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Safety and Efficacy of Donepezil 10 mg/day in Patients with Mild to Moderate Alzheimer's Disease

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Abstract.
Background: Efficacy and dose-effect relationship of donepezil for treating patients with Alzheimer's disease (AD) have been proven. However, few studies focused on the safety of donepezil, particularly in Chinese patients.
Objective: To assess the safety of donepezil 10 mg/day in Chinese patients with mild-to-moderate AD.
Methods: In this single-arm, prospective, multicenter trial, 241 patients with mild to moderate AD who had been treated with donepezil 5 mg/day for at least 4 weeks were enrolled. All patients received donepezil 10 mg/day for 20 weeks. Primary outcome was the incidence of adverse events (AEs). Safety profile was evaluated by physical examinations including vital signs and weight, clinical laboratory tests and electrocardiograms, and also correlation analysis between AEs and *APOE* genotypes.
Results: 241 patients were enrolled. Of which, 38.59% patients experienced at least one AE and 17.43% discontinued due to AEs. Most AEs were mild to moderate, with diarrhea, vomiting, and nausea the most frequently reported. Risk of AEs was significantly increased by concomitant use of drugs for cardiovascular and cerebrovascular diseases. Mean changes in heart rate and corrected QT relative to baseline were -1.08 ± 6.02 beat/min ($p = 0.009$) and -3.91 ± 18.68 ms ($p = 0.0062$) at week 4 and -1.48 beat/min ± 7.18 ($p = 0.0028$) and -0.66 ms ± 19.66 ($p = 0.6561$) at week 20, respectively. There were no significant changes in other vital sign parameters. Patients' MMSE scores improved significantly after treatment ($p = 0.0038$), especially for non-*APOE* ε4 allele carriers and patients $\leq$75 years.
Conclusion: Donepezil 10 mg/day can be tolerated and is effective in Chinese patients with mild-to-moderate AD.

Keywords: Alzheimer's disease, Chinese, clinical trial, donepezil, safety

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the elderly [1, 2]. It is an age-related disease, and is characterized by progressive decline in memory and cognition and dysregulation

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of neurobehavior [1–4]. Since the world is shifting toward a more aged population, the prevalence of patients with AD is rapidly increasing [1, 4, 5]. In China, the prevalence of dementia in people ≥65 years is 5.14%, and 3.21% of those with dementia have AD; this means that there are about 6 million AD patients in China [4].

Donepezil hydrochloride is a potent, reversible, non-competitive, peperidine-based acetylcholinesterase (AChE) inhibitors (AChEIs) used to slow cognitive decline in patients with AD [1, 3, 4]. It is indicated for the treatment of mild-to-severe AD [4, 6]. AD is accompanied by losses of presynaptic cholinergic function in the brain [1], and donepezil can increase acetylcholine concentration in the synaptic gap of hippocampus and cortex neuron by blocking AChE [1, 3]. Its efficacy and safety have been proven repeatedly [1, 4, 5, 7–11]. Additionally, dose-response effect has been established for donepezil by various studies, that is, patients receiving donepezil 10 mg/day showed greater cognitive improvement than patients taking donepezil 5 mg/day [9, 10, 12]. Such dose-response effect raises concerns as to whether donepezil 10 mg/day treatment could lead to more cholinergic side effects and less tolerability than the 5 mg/day treatment. One 24-week, randomized, double-blind study found higher percentage of patients taking donepezil 10 mg/day affected by cholinergic adverse events (AEs) than those patients on 5 mg/day; however, such higher incidence of AEs was considered to be due to the rapid up-titration used in the study, as in another open-label, placebo-controlled study, when patients took donepezil 10 mg/day after 4–6 week of taking 5 mg/day, the incidence of cholinergic AEs of the 10 mg/day group was comparable to the 5 mg/day and the placebo groups [10, 12]. Most of the donepezil-related AEs occurred because although donepezil acts mainly on the central nervous system (CNS), it could increase cholinergic activity in the peripheral nervous system as well [6]. These AEs are generally mild and transient such as gastrointestinal disturbance, fatigue, and dizziness [9, 10, 12]. Certain cardiovascular system AEs also raised some concerns, as abundant cholinesterase is present in the heart, and its inhibition by donepezil could affect cardiac function [2, 6]. In patients taking donepezil, there have been case reports of bradycardia, syncope, prolonged QT/corrected QT (QTc), and torsade de pointes [2, 6, 13]. Prolonged QT could result in life-threatening ventricular arrhythmias such as torsade de pointes and ventricular fibrillation [2]; therefore such potential cardiovascular side effects should be further studied. On the other hand, a couple of studies found unchanged or reduced heart rate (HR) and no QT prolongation associated with donepezil therapy [14–17].

As for donepezil's safety in Chinese patients with AD, there have been only a few randomized, double blind studies reporting its efficacy and safety, and there are even fewer reports on patients taking donepezil 10 mg/day, some of which only used donepezil as control [4, 5, 18, 19]. Although donepezil's efficacy has been demonstrated by these studies, these studies have somewhat inconsistent results regarding the prevalence of AEs in patients taking donepezil 10 mg/day, ranging from 13.17% [18] to 71.8% [5], and none of these studies was a safety study that had safety of donepezil 10 mg/day as their primary outcome. As Chinese patients' response to donepezil might differ from Caucasian patients due to such factors as cytochrome P450 enzyme (CYP) polymorphism and the lower apolipoprotein E (*APOE*) $\varepsilon 4$ allele frequency in Chinese versus Westerners [20, 21], we aimed to conduct a single-arm, prospective, multicenter clinical trial with safety of donepezil 10 mg/day in patients with mild-to-moderate AD as its primary outcome, and this is the first safety study of donepezil 10 mg/day treatment conducted in China.

