RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Multicenter, randomized, placebo-controlled, double-blind clinical trial of escitalopram on the progression-delaying effects in Alzheimer's disease

Young Min Choe[1], Ki Woong Kim[2], Jin Hyeong Jhoo[3], Seung Ho Ryu[4], Eun Hyun Seo[5], Bo Kyung Sohn[6], Min Soo Byun[7], Jae-Hwa Bak[7], Jong-Min Lee[8], Hyuk Jin Yun[8], Myeong-il Han[9], Jong Inn Woo[7] and Dong Young Lee[7]

[1]Department of Neuropsychiatry, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, Korea
[2]Department of Neuropsychiatry, Seoul National University Bundang Hospital, Seongnam, Korea
[3]Department of Neuropsychiatry, Kangwon National University Hospital, Chunchon, Korea
[4]Department of Neuropsychiatry, Konkuk University Hospital, Seoul, Korea
[5]Division of Natural Medical Sciences, College of Health Science Chosun University, Gwangju, Korea
[6]Department of Neuropsychiatry, SMG-SNU Boramae Medical Center, Seoul, Korea
[7]Department of Neuropsychiatry, Seoul National University Hospital, Seoul, Korea
[8]Department of Biomedical Engineering, Hanyang University, Seoul, Korea
[9]Department of Psychiatry, Maeumsarang Hospital, Wanju, Korea
Correspondence to: D. Y. Lee, E-mail: selfpsy@snu.ac.kr

Objectives: A series of preclinical studies have suggested that selective serotonin reuptake inhibitor antidepressants not only stimulate neurogenesis but also have neuroprotective effects. The present study primarily aimed to investigate whether escitalopram would decelerate the brain atrophy of patients with mild-to-moderate Alzheimer's disease (AD). We also assessed the effects of escitalopram on the cognitive function and neuropsychiatric symptoms of these participants.

Methods: Seventy-four probable AD patients without major depression were recruited from four dementia clinics of university hospitals and randomly assigned in a 1:1 ratio. Each group received 20 mg/day of escitalopram or placebo for 52 weeks. The primary outcome measures were the change rates of hippocampal and whole brain volume on magnetic resonance imaging for 52 weeks. The Alzheimer's Disease Assessment Scale—cognitive subscale, Mini-Mental State Examination, Neuropsychiatric Inventory, and Cornell Scale for Depression in Dementia (CSDD) were also applied.

Results: We did not find any significant differences in the changes of hippocampal or whole brain volume between the groups. Escitalopram showed significant beneficial effects on the CSDD score at 28 weeks compared with placebo ($t = -2.17$, $df = 50.42$, $p = 0.035$), but this finding did not persist throughout the study.

Conclusion: The findings of the present study do not support the role of escitalopram as a progression-delaying treatment for AD. However, the negative results of the present trial should be interpreted cautiously because of the relatively small sample size. Further large-scale escitalopram trials targeting the earlier stages of AD, even prodromal AD, are still needed. Copyright © 2015 John Wiley & Sons, Ltd.

Key words: clinical trial; escitalopram; selective serotonin reuptake inhibitor; magnetic resonance imaging; brain atrophy; Alzheimer's disease
History: Received 5 March 2015; Accepted 1 October 2015; Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/gps.4384

Introduction

Serotonin [5-hydroxytrptamien (5-HT)] regulates behaviors such as sensorimotor control, cognition, and mood (Struder and Weicker, 2001). In addition to modulating synaptic function, serotonin is known to promote neurogenesis and the survival of neurons in the brain via the stimulation of brain-derived neurotrophic factor (BDNF) expression (Mattson *et al.*, 2004). This neurotransmitter is also linked with

Alzheimer's disease (AD) pathologies through the observation that 5-HT levels are correlated with memory performance and there are dense populations of serotonergic receptors in the hippocampus (Chow *et al.*, 2007). Additionally, the levels of 5-HT and 5-hydroxy-indole acetic acid were significantly decreased in the postmortem brains of AD patients (Nazarali and Reynolds, 1992).

A series of preclinical studies indicates that selective serotonin reuptake inhibitors (SSRIs) are neuroprotective. The studies showed that SSRIs including fluoxetine, citalopram, sertraline, paroxetine, and escitalopram not only stimulate hippocampal neurogenesis (Malberg *et al.*, 2000; Santarelli *et al.*, 2003; Kim *et al.*, 2013) but also protect neurons against various neurotoxic insults (Haynes *et al.*, 2004; Kolla *et al.*, 2005). More specifically, a study investigating Huntingtin mutant mice demonstrated that the administration of paroxetine decelerates the neurodegenerative disease process itself (Duan *et al.*, 2004), and another study found that administration of paroxetine even suppresses amyloid-β and tau pathology in a mouse model of AD (Nelson *et al.*, 2007).

