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Vortioxetine Treatment for Depression in Alzheimer's Disease: A Randomized, Double-blind, Placebo-controlled Study

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Objective: Vortioxetine, a new antidepressant, has been demonstrated to have effects on depression and cognitive function. This study aimed to investigate the anti-depressive efficacy of vortioxetine through a well-designed double-blind, placebo-controlled study in Alzheimer's disease (AD) patients, and to confirm the presence of secondary benefits, including the improvement of cognitive function and activities of daily living (ADL).
Methods: The present study included 100 AD patients with depression who were assigned randomly to 12 weeks of daily treatment with either vortioxetine or placebo. The primary efficacy measure was the change in the Cornell Scale for Depression in Dementia score from baseline to 12 weeks. Several secondary efficacy measures were evaluated, including the Korean version of the Short form of Geriatric Depression Scale and several cognitive function domains. The safety and tolerability of vortioxetine were also assessed. We performed modified intention-to-treat analysis using mixed modeling (the Mixed Models for Repeated Measures).
Results: There was no statistically significant difference between the two groups in terms of depressive symptoms, cognitive functions, and ADL. Further, the percentage of adverse events and drug discontinuation between the vortioxetine and placebo groups was similar.
Conclusion: Our results suggest that vortioxetine might not be effective in reducing depressive symptoms or cognitive impairment in AD patients with depression. However, general drug tolerance and patient safety were similar to those of placebo. Thus, additional studies are needed to replicate the effectiveness and tolerability of vortioxetine in AD patients with depression.

KEY WORDS: Alzheimer's disease; Depression; Cognitive function; Vortioxetine.

INTRODUCTION

Dementia (including Alzheimer's disease, AD) is the most representative and common mental illness of old age, and can show severe behavioral and psychological symptoms [1]. Likewise, neurodegenerative disorders include various behavioral and psychological symptoms (behavioral and psychological symptoms of dementia, BPSD) along with decreased cognitive function, which interfere with the maintenance of daily life and have a negative effect on the progress and outcome of the disease. In particular, depression is one of the most common BPSDs in neurodegenerative disorders. In other words, depression is one of the most common comorbidities in patients with AD. It has been estimated that 40−50% of AD patients experience depressive symptoms, and 10−20% of them have major depression [2-4]. An important reason for considering the relationship between neurodegenerative disorders and depression is that, depending on whether they manifest depressive symptoms, patients with the same neurodegenerative disorder exhibit different degrees of actual functioning. Depression in AD patients may result in worsening of cognitive status [5], loss of the ability to perform daily activities [6,7], and associated behavioral disturbances [7]. In summary, depression in AD is associated with a more severe functional degradation in

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a wide range of cognitive areas than without AD, which in turn has a negative impact on daily functioning and social activities [8].

The use of antidepressants is very common in elderly patients with cognitive impairment because of comorbidities like dementia and depression. Unlike studies of depression in older people without dementia, prior clinical studies on the use of antidepressants in patients with AD have produced contradictory findings; therefore, the efficacy of antidepressants in AD remains uncertain [9]. Thus, whether the mechanisms underlying depression in patients with AD differ from that in patients without AD is also an open question [10]. The efficacy of antidepressants, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs), is reportedly ambiguous in AD patients with depression [9,11-13]. Therefore, it is necessary to investigate new antidepressants with higher effectiveness and fewer side effects than conventional ones for AD patients with depression.

Vortioxetine is a novel multimodal compound used for the treatment of major depressive disorder (MDD) with direct effects on serotonin (5-HT) receptor activity and 5-HT transporter inhibition [14,15]. "Multi-modality" antidepressants having both pre and post-synaptic monoaminergic effects, including direct receptor effects, may enhance neurotransmitter modulation, and there is some evidence that such agents may treat cognitive deficits, as well [16]. Specifically, the 5-HT system engages in mood regulation and in the regulation of cognitive function. Vortioxetine showed antidepressant effects in not only classical monoamine-sensitive behavioral models of depression but also in old mice models insensitive to SSRIs/SNRIs. Also, unlike other antidepressants including SSRIs, vortioxetine enhanced cognitive functions such as attention/vigilance, executive function memory, and learning [16]. Recently, vortioxetine was shown to be effective for treating depression in the elderly [17], and for patients with MDD who failed to respond to other drugs such as SSRIs or SNRIs [18]. Further, vortioxetine treatment was found to improve cognitive function and activities of daily living (ADL) in adults with MDD [19].