MATERIALS AND METHODS

Study design

The present study was a 20-week, single-arm, prospective, multicenter study conducted at 16 sites in China. This study was designed and conducted according to Good Clinical Practice (GCP) [22] and the Declaration of Helsinki [23], and had been approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) of each center before the study began. All patients or their caregivers gave written informed consent before screening. This study is registered at ClinicalTrials.Gov (Identifier: NCT02787746).

Patients

Inclusion criteria

All patients between 50 and 85 years of age who had a diagnosis of AD consistent with the Diagnostic and Statistical Manual of Mental Disorders, 4th Edi-

tion, Text Revision (DSM-IV-TR) criteria [24] and National Institute of Neurologic and Communicative Disorders and Stroke–AD and Related Disorders Association (NINCDS-ADRDA) criteria [25] for probable AD; patients with mild to moderate AD as assessed with a Mini-Mental State Examination (MMSE) score [26] (a score range of 0 to 30, with higher scores indicating better cognitive function) of between 10 and 24 (inclusive), Modified Hachinski Ischemia Scale (MHIS) [27] $\leq$4, Activity of daily life scale (ADL) [28] $\geq$23, and Hamilton Depression Scale (HAMD) [29] <7 at screening. The diagnosis of AD should also be supported by magnetic resonance imaging (MRI) scans (medial temporal lobe atrophy, Fazekas scale of white matter lesions $\leq$2 within 6 months prior to the screening). The patients should have been taking donepezil 5 mg/day for at least 4 weeks before the screening. In addition, each eligible patient should have an exclusive caregiver, should be ambulatory or ambulatory aided by a walker or cane, should have good eyesight and hearing, and could cooperate with the examination and treatment.

Exclusion criteria

1) Patients with vascular dementia, other types of dementia or with other psychiatric or neurological disorders (e.g., delirium, depression, Parkinson's disease, etc.); 2) patients with type I diabetes, obstructive lung disease or asthma, vitamin B_{12} or folic acid deficiency, thyroid dysfunction, severe liver or kidney dysfunction, severe cardiac insufficiency (congestive heart failure, myocardial infarction, sick sinus syndrome, II-III degree atrioventricular block or heart rate <50 beats/minute [bpm]); 3) epilepsy or head trauma resulting in unconsciousness that occurred in the two years prior to the screening; 4) patients with hematologic diseases (such as anemia, granulocytes, leukemia, etc.), tumor, neoplasms within 2 years prior to the screening; 5) patients with a history of alcohol dependence and drug abuse; 6) patients with known hypersensitivity to medicines or foods; 7) patients taking anticholinergic agents or antihistaminic agents; 8) patients who had been hospitalized continuously for more than 3 months before the screening.

Intervention and procedure

Each enrolled patient received donepezil 10 mg/day (Aricept, two 5 mg-pills, Eisai China Inc, SuZhou, China) every night before sleeping for 20 weeks. If a patient could not tolerate 10 mg/day, the dosage for the patient could be reduced to 5 mg/day for 4 weeks and then increased back to 10 mg/day. If this patient still could not tolerate the 10 mg/day dosage and returned back to 5 mg/day or discontinued the donepezil treatment, he/she should be deemed to have quit the study. Visits were conducted at week 0 (baseline, visit 1) and the end of weeks 4 and 20 (visits 2 and 3, respectively).

Endpoints

The primary endpoint for the present study was the incidence of AEs evaluated by physical examinations such as vital signs and weight, clinical laboratory tests, and electrocardiograms (ECGs) during the 20 weeks. Correlation analysis between AEs and APOE genotype was conducted. AEs were graded on a 3-point scale (mild: discomfort noticed, but no disruption of normal daily activity; moderate: discomfort grave enough to reduce or affect normal daily activity; severe: incapacitation presented as inability to work or to perform normal daily activity). A serious AE (SAE) was defined as any AE that was life-threatening or resulted in death, hospitalization or prolongation of existing hospitalization, occurrence of persistent or significant disability/incapacity, a congenital anomaly, or other important medical events. The investigator would assess the relationship between each AE and donepezil use (certainly related, very likely related, and possible related).

Secondary outcomes were the number of patients who withdrew from the trial due to adverse events during the study, changes from baseline at weeks 4 and 20 of MMSE score and Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) (a score range of 0 to 78, a higher score indicates better ADL function) [30], and correlation between APOE genotypes and AEs.

Statistical analysis

Safety analysis was conducted on the safety set (SS, patients who received at least one dose of donepezil 10 mg/day and had at least one safety evaluation). Efficacy analysis was conducted on the per protocol analysis set (PPS, patients who completed the study with no major protocol violations) with last observation carried forward (LOCF) as well as the full analysis set (FAS, all enrolled patients

were included) LOCF. In addition, in order to test the robustness and accuracy of our results, efficacy analysis was further conducted on the PPS and FAS wherein missing data was not filled in and not included and thus only actual data of every patient who took the efficacy test was included (FAS [actual number] and PPS [actual number], respectively).