Despite these preclinical findings, few studies have investigated the beneficial effects of SSRIs in human subjects. A recent retrospective study using Pittsburgh Compound B positron emission tomography (PiB-PET) imaging demonstrated that the cumulative time of SSRI use within previous 5 years is correlated with a lesser degree of amyloid-β load in cognitively normal individuals (Cirrito *et al.*, 2011). To date, however, no clinical trials have elucidated the disease-modifying effects of SSRIs in patients with neurodegenerative diseases such as AD.

Escitalopram is the most selective SSRI and has attractive pharmacokinetic features for the treatment of older patients (Owens *et al.*, 2001). It has negligible effects on cytochrome P450 *in vitro*, which suggests a low risk of the development of clinically relevant pharmacokinetic drug–drug interactions (Burke, 2002). Accordingly, several clinical trials have reported that escitalopram is efficacious for treatment of depression in AD patients and is well tolerated by older populations (Kasper *et al.*, 2006; Rao *et al.*, 2006).

Thus, in this context, the present multicenter, randomized, placebo-controlled, double-blind clinical trial was conducted to investigate whether escitalopram would decelerate the brain atrophy of patients with mild-to-moderate AD over a 52-week period. The secondary objective of this study was to assess the effects of escitalopram on the cognitive function and neuropsychiatric symptoms of these participants.

Methods

Participants

The present study included 74 AD patients who were recruited from four dementia clinics of university hospitals between September 2009 and October 2010. All participants met the criteria for dementia according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 1994) and the criteria for probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984). The inclusion criteria consisted of being between 40 and 90 years of age, having a Clinical Dementia Rating (CDR) score (Morris, 1993) ranging between 0.5 and 2, and a Modified Hachinski Ischemic Score (Rosen *et al.*, 1980) of less than 4. All of the participants had been taking a stable dose of donepezil (5–10 mg/day) in the 2 months prior to their inclusion in the study. The following exclusion criteria were also applied: illiteracy, the absence of a reliable informant, the presence of severe behavioral or communication problems that would make a clinical or imaging examination difficult, the presence of any serious medical or neurological disorders (other than AD) that could affect mental function, the presence of a current major depressive disorder or other major psychiatric illness, the use of any antidepressant medication within the last 4 weeks, and a history of alcohol or other substance dependence.

Ethics

After obtaining approval from local Institutional Review Boards, four sites contributed participants for the present study. Additionally, written informed consent was obtained from all participants or their legally authorized representatives after they received a full explanation of the procedure of the study and the possible side effects of the drug.

Study design

Following enrollment into the study, a period of 30 days was allowed for the performance of screening procedures, which included a clinical assessment based on the protocol of the Consortium to Establish a Registry for AD (Lee *et al.*, 2002), clinical laboratory tests, and electrocardiograms. All participants were stratified according to the research site from which they were recruited and their age at the onset of AD

(<60 or ≥60 years of age) and then randomly assigned to either the escitalopram or placebo group in a 1:1 ratio. A block randomization with block sizes of 4 or 6 was performed using a web-based randomization system provided by the Medical Research Collaborating Center at the Seoul National University Hospital. The randomization list was kept concealed, and all investigators and participants were blind to the intervention allocation throughout the study.

Either escitalopram or a placebo was dispensed at baseline and weeks 2, 4, 8, 16, 28, 40, and 52. Magnetic resonance imaging (MRI) scans were obtained at baseline and week 52, while secondary outcome measures were assessed at baseline and weeks 8, 28, and 52.

Study medication

The study drugs were supplied by H. Lundbeck A/S (Copenhagen, Denmark) and stored at room temperature (1–30 °C). Participants were instructed to take their drugs after breakfast. To minimize the occurrence of adverse events, all participants received 5 mg/day of escitalopram for the initial 2 weeks of the treatment period, 10 mg/day for the next 2 weeks, and then 20 mg/day for the remaining 48 weeks. A dose reduction from 20 to 10 mg/day or from 10 to 5 mg/day was allowed in the case of adverse events that appeared to be drug related, and unscheduled visits were allowed for the evaluation of adverse events or a dose adjustment. Donepezil was maintained at a stable dose throughout the trial period. The use of concomitant medications such as anticonvulsants, lithium, antidepressants, and cholinergic agonists or antagonists was not allowed, but the use of psychotropic drugs, including antipsychotics and benzodiazepines, was allowed. Compliance was monitored based on caregiver reports and counts of returned medications.

Outcome measures

The primary outcome measures included the rate of hippocampal and whole brain volume changes over the 52-week treatment period and were calculated as follows: [(volume at 52 weeks − volume at baseline) / volume at baseline × 100]. The hippocampal and whole brain volumes were measured using three-dimensional (3D) MRI images.

The secondary outcome measures included scores on the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog) (Youn *et al.*, 2002), the Mini-Mental State Examination (MMSE) (Lee *et al.*, 2002), the Neuropsychiatric Inventory (NPI) (Choi *et al.*, 2000), and Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos *et al.*, 1988).

Safety was evaluated at each visit except for the baseline session. A vital sign check, physical and neurological examinations, and clinical laboratory evaluations were also performed to monitor any potential adverse events at baseline and at weeks 8 and 52.