Since vortioxetine may have a different mechanism of action from commonly prescribed antidepressants, it may be considered as an alternative for the treatment of depression in patients with AD.

Therefore, we aimed to evaluate the clinical efficacy of vortioxetine for AD patients with depressive symptoms. In addition, we investigated whether vortioxetine treatment improves overall function, including cognitive function and ADL.

METHODS

Participants and Procedures

This study was conducted in the psychiatry unit at Chuncheon Sacred Heart Hospital, a teaching hospital affiliated with the Hallym University, College of Medicine, Republic of Korea; and registered with the Clinical Trials Registry Korea (registration: KCT0004083). The present study was approved by the Institutional Review Board of Chuncheon Sacred Heart Hospital, Republic of Korea (approval no. 201609118). All participants provided written informed consent. Patients $>$ 60 years with comorbid AD and depression were recruited for the study.

The inclusion criteria for the study were as follows: patients who (a) met the criteria for AD according to the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders [20]; (b) showed $\geq$ 3 symptoms from the Olin Diagnosis Criteria for Depression in Alzheimer's disease [21]; (c) had a score of 0.5 to 2 on the Clinical Dementia Rating Scale [22]; (d) had a total score of 10−26 on the Korean version of the Mini-Mental State Examination (MMSE-KC) [23,24]; (e) had a total score $>$ 5 on the Korean version of the Short form of Geriatric Depression Scale (SGDS-K) [25]; and (f) had a caregiver who could accompany them on all study visits at screening/baseline visits. Participants were excluded if they (a) had a history of taking antidepressants, alcohol or other drugs within 4 weeks before inclusion; (b) treated with memantine medication $\geq$ 4 weeks; (c) had other major mental disorders or three times the normal levels of aspartate aminotransferase or alanine aminotransferase liver function; (d) showed evidence of severe cerebrovascular disease; (e) had Parkinson's disease, stroke, brain tumor or normal brain pressure hydrocephalus, or critical or unstable (for example, uncontrolled diabetes with symptoms) diagnoses as per specialists in internal medicine.

Prior to treatment, the participants were randomized (1:1) to receive double-blinded treatment with either vortioxetine (5 mg/d) or placebo for 12-weeks, using random

numbers generated by a computer program in blocks of six. All investigators, trial personnel, and subjects were blinded to treatment assignment during the study except in the case of serious adverse events (AEs). Patients in the treatment and placebo groups received 5 mg/d vortioxetine and placebo, respectively, from weeks 1 to 12. However, if the clinical effects were insufficient, both subject groups were administered up to 20 mg/d of the respective agent, from weeks 4 to 12. Depressive symptoms were rated at every patient visit: at baseline, and at weeks 4, 8, and 12, while the assessment of cognitive function and ADL were rated at baseline and at the final visit. Patients who withdrew prior to study completion were evaluated at the earliest possible date after their withdrawal. Study medications were administered as capsules of identical appearance. Following randomization, patients were instructed to orally take one capsule per day, preferably in the morning, and to maintain the treatment with acetylcholinesterase inhibitors (donepezil, 5−10 mg/d; rivastigmine, 3−12 mg/d; galantamine, 8−16 mg).

Clinical Measures

To determine the clinical efficacy of the vortioxetine treatment, trained raters blinded to participants' clinical/treatment information, scored the participants using the Cornell Scale for Depression in Dementia (CSDD) from baseline, and at weeks 4, 8, 12 [26]. The CSDD is a 19-item clinician-administered instrument specifically designed to rate the symptoms of depression in patients with dementia. It uses information from interviews with both a patient and their caregiver.