For the safety analysis, overall incidence of AEs and SAEs, incidence of AEs and SAEs by organ systems, severity, and AEs' relationship to donepezil were calculated and/or assessed by calculating the number of patients having AEs and SAEs, the prevalence of AEs and SAEs, and their 95% confidence intervals (95% CI). Laboratory abnormalities such as changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and changes in EKG and ECG such as HR, QT, and QTc were summarized and described using means, standard deviation (SD), median, maximal, minimal, 25th and 75th percentile values, and further analyzed with paired *t*-test. Correlations of AEs and various risk factors were first assessed with univariate logistic regression analysis, and variables included patients' medical history (history of neurological, cardiovascular, mental, liver, and gastrointestinal diseases), age (grouped into $\leq$75 and >75 years), gender, body weight ($\leq$55 kg and >55 kg), *APOE* genotype ($\varepsilon2/\varepsilon2$, $\varepsilon3/\varepsilon3$, $\varepsilon4/\varepsilon4$, $\varepsilon2/\varepsilon3$, $\varepsilon2/\varepsilon4$, and $\varepsilon3/\varepsilon4$), the presence or absence of *APOE* $\varepsilon4/\varepsilon4$, concomitant medications (cardiovascular and cerebrovascular, gastrointestinal, liver, neurological, mental, and hypoglycemic medications), and duration of donepezil 5 mg/day treatment prior to the study (days). Forward stepwise multivariate logistic regression analysis was subsequently performed to further assess correlations between various risk factors and incidence of AEs using variables chosen from those used in the univariate analysis (SLSTAY = 0.3, a significance value of 0.3 was required for a variable to stay in the multivariate model).

MMSE and ADCS-ADL were assessed at each visit. Their changes at each visit from baseline were calculated. Factors affecting MMSE and ADCS-ADL changes were assessed with a mixed model-repeated measures using an autoregressive covariance structure. Variables were the same as those used in the univariate analysis of correlations between AEs and various risk factors

All analyses were performed with SAS 9.4 (SAS Institute Inc.; Cary, NC, USA), data was analyzed with a two-tailed hypothesis, and a p value < 0.05 was considered to indicate statistical significance.

RESULTS

Demographics and baseline characteristics

A total of 241 participants were enrolled into the study, and their demographics and baseline characteristics were shown in Table 1. Prior to their enrollment into the study, these patients had been taking donepezil for a mean ($\pm$SD) of 70.97 $\pm$ 123.95 days. 115 of these patients had their APOE genotype analyzed by Sanger sequencing. Patient's allele distributions for APOE polymorphism were as follows: $\varepsilon2/\varepsilon2$ 1 (0.87%), $\varepsilon3/\varepsilon3$ 58 (50.43%), $\varepsilon4/\varepsilon4$ 7 (6.09%), $\varepsilon2/\varepsilon3$ 11 (9.57%), $\varepsilon2/\varepsilon4$ 1 (0.87%), and $\varepsilon3/\varepsilon4$ 37 (32.17%) (Table 1).

241 patients were included in the FAS and SS. 148 patients discontinued and 93 patients completed the study. The 93 patients who completed study also constituted the PPS. The most common reasons for discontinuation were withdrawal of consent with no given reason (27.80%) and AEs (17.43%). Patients' disposition during the study was shown in Fig. 1.

Overall safety

Overall, 93 out of the 241 (38.59%) patients experienced at least 1 AE and 156 AEs were recorded during the study. The most common AEs that occurred in >2% of the patients were diarrhea (13/241, 5.39%), nausea (8/241, 3.32%), vomiting (7/241, 2.90%), sleep disorders (6/241, 2.49%), dizziness (5/241, 2.07%), urinary tract infections (5/241, 2.07%), and muscle spasm (5/241, 2.07%). Most of the AEs were mild or moderate in severity (82.69% [129/156] mild, 14.74% [23/156] moderate, and 2.56% [4/156] severe). No syncope or fall was reported and no death occurred.

Among the 156 AEs, 52 AEs recorded from 33 (13.69%) of the 241 enrolled patients were considered related (certainly, very likely, or possible) to donepezil and there were no SAEs among these 52 AEs (80.77% [42/52] mild and 19.23% [10/52] moderate). Donepezil-related AEs that occurred in different body system were shown in Table 2. The most common donepezil-related AEs that occurred in >2% of the 241 patients were diarrhea (2.9%, [7/241]) and vomiting (2.07%, [5/241]). 36 (69.2%) of the 52 donepezil-related cases occurred during the first 4 weeks, and 16 (30.8%) occurred during the following 16 weeks. For the cases of donepezil-related cardiovascular AEs reported by 4 patients, none of these patients had been taking concomitant β-blocker(s),

Table 1
Patients demographics and baseline characteristics (FAS LOCF)