MRI image acquisition and analysis

At three sites, the scanner field strength was 3 T, and at one site, it was 1.5 T. Two sites used General Electric scanners (Milwaukee, WI, USA), and two sites used Philips Medical Systems scanners (Best, the Netherlands). At all sites, a 3D T1-weighted sequence was obtained for volumetric tracing and anatomical localization. Additionally, fluid-attenuated inversion recovery and T2-weighted images were also obtained for qualitative clinical reading. Each follow-up scan was performed on the same scanner using the same protocol as baseline. None of the scanners were changed or underwent major upgrades during the study period. Acquired MRI images were sent to the Seoul National University Hospital for centralized analysis. If acquired MRI was unsuitable because of motion artifacts or any other technical reason, the subject was excluded from final analysis.

Hippocampus volume. The anatomical boundaries of hippocampus were traced manually on 3D T1-weighted images using Analyze AVW 5.0 (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN, USA), and all traces were drawn blind to allocation, sex or subject demographics. The details of the tracing process including the borders of hippocampus were described previously (Choo *et al.*, 2010). To determine the reliability of volumetric measurements, the same rater, unaware of previous readings, repeated volume tracing on 10 randomly selected subjects. Reliability, expressed as intraclass correlation coefficients, was 0.97. The mean volume of the left and right hippocampus was used for further analyses.

Whole brain and total intracranial volume. Images were processed using the standard Montreal Neurological Institute anatomical pipeline. The native T1 images were normalized into a standardized stereotaxic space using a linear transformation and corrected for intensity non-uniformity (Collins *et al.*, 1994; Sled *et al.*, 1998). Each subject's brain, which was transformed and corrected, was classified into white matter (WM), gray matter (GM), cerebrospinal fluid, and

background using a 3D stereotaxic brain mask and the Intensity-Normalized Stereotaxic Environment for Classification of Tissues algorithm (Zijdenbos *et al.*, 1996). Whole brain volume was calculated as the sum of WM and GM volume that was inverse transformed to native space. We calculated the total intracranial volume by measuring the volume of voxels within the brain mask. The brain mask was generated using the brain extraction tool (Smith, 2002).

Apolipoprotein E genotyping

Apolipoprotein E (*ApoE*) genotype was determined and compared between the groups because *ApoE* epsilon4 allele is known to be correlated with hippocampal atrophy in AD (Mori *et al.*, 2002). Genomic DNA was extracted from venous blood, and *ApoE* genotyping was performed according to previously described methods (Kim *et al.*, 1999).

Statistical analyses

Because no clinical trial has investigated the atrophy-delaying effects of SSRIs in AD, the present study performed a sample size calculation using a study on the effects of donepezil on brain atrophy in AD (Hashimoto *et al.*, 2005). A total of 66 participants (33 in each group) was required for a two-tailed *t*-test with an alpha error of 0.05 and a beta error of 0.2 (power: 0.8) when the between-group difference and standard deviation were estimated as 1.7% and 2.4%, respectively. To account for an expected 20% dropout rate, it was determined that approximately 80 participants should be recruited for the present trial.

The rate of discontinuation and the occurrences of adverse events were compared using a Chi-squared test or a Fisher's exact test. Imbalances in the baseline characteristics were tested using a two-tailed *t*-test for continuous measures. Categorical variables, which included gender, CDR, and *ApoE ε4* allele, were evaluated by using a Chi-squared test or a Fisher's exact test. The primary outcome analyses were conducted for per-protocol (PP) sample using only participants who had both baseline and follow-up MRI data that were suitable for analysis. Analysis of covariance (ANCOVA) was used to evaluate the group differences in the primary outcome measures. ANCOVA models included hippocampal and whole brain volume changes as dependent variables and intervention group as the independent variable. The baseline MMSE score was entered as a covariate, because it was unbalanced in the PP sample ($t = 2.1$, $df = 55$, $p = 0.043$). Effect sizes were calculated as Cohen's *d* (Cohen, 1988). The secondary outcome measures were analyzed with a linear mixed model (LMM) that included intercept, intervention group, time of visit, and intervention-by-time interaction as fixed effects and random intercept per subject as a random effect. Student's *t*-test was used to compare between-group differences in the secondary outcomes at the various post-baseline assessment sessions. The LMM analyses and Student's *t*-tests were conducted as intent-to-treat (ITT) analyses and included all participants who were randomized and had suitable data from the baseline assessment and at least one post-baseline assessment. A p value < 0.05 was considered to indicate statistical significance, and all statistical analyses were performed using the SPSS software (version 18.0 for Windows, SPSS Inc.; Chicago, IL, USA).

Results

Study participants and follow-up

The flow of the trial is summarized in Figure 1. Of the initial 81 participants screened for the present study, 74 met the inclusion criteria and underwent the randomization procedure, with 37 participants assigned to the escitalopram group and 37 assigned to the placebo group. Of these 74 participants, 29 in the escitalopram group and 34 in the placebo group completed the trial. The number of dropouts did not significantly differ between the groups (chi-square = 2.67, $df = 1$, $p = 0.102$); the reasons for discontinuation included failure of the MRI scan, withdrawal of consent, and serious adverse events.