Subjective depressive symptoms, cognitive function and ADL were evaluated for secondary efficacy. Subjective depressive symptoms were also evaluated using the SGDS-K [25], which is a 15-item self-reporting scale used to rate the symptoms of depression in patients with dementia. The higher the score, the more depressive symptoms patients show. Cognitive function was evaluated using the MMSE-KC [23], the Boston Naming Test [27], The Seoul Verbal Learning Test (SVLT) [28], Digit Span (Digits) [29], Verbal Fluency Test, the Digit Symbol Substitution Test (DSST), contrasting program (contrasting), go-no-go, constructional praxis test, and word list. The Boston Naming Test, Verbal Fluency Test, and SVLT used in this study are part of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease [23], and the Digits and DSST, contrasting, go-no-go, constructional praxis test, and word list are components of the Seoul Neuropsychological Screening Battery [28]. Furthermore, we assessed functional abilities using the Basic Activities of Daily Living (BADL; six items, range 0−12) [30], the Instrumental Activities of Daily Living (IADL; eight items ranging from 0−16) [31] at baseline and at the final visit. For the cognitive function, the higher the score, the better cognitive function, and for ADL, the lower the score, the better function in activities of daily living.

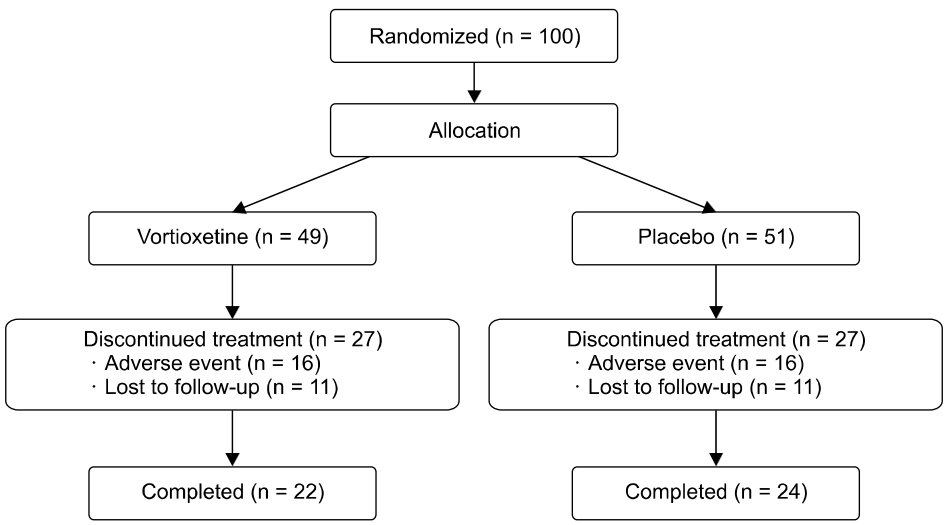

Fig. 1. Participant flow.

Statistical Analysis

Demographics were reported using mean, standard deviation, number, percentage, and quartiles. Efficacy analyses were based on a modified intention-to-treat set, comprising all patients in the complete-patients-treated set who had ≥ 1 valid post-baseline assessment of primary