	$n = 241$, mean ± SD or n (%)
Gender	
Male	107 (44.4%)
Female	134 (55.6%)
Age	
<65	44 (18.26%)
65∼75	84 (34.85%)
75∼85	110 (45.64%)
>85	3 (1.24%)
Weight	
≤55 kg	97 (40.25%)
55∼65 kg	74 (30.71%)
65∼75 kg	47 (19.5%)
>75 kg	23 (9.54%)
Heart rate (beat/min)	72.35 ± 9.49
QTc (ms)	419.16 ± 29.9
ALT	18.09 ± 9.2
AST	23.16 ± 14.09
Past Medical history	
Cardiovascular diseases	39 (16.18%)
Neurologic disease	58 (24.07%)
Mental disease	10 (4.15%)
Liver disease	13 (5.39%)
Gastrointestinal diseases	17 (7.05%)
Other disease	46 (19.09%)
Concomitant drugs	
Cardiovascular drugs	22 (9.13%)
Central nervous system drugs	106 (43.98%)
Antipsychiatric drugs	18 (7.47%)
Hepatology drugs	1 (0.41%)
Gastrointestinal diseases drugs	5 (2.07%)
Other drugs	3 (1.24%)
MMSE	18.69 ± 4.35
ADCS-ADL	53.29 ± 11.55
HAMD	3.09 ± 2.56
Previous duration of donepezil 5 mg/d therapy(day)	70.97 ± 123.95
APOE genotype	N = 115
ε2/ ε2	1 (0.87%)
ε3/ ε3	58 (50.43%)
ε4/ ε4	7 (6.09%)
ε2/ ε3	11 (9.57%)
ε2/ ε4	1 (0.87%)
ε3/e4	37 (32.17%)

All values were expressed as mean ± SD or n (%). FAS, full analysis set, LOCF, last observation carried forward; SD, standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MMSE, Mini-Mental State Examination; ADCS-ADL, Alzheimer's disease cooperative study - activities of daily living; HAMD, Hamilton Depression Scale; *APOE*, apolipoprotein E.

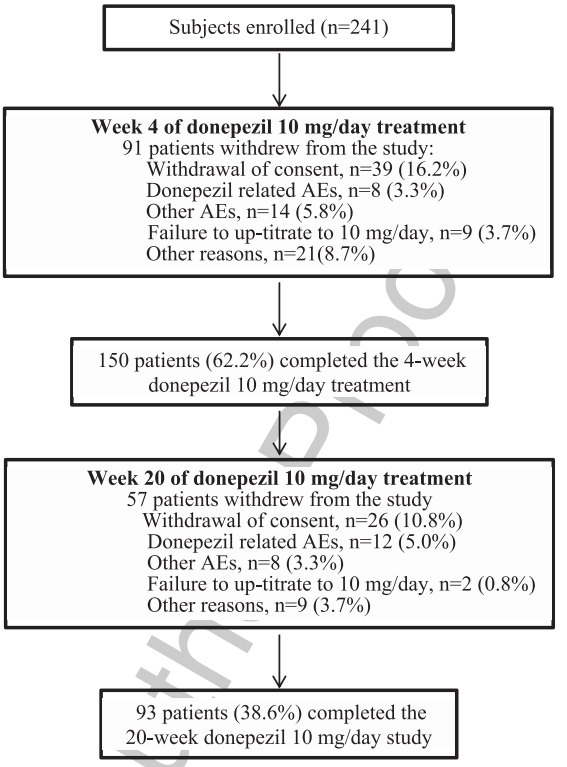

Fig. 1. Patient disposition during the study and study flowchart. AEs, adverse events.

although 2 patients had to be treated for bradycardia prior to their enrollment into the study. A total of 42 (17.43%) patients withdrew from the study due to AEs, among them, withdrawal rates due to donepezil-related AEs and other AEs were 3.3% (8/241) and 5.8% (14/241) at week 4, and 5.0% (12/241) and 3.3% (8/241) at week 20, respectively. Additionally, 49 (43.36%) out of the 113 patients >75 years of age and 44 (34.48%) out of 128 patients ≤75 years of age reported at least 1 AEs, respectively ($p = 0.1533$). Finally, 15 (38.46%) out of the 39 patients with cardiovascular diseases and 78 (38.61%]) out of the 202 patients without cardiovascular diseases reported at least 1 AEs, respectively ($p = 0.9857$).

Multivariate logistic regression analysis demonstrated that compared to non-users, use of concomitant medications for cardiovascular and cerebrovascular diseases was associated with an increased risk of AEs (Odd ratio [OR] 2.22, 95% confidence interval[CI] 1.039–4.748, $p = 0.0396$) (Table 3), although patients with cardiovascular diseases did not have increased risk of AEs (OR 0.94, 95% CI 0.491–2.010, $p = 0.9857$) according to univariate logistic regression analysis. There were 30 donepezil-related AEs reported by patients taking concomitant medications for cardiovascular and cerebrovascular diseases. Among these AEs, diarrhea (5 cases), dizziness (3 cases), and muscle spasm (3 cases) were most common. 80% of the 30 donepezil-related AEs were mild, and 20% were moderate in severity. On the other

Table 2
AEs and laboratory abnormalities considered certainly, very likely or possible related to donepezil (SS)