The PP analyses for primary outcome measures included 28 participants from the escitalopram group and 29 participants from the placebo group. One subject from the escitalopram group and five from the placebo group were excluded because of poor MRI scan quality. The baseline characteristics for the PP sample are displayed in Table 1. There were no significant differences between the groups in terms of baseline characteristics, except for the MMSE score, which was higher in the escitalopram group ($t = 2.1$, $df = 55$, $p = 0.043$). The ITT analyses for primary outcome measures included 37 participants from each group. The baseline characteristics for the ITT sample are presented in Table 2; there were no significant differences between the groups on the baseline characteristics.

Primary outcome measures

The rates of hippocampal and whole brain volume changes over the 52-week treatment period are shown

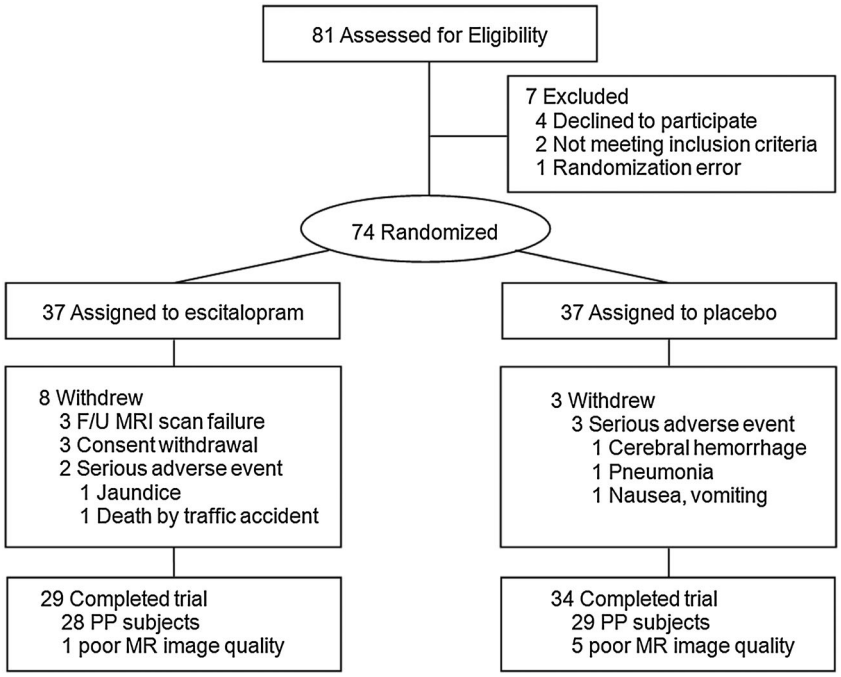

Figure 1 Flow diagram. PP, per-protocol.

Table 1 Baseline characteristics for the per-protocol sample

	Escitalopram ($n = 28$)	Placebo ($n = 29$)	p value
Age (years)	74.33 ± 7.12	74.82 ± 9.19	0.83
Gender, *n* (M/F)	13/15	8/21	0.14
Education (years)	10.36 ± 4.70	8.66 ± 5.64	0.22
CDR (0.5/1/2)	17/8/3	10/16/3	0.11
ApoE ε4 (0/1/2)	11/11/6	14/11/4	0.69
WBV (ICV%)	83.5 ± 0.06	81.2 ± 0.07	0.17
HCV (ICV%)	0.13 ± 0.03	0.12 ± 0.03	0.22
ADAS-cog	22.35 ± 7.84	24.68 ± 10.15	0.69
MMSE	18.25 ± 4.93	15.66 ± 4.51	0.04
NPI	11.61 ± 10.74	10.31 ± 10.58	0.65
CSDD	2.43 ± 2.19	2.90 ± 4.18	0.60

Data are presented as mean ± SD. WBV and HCV were corrected for ICV (%). Comparison of groups was carried out by Student's *t*-test except chi-square test for gender and *ApoE ε4* allele, and Fisher's exact test for CDR. CDR, Clinical Dementia Rating; *ApoE*, apolipoprotein E; WBV, whole brain volume; HCV, hippocampus volume; ICV, total intracranial volume; ADAS-cog, Alzheimer Disease Assessment Scale—cognitive subscale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; CSDD, Cornell Scale for Depression in Dementia.