Table 1. Demographics and clinical characteristics at baseline

Characteristic		Vortioxetine (n = 49)	Placebo (n = 51)	*t*
Age (yr)		80.76 ± 7.53	77.90 ± 6.90	1.98
Sex, female		33 (67.30)	41 (80.40)	2.21[a]
Education (yr)	Q1	0.00	0.00	
	Q2	1.00	0.00	
	Q3	3.75	6.00	
Diabetes		10 (20.41)	18 (35.29)	3.12[a]
Hypertension		13 (26.53)	19 (37.25)	1.24[a]
Smoking		8 (16.33)	6 (11.76)	0.55[a]
CDR	0.5	14	16	7.35[a]
	1	20	25	
	2	8	1	
Depressive symptoms				
CSDD		16.73 ± 6.54	15.88 ± 6.22	0.63
SGDS.K		9.81 ± 3.45	10.17 ± 5.18	−0.38
Cognitive function				
Word fluency		5.47 ± 2.95	5.43 ± 3.03	0.06
Naming		4.89 ± 2.72	5.30 ± 2.87	−0.70
MMSE.KC		13.64 ± 4.80	14.19 ± 4.39	−0.58
Word list memory		7.36 ± 4.19	6.29 ± 3.12	1.12
Construction		5.50 ± 2.35	5.79 ± 2.38	−0.58
Word list recall	Q1	0.00	0.00	
	Q2	0.00	1.00	
	Q3	1.00	1.00	
Word list recognition		5.21 ± 3.07	4.26 ± 2.68	1.28
Construction recall	Q1	0.00	0.00	
	Q2	0.00	0.00	
	Q3	1.75	2.00	
SVLT		6.02 ± 4.13	6.80 ± 3.60	−0.96
DS.F.		3.77 ± 1.48	3.91 ± 0.94	−0.54
DS.B.	Q1	0.00	0.00	
	Q2	0.00	0.00	
	Q3	2.00	2.00	
Contrasting		11.51 ± 6.83	10.33 ± 6.74	0.81
Go-no-go		8.68 ± 5.94	8.28 ± 5.44	0.33
SVLT.delayed recall	Q1	0.00	0.00	
	Q2	0.00	0.00	
	Q3	1.00	1.00	
SVLT.recognition		6.17 ± 2.92	6.50 ± 3.33	−0.50
DSST	Q1	0.00	0.00	
	Q2	0.00	0.00	
	Q3	2.00	4.50	
ADL				
BADL		3.09 ± 2.62	3.56 ± 2.63	−0.85
IADL		21.69 ± 9.07	21.41 ± 9.24	0.14

Values are presented as mean ± standard deviation or number (%).
CDR, Clinical Dementia Rating; CSDD, the Cornell Scale for Depression in Dementia; SGDS, the Korean version of the short form of Geriatric Depression Scale; MMSE.KC, the Korean version of the Mini-Mental State Examination; BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; SVLT, the Seoul Verbal Leaning Test; DS.F, Digit Span Forward; DS.B, Digit Span Backward; DSST, the Digit Symbol Substitution Test; Q, Quartile (Q1 = Lower Quartile; Q2 = Middle Quartile; Q3 = Upper Quartile).
[a]Pearson χ^2.

efficacy. Both primary and secondary efficacy analyses were evaluated with hierarchical linear growth models using the software program R and add-on package 'multilevel', a multilevel regression framework also known as mixed modeling (the Mixed Models for Repeated Measures) [32]. In this study, we analyzed whether the change in mean of variable over time is significant at level 1, and whether the difference in the change between two groups (intervention or control conditions) is significant and at level 2.

Safety analyses were based on the complete-patients-treated set, comprising all randomized patients who took ≥ 1 dose of study medication. Descriptive statistics were used for safety and tolerability, tabulating adverse events frequency by treatment groups. Statistical analysis was performed using Fisher's exact test for the evaluation of differences between the two groups. The significance level was set at $p = 0.05$.

RESULTS

Subjects

As shown in Figure 1, of the 100 subjects screened and randomized, 49 were allocated to vortioxetine and 51 to placebo groups. In the vortioxetine group, 27 subjects discontinued treatment due to AEs (n = 16) or were lost to follow-up (n = 11). In placebo group, 27 subjects discontinued treatment due to AEs (n = 16) or were lost to follow-up (n = 11). Twenty-two subjects from the treatment group, and 24 subjects from the placebo group were included in the final analyses.

Demographics and baseline clinical characteristics are shown in Table 1. Approximately 67% of the vortioxetine group population was female, as was 80% of the placebo group population. The mean ± standard devition age in the vortioxetine group was 80.76 ± 7.54 years, while in the placebo group was 77.9 ± 6.90. Patients had a median education of 1 year (range 0−16) in the vortioxetine group, while in the placebo group was 0 (range 0−13). The mean dosage administered at the first visit was 5 mg, 8.86 mg at the second, 9.77 mg at the third. At baseline, there were no clinically relevant differences in demographic or clinical characteristics between treatment groups (Table 1).