AEs	Cases N (%)	Severity (n)	
		Mild	Moderate
Cardiovascular system			
Angina pectoris	1 (0.41)		1
Bradycardia	2 (0.83)	1	1
Cardiac discomfort	1 (0.41)	1	
Gastrointestinal System			
Constipation	1 (0.41)	1	
Diarrhea	7 (2.9)	6	1
Gastritis	2 (0.83)	1	1
Nausea	4 (1.66)	4	
Vomiting	5 (2.07)	5	
Metabolic and nutritional system			
Decreased appetite	2 (0.83)	1	1
Musculoskeletal system			
Muscle spasm	3 (1.24)	3	
Nervous system			
Dizzy	3 (1.24)	3	
Somnolence	2 (0.83)	2	
Insomnia	2 (0.83)	1	1
Sleep disorder	2 (0.83)	2	
Hallucination	1 (0.41)	1	
Skin and subcutaneous tissue system			
Hyperhidrosis	3 (1.24)	2	1
Rash	1 (0.41)	1	
Vascular and lymphatic system			
Flushing	1 (0.41)		1
Laboratory examination			
Elevated ALT	1 (0.41)	1	
Elevated serum bilirubin	1 (0.41)	1	
Elevated serum creatinine	1 (0.41)	1	
Abnormal ECG	2 (0.83)	1	1
Heart rate reduction	4 (1.66)	2	2

AEs, adverse events; SS, safety set; ALT, alanine aminotransferase; ECG, electrocardiogram.

Table 3
Multivariate analysis of risk factors for AEs (SS)

Factors	OR	95% CI	*p*
Age (>75 y versus ≤75 y)	0.988	0.466, 2.095	0.9744
APOE ε4 (carrier versus non-carrier)	3.420	0.290, 40.354	0.3288
Concomitant medication			
Gastrointestinal drugs	2.107	0.158, 28.171	0.5732
Hypoglycemic drugs	0.976	0.281, 3.387	0.9694
Cardiovascular and cerebrovascular drugs	2.221	1.039, 4.748	0.0396
Hepatology drugs	2.056	0.151, 28.074	0.5889
Duration of previous donepezil 5 mg/d therapy (day)	1.004	0.999, 1.008	0.1181

AEs, adverse events; SS, safety set; OR, odd ratio; CI, confidence interval; *APOE*, Apolipoprotein E.

hand, age, the presence of *APOE* ε4 allele, concomitant medication for diseases other than cardiovascular and cerebrovascular diseases or duration of previous donepezil 5 mg/d therapy had no effect on risk of AEs.

ECG

There were small changes in HR, QT, and QTc when compared with the baseline during the 20-week study (Table 4). The HR changes from baseline were -1.08 ± 6.02 bpm ($p = 0.009$) at week 4 and -1.48 ± 7.18 bpm ($p = 0.0028$) at week 20. No significant QTc prolongation was found at the end of the study (-0.66 ± 19.66 ms, $p = 0.6561$), although it was statistically significantly shortened at week 4 (-3.91 ± 18.68 ms, $p = 0.0062$) (Table 4).

Out of the 241 patients, a total of 10 (4.15%) and 9 (3.73) patients had clinically significant HR decrease

Table 4
Patients' ECG parameters at baseline, week 4, and week 20 (SS)

	Baseline	Week 4	Change From baseline at week 4	Week 20	Change from baseline at week 20
HR, bpm	72.35 ± 9.49	71.32 ± 9.45	–1.08 ± 6.02**	70.66 ± 9.59	–1.48 ± 7.18**
QT, ms	395.26 ± 34.76	397.69 ± 36.71	2.36 ± 21.31	399.66 ± 36.12	4.47 ± 23.27*
QT_C, ms	419.16 ± 29.9	414.73 ± 29.76	–3.91 ± 18.68**	417.71 ± 27.88	–0.66 ± 19.66

All values were expressed as mean ± SD. SS, safety set; HR, heart rate; bpm: beat per minute; QT, QT interval; QTc: corrected QT interval by heart rate. *$p < 0.05$, **$p < 0.01$.

(defined as HR ≤50 bpm or 20% HR decrease from baseline) at weeks 4 and 20, respectively. A subgroup analysis further revealed that among the 218 patients with a baseline HR ≥60 bpm, 7 (3.21%) and 7 (3.21%) patients experienced clinically significant HR decrease at weeks 4 and 20, respectively; and that 3 (13.04%) and 2 (8.7%) patients among the 23 patients with a baseline HR ≤60 bpm (bradycardia) experienced clinically significant HR decrease at weeks 4 and 20, respectively. The difference between the two subgroups was not statistically significant at week 4 ($p = 0.0586$) nor at week 20 ($p = 0.2078$).

1 and 3 cases of clinically significant QTc prolongation (QTc extended to more than 500 ms or >60 ms prolongation from baseline) occurred at weeks 4 and 20, respectively. Among these 4 cases, 2 cases were from 1 patient, whose QTc was 505 ms at baseline, and this patient decided to withdraw from the study at visit 3 (week 20). Only 1 case of mild QTc prolongation from a patient with complete right bundle branch block (CRBB) at baseline was judged to be related to donepezil.

Other safety measures

Patients' arterial blood pressure of the patients remained unchanged at weeks 4 and 20 from baseline ($p > 0.05$). Additionally, no weight loss was reported, and patients' mean weight change from baseline was insignificant (–0.13 ± 2.78 kg and was –0.16 kg ± 2.54 kg at weeks 4 and 20, respectively, $p > 0.05$). Finally, patients' laboratory tests and physical examinations did not reveal any significantly changes.