Table 2 Baseline characteristics for the intent-to-treat sample

	Escitalopram ($n = 37$)	Placebo ($n = 37$)	p value
Age (years)	74.25 ± 7.42	75.40 ± 8.37	0.53
Gender, *n* (M/F)	18/19	10/27	0.06
Education (years)	10.51 ± 4.53	8.51 ± 5.98	0.11
CDR (0.5/1/2)	18/15/4	13/20/4	0.51
ApoE ε4 (0/1/2)	15/16/6	17/16/4	0.77
WBV (ICV%)	81.0 ± 0.15	79.0 ± 0.15	0.60
HCV (ICV%)	0.13 ± 0.03	0.12 ± 0.03	0.16
ADAS-cog	22.97 ± 8.92	23.85 ± 9.89	0.69
MMSE	17.03 ± 5.87	15.62 ± 4.34	0.25
NPI	11.00 ± 11.34	9.30 ± 9.73	0.49
CSDD	2.24 ± 2.09	2.59 ± 3.81	0.62

Data are presented as mean ± SD. WBV and HCV were corrected for ICV (%). Comparison of groups was carried out by Student's *t*-test except chi-square test for gender and *ApoE ε4* allele, and Fisher's exact test for CDR. CDR, Clinical Dementia Rating; *ApoE*, apolipoprotein E; WBV, whole brain volume; HCV, hippocampus volume; ICV, total intracranial volume; ADAS-cog, Alzheimer Disease Assessment Scale—cognitive subscale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; CSDD, Cornell Scale for Depression in Dementia.

in Table 3. After controlling for the baseline MMSE score, there were no significant differences between the escitalopram and placebo groups for either hippocampal or whole brain atrophy.

Secondary outcome measures

The LMM analyses did not reveal a significant intervention-by-time interaction for any of the

Table 3 Hippocampal and whole brain volume changes for the per-protocol sample

	Escitalopram ($n = 28$)		Placebo ($n = 29$)		ANCOVA		Effect size: Cohen's *d*
	Mean	SD	Mean	SD	*F*	*p*	
Hippocampus	−7.63	7.32	−7.28	5.76	0.51	0.48	0.20
Whole brain	−3.27	2.69	−2.30	3.08	2.04	0.16	0.39

ANCOVA, analysis of covariance. ANCOVA model adjusted for baseline MMSE. Effect size (*d*) calculated from adjusted mean and mean square error. Volume change (%) = (volume at 52 weeks − volume at baseline) / volume at baseline × 100.

secondary outcome measures, which indicates that escitalopram did not have a significantly greater effect than the placebo (Figure 2). The time effect was significant for the ADAS-cog, MMSE, and NPI scores but not the CSDD score. While Student's *t*-test revealed a significantly lower CSDD score in the escitalopram group compared with the placebo group at 28 weeks ($t = -2.17$, $df = 50.42$, $p = 0.035$), this difference did not persist throughout the trial.

Safety data

The escitalopram intervention was well tolerated by the participants of the present study (Table 4). In the ITT sample, the numbers of subjects who experienced adverse events (13 in the escitalopram group and 12 in the placebo group) or serious adverse events (two in the escitalopram group and three in the placebo group) did not differ significantly. Furthermore, none of the serious adverse events were believed to be related to the escitalopram intervention.

Discussion

To date, this is the first double-blind, placebo-controlled, randomized clinical trial to assess the efficacy of an SSRI for delaying the progression of

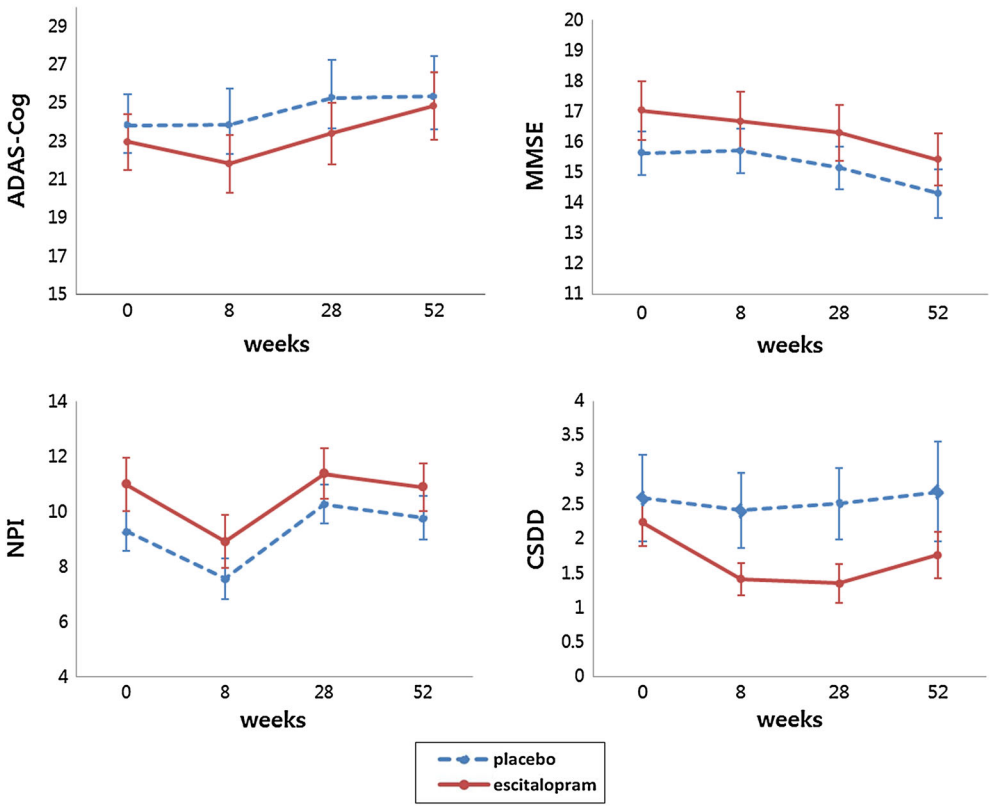

Figure 2 Time courses of the ADAS-cog, MMSE, NPI, and CSDD scores for the intent-to-treat sample. This figure shows the means of the secondary outcome measures; error bars indicate standard error of the mean. ADAS-cog, Alzheimer Disease Assessment Scale—cognitive subscale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; CSDD, Cornell Scale for Depression in Dementia.