Reported AEs are shown in Table 2. Table 2 shows the adverse events reported in the two groups; the most commonly reported were nausea (14.29%) and diarrhea (6.12%) in the vortioxetine group and dizziness (9.80%) and nausea (3.92%) in the placebo group. No deaths or serious adverse events occurred during the study. Neither clinically relevant changes over time nor differences between treatment groups were observed.

Level 1 analyses were run without any Level 2 predictor to test whether the slope of each outcome significantly changed over time. For the SGDS-K ($t = -2.88$, $p = 0.01$), CSDD ($t = -4.95$, $p = 0.00$), MMSE ($t = 2.79$, $p = 0.01$), word fluency ($t = 3.76$, $p = 0.00$), naming ($t = 3.02$, $p = 0.00$), word list memory ($t = 2.10$, $p = 0.05$), Digit Span Backward (DS.B; $t = 2.57$, $p = 0.01$), go-no go ($t = 2.34$, $p = 0.02$), and SVLT ($t = 2.55$, $p = 0.01$) outcomes showed significant effects over time. However, the outcomes of construction ($t = 1.14$, $p = 0.26$), word list recognition ($t = 0.15$, $p = 0.88$), word list recall ($t = 1.33$, $p = 0.20$), Digit Span Forward (DS.F) ($t = 1.23$, $p = 0.23$), DSST ($t = 1.52$, $p = 0.13$), contrasting ($t = 1.87$, $p = 0.07$), SVLT delay ($t = 0.82$, $p = 0.42$), SVLT recognition ($t = 1.05$, $p = 0.30$), BADL ($t = -1.60$, $p = 0.12$), SIADL ($t = -0.50$, $p = 0.62$) showed no significant changes over time (Table 3).

Thereafter, we entered Level 2 predictors of group (vortioxetine vs placebo), but no significant Group × Time interactions from pre-treatment to post treatment (SGDS; $t = 0.24$, $p = 0.41$), CSDD ($t = 0.49$, $p = 0.31$), MMSE ($t = 0.18$, $p = 0.43$), word fluency ($t = 0.08$, $p = 0.47$), naming ($t = 0.03$, $p = 0.49$), construction ($t = 0.04$, $p = 0.48$), word list memory ($t = 0.07$, $p = 0.47$), word list recognition ($t = 0.07$, $p = 0.47$), word list recall ($t = 0.03$, $p = 0.49$), DS.F ($t = 0.01$, $p = 0.50$), DS.B ($t = 0.01$, $p = 0.50$), DSST ($t =$

Table 2. Treatment emergent adverse events reported

TEAEs	Vortioxetine group (n = 49)	Placebo group (n = 51)
Vomiting	1 (2.04)	2 (3.92)
Nausea	4 (8.16)	2 (3.92)
Headache	1 (2.04)	1 (1.96)
Dizziness	1 (2.04)	4 (7.84)
Constipation	0 (0.00)	1 (1.96)
Diarrheas	3 (6.12)	2 (3.92)
Irritability	1 (2.04)	0
Heartburn	2 (4.08)	2 (3.92)
General weakness	2 (4.08)	0 (0.00)
Paresthesia	1 (2.04)	0
Belching	1 (2.04)	1 (1.96)

Values are presented as number (%).

Table 3. Change from Baseline in all variances at Week 12 for all Efficacy Endpoints