Efficacy

MMSE change from baseline was shown in Table 5. Mean change from baseline at week 20 were 0.39 ± 2.64 (95% CI: 0.05, 0.72; $p = 0.0249$) in the FAS LOCF and 0.66 ± 2.74 (95% CI: 0.22, 1.11; $p = 0.0038$) in the PPS LOCF. Similar results were observed in the FAS (actual number) (mean change 0.97 ± 3.18 [95%CI: 0.32, 1.62, $p = 0.004$]) and PPS (actual number) (mean change 0.94 ± 3.18 [95%CI: 0.28, 1.59, $p = 0.0056$]) (Table 5). According to the mixed model-repeat measures analysis, age and the presence/absence of *APOE* ε4 had a statistically significant effect on MMSE change from baseline; while weight, gender, concomitant medications, and the duration of donepezil 5 mg/day therapy did not. Judging by their MMSE change, patients ≤75 years showed better treatment response to donepezil 10 mg/day compared to patients >75 years ($p = 0.0179$), and non-*APOE* ε4 carriers responded better to the treatment than *APOE* ε4 carriers ($p = 0.0008$) (Table 6).

As to ADCS-ADL, mean change of the ADCS-ADL total score from baseline at week 20 were 0.33 ± 7.47 in FAS LOCF and –0.12 ± 6.44 in PPS LOCF. There was no significant ADCS-ADL difference before and after treatment ($p > 0.05$). FAS (actual number) and PPS (actual number) produced similar results (Table 5).

DISCUSSION

In this first comprehensive safety study of donepezil 10 mg/day treatment in Chinese patients with mild-to-moderate AD, we found that donepezil 10 mg/day could be tolerated and was safe. 93 (38.59%) out of the 241 enrolled patients reported at least 1 AE (156 AEs, 2.56% of which were SAEs), and 56 of the 156 AEs reported by 33 (13.69%) patients were donepezil-related, none of which was SAE. Use of concomitant medications for cardiovascular and cerebrovascular diseases was associated with an increased risk of AEs. Although patients' HR decreases at week 4 and at the end of the study were statistically significant, their magnitudes were both very small, and mean QTc showed no significant change by the end of the 20-week study although there was statistically significant but very small QTc shortening at week 4. Other safety evaluations did

Table 5
Patients' MMSE and ADCS-ADL scores at baseline, week 4, and week 8 (FAS LOCF, FAS [actual data], PPS LOCF and PPS [actual data])

	Baseline			Week 4				Change from baseline at week 4				Week 20				Change from baseline at week 20			
	FAS LOCF	FAS (actual data)	PPS LOCF	PPS (actual data)	FAS LOCF	FAS (actual data)	PPS LOCF	PPS (actual data)	FAS LOCF	FAS (actual data)	PPS LOCF	PPS (actual data)	FAS LOCF	FAS (actual data)	PPS LOCF	PPS (actual data)	FAS LOCF	FAS (actual data)	PPS LOCF	PPS (actual data)
MMSE	18.69 ± 4.35	18.69 ± 4.35	18.45 ± 4.39	18.45 ± 4.39	19.12 ± 5.06	18.87 ± 5.76	19.22 ± 5.18	19.33 ± 5.53	0.44 ± 2.51**	0.72 ± 3.19**	0.77 ± 2.53**	1.01 ± 2.86**	19.07 ± 5.30	19.62 ± 5.8	19.11 ± 5.54	19.57 ± 5.81	0.39 ± 2.64*	0.97 ± 3.18**	0.66 ± 2.74**	0.94 ± 3.18**
ADCS-ADL	53.29 ± 11.55	54.76 ± 14.04	54.31 ± 10.63	53.31 ± 13.58	53.71 ± 12.97	53.31 ± 13.75	54.35 ± 12.50	32.71 ± 13.5	0.43 ± 7.34	–0.66 ± 6.04	0.04 ± 6.20*	–0.65 ± 6.69	53.62 ± 12.82	30.86 ± 11.01	54.19 ± 12.25	30.9 ± 11.07	0.33 ± 7.47	–1.15 ± 11.04	–0.12 ± 6.44	–1.13 ± 11.11

All values were presented as mean ± SD. FAS, full analysis set; LOCF, last observation carried forward; PPS, per protocol set; MMSE: Mini-mental State Examination. *$p < 0.05$; **$p < 0.01$ versus baseline.

not reveal any significant changes. Regarding efficacy of donepezil 10 mg/day treatment, the patients' MMSE showed significant improvement, although their ADCS-ADL did not change significantly by the end of the study. Judging from the MMSE improvement, patients ≤75 years had better treatment response to donepezil 10 mg/day compared to patients >75 years, and non-*APOE* ε4 carriers responded better to the treatment than *APOE* ε4 carriers.