Table 4 Adverse events

Symptoms	Escitalopram ($n = 37$)	Placebo ($n = 37$)
Dizziness	4 (10.8)	0 (0)
Vomiting	0 (0)	2 (5.4)
Nausea	0 (0)	1 (2.7)
Anorexia	1 (2.7)	1 (2.7)
Abdominal pain	0 (0)	1 (2.7)
Diarrhea	1 (2.7)	0 (0)
Constipation	0 (0)	1 (2.7)
Hepatopathy	1 (2.7)	0 (0)
Cough	1 (2.7)	0 (0)
Pneumonia	0 (0)	1 (2.7)
Bronchitis	0 (0)	1 (2.7)
Somnolence	1 (2.7)	0 (0)
Tremor	1 (2.7)	0 (0)
Fall	0 (0)	1 (2.7)
Violent behavior	1 (2.7)	0 (0)
Urinary incontinence	1 (2.7)	0 (0)
Cerebral hemorrhage	0 (0)	1 (2.7)
Hypoglycemia	1 (2.7)	0 (0)
Cancer	1 (2.7)	1 (2.7)
Death by traffic accident	1 (2.7)	0 (0)

Data are number (%) of subjects who experienced adverse events at least once during the trial.

AD. A 52-week intervention with escitalopram did not slow the progression of hippocampal or whole brain atrophy compared with placebo in mild-to-moderate AD patients taking donepezil. Additionally, there were no significant beneficial effects of escitalopram on cognitive function or neuropsychiatric symptoms compared with placebo. The escitalopram intervention did benefit the CSDD score at 28 weeks, but this finding did not persist throughout the study.

Contrary to the findings of preclinical studies, escitalopram intervention for 52 weeks did not have positive effects on the progression of brain atrophy in AD patients. There are several plausible explanations for the present findings. First, the present study had a relatively small sample size and a short trial period. The sample size was determined based on a previous study of the influence of donepezil on brain atrophy in AD patients (Hashimoto *et al.*, 2005) because no previous trials have evaluated the atrophy-delaying effect of SSRIs in this population. Moreover, the statistical power of the present study was further reduced because the number of PP subjects (28 in the escitalopram group and 29 in the placebo group) was smaller than the required number of participants calculated by the sample size estimation (33 per group). Previous animal studies have demonstrated the neuroprotective effects of SSRIs after chronic, but not acute, administration (Haynes *et al.*, 2004), and hippocampal neurogenesis in the adult rat was prominent after 14 days of SSRI administration (Malberg *et al.*, 2000). Given that 1 year of human life is equal to approximately 11.8 days for an adult rat (Quinn, 2005), the study period of 52 weeks used here might be too short to detect long-term effects of escitalopram.

Second, the preclinical evidence demonstrating the neuroprotective effects of SSRIs in animals may be limited in that a majority of these studies employed animal models with singular types of brain damage (Haynes *et al.*, 2004; Kolla *et al.*, 2005) rather than the chronic long-term brain insults that are associated with neurodegenerative diseases such as AD. The null findings of the present study suggest that the neuroprotective properties of SSRIs may not be sufficient to protect the human brain from chronic and long-term AD-related degenerative brain insults.

Third, it should be noted that all participants maintained a therapeutic regimen of donepezil, an acetylcholinesterase inhibitor (AChEI), at a stable dose. The neuroprotective and neurogenesis-inducing effects of AChEIs and SSRIs have several underlying mechanisms in common. A prospective cohort study demonstrated that donepezil slows the progression of hippocampal atrophy in AD patients and postulated that the mechanism may be a decrease in amyloid-β production that is associated with cholinergic stimulation (Hashimoto *et al.*, 2005). SSRIs also exert neuroprotective actions, at least in part, via reductions in the amount of cerebral amyloid-β (Nelson *et al.*, 2007; Cirrito *et al.*, 2011). In addition, preclinical studies showed that the chronic administration of SSRIs activates BDNF expression (Malberg *et al.*, 2000; Mattson *et al.*, 2004), which is also associated with the influence of AChEIs on neurogenesis (Leyhe *et al.*, 2008). Therefore, the influence of escitalopram may have been masked because these shared mechanisms were saturated or fully expressed following treatment with donepezil, which was initiated in each participant at least 2 months prior to the current escitalopram trial.

