea University Anam Hospital), Seok Woo Moon (Kunkuk University Chung-ju Hospital), Seung Ho Ryu (Konkuk University Medical Center), JinKyung Park (Kyung Hee University Hospital At Gangdong), Seung Hee Won (Kyungpook National University Hospital), Eui Joong Kim (Nowon Eulji Medical Center, Eulji University), Mal Rye Choi (Presbyterian Medical Center), Yeong Min Lee (Pusan National University Hospital), Min-Jeong Wang (Roa Neurology Clinic), Yong Min Ahn (Seoul National University Hospital).

■ Conflicts of Interest

The authors Sungwon Roh, Kang Soo Lee, and Jae-Min Kim had received honoraria as speakers and/or consultants from Pfizer Pharmaceuticals Korea Ltd. Songhwa Choi is a full-time employee of, and holds stock in, Pfizer Inc.

■ Author Contributions

Data acquisition: Sungwon Roh, Kang Soo Lee, Jae-Min Kim and all study investigators. Data analysis & interpretation: Sungwon Roh, Kang Soo Lee, Songhwa Choi, Jae-Min Kim. Supervision: Jae-Min Kim. Writing－original draft: Sungwon Roh, Songhwa Choi. Writing－review & editing: Sungwon Roh, Kang Soo Lee, Songhwa Choi, Jae-Min Kim.

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