As AD progresses, there is a decrease in the number of acetylcholinergic cells that leads to a weaker treatment response to AChEI therapy such as donepezil. It has been demonstrated that higher-dose donepezil could improve cognition in patients with diminished response to donepezil 5 mg/day treatment [7]. Additionally, numerous studies have reported that patients on donepezil 10 mg/day treatment showed greater cognitive improvement than patients on donepezil 5 mg/day treatment [9. 10, 12]. As increased efficacy associated with higher-dose donepezil has been proven, its safety and tolerability become important issues. AEs associated with donepezil, an AChEI, are mostly due to its well-known and well-documented cholinergic activity [12], Although donepezil acts selectively and preferentially on CNS, it could also increase cholinergic activity in peripheral nervous system [6]. The most common AEs experienced by our patients were gastrointestinal disturbance such as diarrhea, nausea, and vomiting, plus sleep disorders, dizziness, urinary tract infections, and muscle spasm. The overall AE profile reported by our study (Table 2) was consistent with known safety profile of donepezil 10 mg/day treatment in both Western and Chinese populations [4, 5, 9, 10, 19, 31]. In our study, 93 (38.59%) patients experienced at least 1 AE (total 156 AEs) and 33 (13.69%) patients encountered 52 donepezil-related AEs, most of which were mild or moderate. The prevalence of AEs experienced by our patients was certainly significantly lower than those reported by most Western studies, some of which showed that more than 80% of patients taking donepezil 10 mg/day reported at least 1 AE [12, 32, 33]. Even studies conducted on Chinese patients taking donepezil 10 mg/day produced inconsistent results, the prevalence of patients reporting at least 1 AEs ranged from 13.17% [18] to 71.8% [5]. Obviously, our results were more consistent with Jia et al. (43.4%) [4] and Yatabe et al. (Japanese population, 40.7%) [7], both of which concluded that donepezil 10 mg/day treatment was safe. The 17.4% AEs-caused withdrawal rate of our study was con-

Table 6
Mixed model-repeat measures analysis of factor affecting MMSE change from baseline (PPS)

Factors	Estimate	Standard error	*t*	*p*
Age (≤75 y versus >75 y)	1.2090 versus 0.0000	0.5084	2.38	0.0179
APOE ε4 (carrier versus non-carrier)	–2.0085 versus 0.0000	0.5954	–3.37	0.0008
Weight (≤55 kg versus >55 kg)	–0.7194 versus 0.0000	0.5803	–1.24	0.2157
Gender (male versus female)	0.9556 versus 0.0000	0.5437	1.76	0.0796
Concomitant medication (yes versus no)	1.0811 versus 0.0000	0.5791	1.87	0.0626
Duration of previous donepezil 5 mg/d therapy (day)	–	–	–	0.5886

MMSE, Mini-mental State Examination; PPS, per protocol set.

sistent with Burns et al. (18%) which also concluded that donepezil 10 mg/day treatment was well tolerated and safe [32]. Inter-study variability such as study design (presence of absence of a lead-in phase and the number of study sites), patients' age, severity of AD, and treatment duration could also contribute to the different results obtained by different studies [3].

Our multivariate logistic regression analysis demonstrated that compared to non-users, use of concomitant medications for cardiovascular and cerebrovascular diseases was associated with an increased risk of AEs; this was inconsistent with previous reports that taking concomitant medications such as beta-blockers, calcium-channel blockers, or digoxin was not associated with increased risk of bradycardia [34–36]. Curiously, consistent with Frölich et al. [37], our univariate logistic regression analysis indicated that patients with cardiovascular disease did not have increased risk of AEs compared to patients with cardiovascular diseases. Considering that comorbidities such as cardiovascular and cerebrovascular diseases and use of cardiovascular and cerebrovascular medications are more prevalent in older AD patients than younger patients [34], that AD patients took a larger number of medications than people without AD [38] and that risk of adverse drug interactions (a common cause of AEs in patients taking multiple types of medications) increased substantially with the number of medications taken by the patients [36, 39], whether use of concomitant medications for cardiovascular and cerebrovascular diseases was associated with an increased risk of AEs warrants further investigation.

Although our findings that 38.59% of our patients experienced at least 1 AE (most of which were mild or moderate) and that 17.43% of our patients withdrew from the study due to AEs were consistent with some previous studies, and all of these studies concluded that donepezil 10 mg/day treatment was safe [4, 7, 32], we still think that patients taking concomitant medications for cardiovascular and cerebrovascular diseases had an increased risk of AEs.

Our study further demonstrated that although donepezil 10 mg/day treatment led to statistically significant HR decrease, the magnitude of such decrease was small, and mean QTc and blood pressure did not change significantly by the end of the treatment. This was consistent with previous reports [14, 15, 40]. Additionally, the percentage of patients developing clinically significant HR decrease was low. As to individual cases of QTc prolongation, 4 cases of clinically significant QTc prolongation were reported from 3 patients, and only 1 was deemed to be related to donepezil treatment wherein the patient had CRBB. There have been case reports of QTc prolongation in patients taking donepezil [13, 40–42], and all of these patients had some type of cardiovascular diseases. Donepezil-related cardiovascular side effects are of particular interest due to abundant presence of cholinesterase in the heart, and donepezil's inhibition of cardiac cholinesterase could affect cardiac function [2, 6]. Prolonged QT could result in life-threatening ventricular arrhythmias such as torsade de pointes and ventricular fibrillation, and as the elderly population has an increased occurrence of cardiovascular diseases [2, 5, 43], QT prolongation is a condition that should be monitored, particularly in those patients who are female, elderly, had metabolic abnormality or pre-existing abnormal rhythm such as slow atrial fibrillation, sinoatrial or atrioventricular nodal disease, or on drugs such as β-blockers or non-dihydropyridine calcium antagonists, or on numerous concomitant medications [13, 41–44]. On the other hand, it has been proposed that donepezil could also have cardioprotective effect [44, 45]. It has been found that donepezil use was associated with a significant decrease in cardiovascular mortality in a retrospective cohort study and that AChEI therapy was associated with reduced risk of myocardial infarction and death in a nationwide cohort of subjects