Although the present study did not identify a progression-delaying effect of escitalopram in mild-to-moderate AD patients, there still remains a possibility that escitalopram may be efficacious in the earlier stages of AD progression. A recent PiB-PET study found that the chronic use of SSRIs is correlated with a lessened amyloid-β load in cognitively normal individuals (Cirrito *et al.*, 2011). Given that amyloid-β deposition begins several decades before the onset of the clinical symptoms of AD and plays a key role in its early pathogenesis (Villemagne *et al.*, 2013), the progression-delaying effects of escitalopram via a reduction in amyloid-β burden might be more critical in these earlier stages, including the preclinical or prodromal AD.

The escitalopram intervention in the present study did not significantly improve cognitive function as

measured by the MMSE or ADAS-cog, which implies that escitalopram would not have any further cognitive benefit if combined with AChEIs in AD patients without major depression. This finding is generally in line with the negative results from previous SSRI trials on the cognitive benefit in AD, although most of them have been conducted in AD patients with comorbid depression (Sepehry *et al.*, 2012). Few trials have investigated the cognitive effects of SSRIs in non-depressed AD patients; all also reported null results (Cutler *et al.*, 1985; Finkel *et al.*, 2004; Mowla *et al.*, 2007).

Similarly, the escitalopram intervention in the present study did not significantly improve neuropsychiatric symptoms as measured by the NPI and CSDD. However, this negative finding should be interpreted with caution because the effects of escitalopram on the CSDD (or NPI) were not a primary outcome measure in the current trial, and as a result, the sample size was likely not sufficient to test these variables. The CSDD score of the escitalopram group was significantly lower than that of the placebo group at 28 weeks, but this difference did not persist throughout the trial. Additionally, no large-scale trial has investigated the effects of escitalopram on depression in AD as a primary outcome; the majority of SSRI trials investigating this issue were conducted using sertraline and fluoxetine (Nelson and Devanand, 2011; Sepehry *et al.*, 2012).

Overall, the findings of the present study do not support the role of escitalopram as a progression-delaying treatment for AD. Additionally, these findings do not indicate any benefit of escitalopram regarding the cognitive and neuropsychiatric symptoms associated with AD. Nonetheless, the negative results of the present trial should be interpreted cautiously because of the relatively small sample size. Further large-scale escitalopram trials targeting the earlier stages of AD, even prodromal AD, are still needed.

Conflict of interest

None declared.

Key points

- A 52-week intervention with escitalopram did not slow the progression of hippocampal or whole brain atrophy compared with placebo in mild-to-moderate AD patients taking donepezil.
- Further large-scale escitalopram trials targeting the earlier stages of AD, even prodromal AD, are still needed.

Acknowledgements

Participants were recruited from the dementia clinics of the Seoul National University Hospital, Seoul National University Bundang Hospital, Kangwon National University Hospital, and Konkuk University Hospital, Korea.

The current study was supported by a grant from H. Lundbeck A/S (Copenhagen, Denmark) and a grant from the Ministry of Science, ICT, and Future Planning, Republic of Korea (grant no. NRF-2014M3C7A1046042).

Role of the funders

The funders had no role in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the report for publication.

References

Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. 1988. Cornell Scale for Depression in Dementia. *Biol Psychiatry* **23**: 271–284.

American Psychiatric Association. 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th edn.American Psychiatric Publishing: Washington, DC.

Burke WJ. 2002. Escitalopram. *Expert Opin Investig Drugs* **11**: 1477–1486.

Choi SH, Na DL, Kwon HM, *et al.* 2000. The Korean version of the neuropsychiatric inventory: a scoring tool for neuropsychiatric disturbance in dementia patients. *J Korean Med Sci* **15**: 609–615.

Choo IH, Lee DY, Oh JS, *et al.* 2010. Posterior cingulate cortex atrophy and regional cingulum disruption in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* **31**: 772–779.

Chow TW, Pollock BG, Milgram NW. 2007. Potential cognitive enhancing and disease modification effects of SSRIs for Alzheimer's disease. *Neuropsychiatric Dis Treat* **3**: 627–636.

Cirrito JR, Disabato BM, Restivo JL, *et al.* 2011. Serotonin signaling is associated with lower amyloid-beta levels and plaques in transgenic mice and humans. *Proc Natl Acad Sci U S A* **108**: 14968–14973.

Cohen J. 1988. Statistical Power Analysis for the Behavioral Sciences. L. Erlbaum Associates: Hillsdale, N.J.

Collins DL, Neelin P, Peters TM, Evans AC. 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr* **18**: 192–205.

Cutler NR, Haxby J, Kay AD, *et al.* 1985. Evaluation of zimeldine in Alzheimer's disease. *Cognitive and biochemical measures Archives of neurology* **42**: 744–748.

Duan W, Guo Z, Jiang H, *et al.* 2004. Paroxetine retards disease onset and progression in Huntingtin mutant mice. *Ann Neurol* **55**: 590–594.

Finkel SI, Mintzer JE, Dysken M, *et al.* 2004. A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. *Int J Geriatr Psych* **19**: 9–18.