Variables	Level 1			Level 2				
	Value	*t*	*p* value	Estimate	Ubar	b	*t*	*p* value
Depressive symptoms								
SGDS	−0.59 ± 0.21	−2.88	0.01	−0.07	0.24	0.00	0.24	0.41
CSDD	−1.62 ± 0.33	−4.95	0.00	0.58	0.49	0.00	0.49	0.31
Cognitive function								
MMSE	0.59 ± 0.21	2.79	0.01	0.59	0.18	0.00	0.18	0.43
Word fluency	0.53 ± 0.14	3.76	0.00	−0.19	0.08	0.00	0.08	0.47
Naming	0.25 ± 0.08	3.02	0.00	−0.30	0.03	0.00	0.03	0.49
Construction	0.11 ± 0.10	1.14	0.26	−0.05	0.04	0.00	0.04	0.48
Word list memory	0.29 ± 0.14	2.10	0.05	0.46	0.07	0.00	0.07	0.47
Word list recognition	0.02 ± 0.14	0.15	0.88	0.53	0.07	0.00	0.07	0.47
Word list recall	0.13 ± 0.10	1.33	0.20	0.33	0.03	0.00	0.03	0.49
DS.F	0.07 ± 0.06	1.23	0.23	0.03	0.01	0.00	0.01	0.50
DS.B	0.14 ± 0.06	2.57	0.01	0.12	0.01	0.00	0.01	0.50
DSST	0.43 ± 0.28	1.52	0.13	1.00	0.31	0.00	0.31	0.38
Contrasting	0.62 ± 0.33	1.87	0.07	0.63	0.43	0.00	0.43	0.33
Go-no-go	0.56 ± 0.24	2.34	0.02	0.35	0.23	0.00	0.23	0.41
SVLT	0.44 ± 0.17	2.55	0.01	0.46	0.12	0.00	0.12	0.45
SVLT delay	0.05 ± 0.06	0.82	0.42	0.17	0.01	0.00	0.01	0.50
SVLT recognition	0.17 ± 0.16	1.05	0.30	0.05	0.10	0.00	0.10	0.46
ADL								
BADL	−0.17 ± 0.11	−1.60	0.12	0.09	0.04	0.00	0.04	0.48
IADL	−0.21 ± 0.42	−0.50	0.62	0.39	0.72	0.00	0.72	0.23

Values are presented as mean ± standard error.
Ubar, the mean of the variances; b, the within imputation variance; CSDD, the Cornell Scale for Depression in Dementia; SGDS, the Korean version of the short form of Geriatric Depression Scale; MMSE.KC, the Korean version of the Mini-Mental State Examination, BADL, Basic Activities of Daily Living; IADL, Instrumental Activities of Daily Living; SVLT, the Seoul Verbal Leaning Test; DS.F, Digit Span Forward; DS.B, Digit Span Backward; DSST, the Digit Symbol Substitution Test.

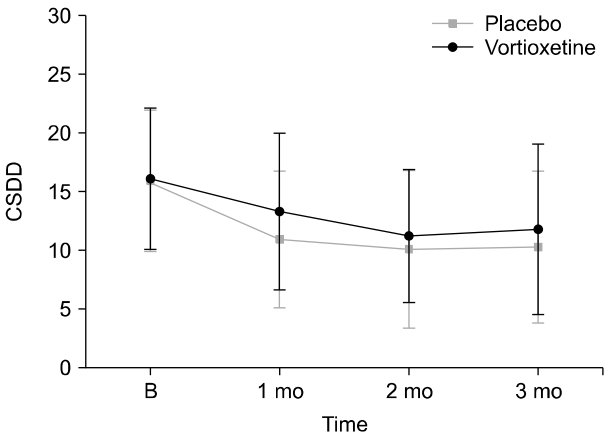

Fig. 2. Change from baseline in CSDD total score.
CSDD, the Cornell Scale for Depression in Dementia.

0.31, $p = 0.38$), contrasting ($t = 0.43$, $p = 0.33$), go-no-go ($t = 0.23$, $p = 0.41$), SVLT ($t = 0.12$, $p = 0.45$), SVLT delay ($t = 0.01$, $p = 0.50$), SVLT recognition ($t = 0.10$, $p = 0.46$), BADL ($t = 0.04$, $p = 0.48$), SIADL ($t = 0.72$, $p = 0.23$) were observed.

As shown in Figure 2, a difference from placebo in terms of the change from baseline in CSDD total score was observed from week 4, but no improvement was observed.