with AD, and that such association became stronger with higher dose of AChEIs [44–46]. AChEIs have anti-inflammatory effects, as atherosclerosis is considered by many to be an inflammatory disease, such anti-inflammatory effects could potentially play some roles in its cardioproective effect [46], Additionally, AChEIs could reduce ambulatory HR without affecting blood pressure, and could therefore lead to a prolonged cardiac cycle [47]. A prolonged cardiac circle could enhance/maintain cardiac function by reducing myocardial consumption of oxygen and increasing ventricular filling volume and coronary flow [47]. Finally, donepezil could induce vagal nerve activation and reduce sympathetic nerve activation and therefore could possibly target cardiac autonomic imbalance, an important feature of chronic heart failure [48]. Of course, more studies are needed to verify these findings.

Besides the safety of donepezil 10 mg/day treatment, we also tested its efficacy in patients with mild-to-moderate AD using MMSE, the most common tool to evaluate cognition used by physicians in their daily practice to diagnose and treat patients with AD [1], and ADCS-ADL. Patients' MMSE improved significantly at weeks 4 and 20, this result was consistent with previous studies wherein patients took donepezil 10 mg/day [1, 4, 9, 26, 32, 45, 49]. On the other hand, patients' ADCS-ADL did not change significantly by the end of our 20-week study. This was also consistent with Cheng et al. (20-week donepezil 10 mg/day following 4-week 5 mg/day donepezil) [28] and Farlow et al. ($\geq$36-week 10 mg/day donepezil) [8]. Such lack of improvement of ADCS-ADL might possibly be due to limitation of this tool as suggested by Farlow et al. [8]. Consistent with previous reports [50, 51], we also found that younger patients ($\leq$75 years) showed better treatment response to the treatment versus older patients (>75 year). Our study also demonstrated that non-*APOE* ε4 carriers responded better to donepezil 10 mg/day than *APOE* ε4 carriers. Whether presence of the *APOE* ε4 allele, a key risk factor for AD, affected treatment response to donepezil or other AChEIs in general has been a controversial topic [11, 52–55]. Of course, more studies are needed to elucidate whether *APOE* ε4 allele has an effect on treatment response to AChEI therapy.

We acknowledge certain limitations in our study. First of all, only 93 out of the 241 enrolled patients completed the study; withdrawal of consent with no given reason was the main cause for such high dropout rate. During the study, many patients and/or their caregiver regretted their decisions to participate in the study as many of them felt that the study consumed too much time and effort, and decided to withdraw their consent, although it is also possible that some of them might have intuitively thought continuing the study was not worthwhile either due to vague feeling of unspecified discomfort or lack of obvious efficacy during early phase of the study. Still, such a high dropout rate was highly unusual for studies on donepezil 10 mg/day treatment regardless ethnicity of the patients [1, 4, 5, 7–11, 18, 19], so it is not a feature of donepezil 10 mg treatment. It could be argued that a high dropout rate might indicate that donepezil 10 mg/day treatment was not well tolerated or was not safe; however, since most of the patients who withdrew their consent did not complain of intolerability or discomfort when they withdrew from the study, the possibility that these patients simply could not tolerate donepezil at 10 mg/day or that the treatment was not safe was low. Such high dropout rate led to a small sample size which put the study's statistical power including the efficacy of donepezil 10 mg/day treatment in question. An argument could be made that patients who withdrew from the study were most likely those who responded poorly to the treatment. To address this concern and to test the robustness and accuracy of our results from the FAS LOCF and PPS LOCF, we also conducted an efficacy analysis on the PPS and FAS wherein missing data was not filled in and not included and thus only actual data of every patients who took the efficacy test was included (FAS [actual number] and PPS [actual number], respectively), and the results from FAS (actual number) and PPS (actual number) were consistent with FAS LOCF and PPS LOCF. In fact, the magnitudes of MMSE increases at weeks 4 and 20 from baseline for the FAS (actual number) and PPS (actual number) were numerically greater than the FAS LOCF and PPS LOCF, respectively (Table 5). The results from this less-biased approach suggested that despite the high dropout, these efficacy data represented a reasonable estimate of the overall effect size. Of course, such high dropout rate is still a major limitation and weakness of the study, and it also indicates the need for better training of doctors in their communication skills with the patients and/or their caregivers as good communications could potentially help patients stay in the study and reduce the dropout rate. Secondly, our study was a single arm study, and as such could not compare safety and tolerability of donepezil 10 mg/day versus 5 mg/day. Finally, our study was a 20-week study, therefore long-term safety

of donepezil 10 mg could not be determined from our study. Preparation for a long-term, randomized safety study with larger sample size is currently underway. On the other hand, the strength of our study is obvious; ours is the first comprehensive safety study of donepezil 10 mg/day treatment conducted in China and it proved that donepezil 10 mg/day can be tolerated and is also effective in Chinese patients with mild-to-moderate AD.

Conclusions

In conclusion, our study demonstrated that donepezil 10 mg/day treatment can be tolerated and is also effective in Chinese patients with mild-to-moderate AD, and thus can be used to treat these patients when their response to donepezil 5 mg/day treatment diminishes.

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