Hashimoto M, Kazui H, Matsumoto K, *et al.* 2005. Does donepezil treatment slow the progression of hippocampal atrophy in patients with Alzheimer's disease? *Am J Psychiat* **162**: 676–682.

Haynes LE, Barber D, Mitchell IJ. 2004. Chronic antidepressant medication attenuates dexamethasone-induced neuronal death and sublethal neuronal damage in the hippocampus and striatum. *Brain Res* **1026**: 157–167.

Kasper S, Lemming OM, de Swart H. 2006. Escitalopram in the long-term treatment of major depressive disorder in elderly patients. *Neuropsychobiology* **54**: 152–159.

Kim KW, Jhoo JH, Lee KU, *et al.* 1999. Association between apolipoprotein E polymorphism and Alzheimer's disease in Koreans. *Neurosci Lett* **277**: 145–148.

Kim HJ, Kim W, Kong SY. 2013. Antidepressants for neuro-regeneration: from depression to Alzheimer's disease. *Arch Pharm Res* **36**: 1279–1290.

Kolla N, Wei Z, Richardson JS, Li XM. 2005. Amitriptyline and fluoxetine protect PC12 cells from cell death induced by hydrogen peroxide. *J Psychiatry Neurosci: JPN* **30**: 196–201.

Lee JH, Lee KU, Lee DY, *et al.* 2002. Development of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K): clinical and neuropsychological assessment batteries. *J Gerontol B Psychol Sci Soc Sci* **57**: 47–53.

Leyhe T, Stransky E, Eschweiler GW, Buchkremer G, Laske C. 2008. Increase of BDNF serum concentration during donepezil treatment of patients with early Alzheimer's disease. *Eur Arch Psychiatry Clin Neurosci* **258**: 124–128.

Malberg JE, Eisch AJ, Nestler EJ, Duman RS. 2000. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* **20**: 9104–9110.

Mattson MP, Maudsley S, Martin B. 2004. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends Neurosci* **27**: 589–594.

McKhann G, Drachman D, Folstein M, *et al.* 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**: 939–944.

Mori E, Lee K, Yasuda M, *et al.* 2002. Accelerated hippocampal atrophy in Alzheimer's disease with apolipoprotein E epsilon4 allele. *Ann Neurol* **51**: 209–214.

Morris JC. 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* **43**: 2412–2414.

Mowla A, Mosavinasab M, Haghshenas H, Borhani-Haghighi A. 2007. Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia? A double-blind, placebo-controlled clinical trial. *J Clin Psychopharm* **27**: 484–487.

Nazarali AJ, Reynolds GP. 1992. Monoamine neurotransmitters and their metabolites in brain-regions in Alzheimers' disease—a postmortem study. *Cell Mol Neurobiol* **12**: 581–587.

Nelson JC, Devanand DP. 2011. A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. *J Am Geriatr Soc* **59**: 577–585.

Nelson RL, Guo Z, Halagappa VM, *et al.* 2007. Prophylactic treatment with paroxetine ameliorates behavioral deficits and retards the development of amyloid and tau pathologies in 3xTgAD mice. *Exp Neurol* **205**: 166–176.

Owens MJ, Knight DL, Nemeroff CB. 2001. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. *Biol Psychiatry* **50**: 345–350.

Quinn R. 2005. Comparing rat's to human's age: how old is my rat in people years? *Nutrition* **21**: 775–777.

Rao V, Spiro JR, Rosenberg PB, *et al.* 2006. An open-label study of escitalopram (Lexapro) for the treatment of 'Depression of Alzheimer's disease' (dAD). *Int J Geriatr Psych* **21**: 273–274.

Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. 1980. Pathological verification of ischemic score in differentiation of dementias. *Ann Neurol* **7**: 486–488.

Santarelli L, Saxe M, Gross C, *et al.* 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* **301**: 805–809.

Sepehry AA, Lee PE, Hsiung GYR, Beattie BL, Jacova C. 2012. Effect of selective serotonin reuptake inhibitors in Alzheimer's disease with comorbid depression: a meta-analysis of depression and cognitive outcomes. *Drug Aging* **29**: 793–806.

Sled JG, Zijdenbos AP, Evans AC. 1998. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging* **17**: 87–97.

Smith SM. 2002. Fast robust automated brain extraction. *Hum Brain Mapp* **17**: 143–155.

Struder HK, Weicker H. 2001. Physiology and pathophysiology of the serotonergic system and its implications on mental and physical performance. Part I. *International Journal of Sports Medicine* **22**: 467–481.

Villemagne VL, Burnham S, Bourgeat P, *et al.* 2013. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol* **12**: 357–367.

Youn JC, Lee DY, Kim KW, *et al.* 2002. Development of the Korean version of Alzheimer's Disease Assessment Scale (ADAS-K). *Int J Geriatr Psych* **17**: 797–803.

Zijdenbos A, Evans A, Riahi F, *et al.* 1996. Automatic quantification of multiple sclerosis lesion volume using stereotaxic space. *Lect Notes Comput Sc* **1131**: 439–448.