DISCUSSION

The main analysis of this study did not show statistically significant differences in the improvement of depressive symptoms between the vortioxetine and placebo groups. This finding might be similar to other pre-existing trials in patients with co-existing dementia and depression. In the study of Banerjee *et al.* [11], the two most used classes of antidepressants, SSRIs (sertraline) and SNRIs (mirtazapine), were not effective when compared with placebo for the treatment of clinically significant depression in patients with dementia. Moreover, in the study of de Vasconcelos Cunha *et al.* [33], venlafaxine was not effective in improving depressive symptoms in patients with dementia. However, in a recent study, Cumbo *et al.* [1], reported

that vortioxetine was effective in reducing depressive symptoms and improving cognitive function in patients with mild AD and depression [1].

Unlike Cumbo *et al.* [1]'s study, ours included patients with mild to moderate AD. Specifically, their study showed a mean MMSE score of around 20.87 points in the treatment group, seven points higher than in our study, which indicates that our subjects were more cognitively impaired. Furthermore, their subjects' mean CSDD baseline score was 13.82, about three points lower than in our study [1]. This suggests that our study included subjects with severe depression, more than just depressive symptoms. Therefore, a possible explanation to our diverging results is that we included patients with more severe cognitive impairment and depressive symptoms. It is possible that the more severe the cognitive impairment in AD patients, the more likely that their response to antidepressant treatment would be poor. Specifically, clinically more depressed patients could show an increase in severe neurodegeneration. Landes and colleagues [34] showed severe depressive symptoms in patients with severe neurodegeneration, caused by depressive-associated (for example, frontal-orbital-crystal and subcutaneous limbic circuits) neurodegenerating processes. The effect of mood control by antidepressants can be considered small when neurodegeneration is already established. In addition, the patients may not have been able to report the effects of vortioxetine due to their severe cognitive decline. These inconsistent results may indicate that the effects of antidepressant therapy in AD patients with depression need further follow-up studies.

The most commonly reported AEs, nausea and diarrhea, were similarly reported in both study groups. The discontinuation rate due to AEs was also similar in both groups (32.65% in vortioxetine group and 31.37% in placebo group). The mean dosage administered at the first visit was 5 mg, 8.86 mg at the second, 9.77 mg at the third. In our study, AD patients, who are more vulnerable than healthy adults, received nearly a standard dose (10 mg) but no significant differences in AEs from placebo were observed, suggesting that vortioxetine does not pose serious concerns in the treatment of patients with AD with depression. However, in the present study, both vortioxetine and placebo groups tend to have high dropouts. According to the dropout rate, the two groups are similar in cases of being eliminated due to side effects, and 11 cases of follow-up loss without any particular reason account for 20% each. This study was conducted on elderly people with an average age of 79 with impaired cognitive function. Restricted factors such as advanced age and cognitive dysfunction seem to have contributed to the increase in the dropout rate.

There is a limitation to the study that should be considered when interpreting the results. Since this study was conducted at a single center, its findings may not be generalizable. Despite this limitation, this study benefitted from patients receiving expert diagnosis, observation, and treatment at a specialized dementia clinic, and also provides valuable information on the safety and effectiveness of vortioxetine in a real-world clinical setting. Moreover, only one other study has examined the effects of vortioxetine for the improvement of depression and cognitive function in dementia patients with depression. The present study provides encouraging evidence of a relatively safe and tolerated usage of vortioxetine in elderly patients with dementia. And to our knowledge, this study might be the second study evaluating the effects of vortioxetine on depression and cognitive function in Alzheimer's disease. Further studies, including larger randomized controlled trials, however, are needed to confirm the effect of vortioxetine on depression in AD patients.

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■ Conflicts of Interest

This work was partially supported by a grant from Lundbeck Korea Co., Ltd. Overall data acquisition, statistical analyses, and interpretation of the study results were implemented with no input from the pharmaceutical

company.

■ Author Contributions

Conceptualization and protocol: Kyung Hee Yoon, Do Hoon Kim. Data acquisition: Chang Hyun Lee. Formal analysis: Chang Hyun Lee, Hye Won Jeong. Supervision: Do Hoon Kim. Writing – original draft: Hye Won Jeong. Writing – review & editing: Hye Won Jeong, Kyung Hee Yoon, Yoo Sun Moon, Do Hoon Kim.

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