

# Donepezil plus memantine versus donepezil alone for treatment of concomitant Alzheimer's disease and chronic obstructive pulmonary disease: a retrospective observational study

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## Abstract

**Objective:** To assess the clinical outcomes of donepezil plus memantine (DM) and donepezil (DO) alone in Asian patients with a concomitant diagnosis of moderate-to-severe Alzheimer's disease and mild-to-moderate chronic obstructive pulmonary disease (AD-COPD).

**Methods:** We conducted a retrospective analysis of patients with AD-COPD who received either DM or DO for 6 months, or until the occurrence of unacceptable adverse events or disease progression, between June 2012 and May 2016. The primary endpoint was the score on the Standardized Mini-Mental State Examination (SMMSE). Secondary endpoints were scores on the caregiver-rated Bristol Activities of Daily Living Scale, Neuropsychiatric Inventory,

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Dementia Quality of Life (DEMQOL)-Proxy, and General Health Questionnaire 12.

**Results:** In total, 154 eligible patients received DM, whereas 156 received DO. Compared with patients who received DO, patients who received DM had significantly higher mean scores on the SMMSE by 2.1 points (95% confidence interval, 1.3–2.5). Significant between-group heterogeneity was not detected in outcomes over time. The benefits of treatment with DM were greater than those of treatment with DO, in terms of the primary endpoint. Significant differences were also detected in terms of secondary endpoints.

**Conclusion:** DM is more effective than DO alone for Asian patients with AD-COPD.

### Keywords

Donepezil, memantine, Alzheimer's disease, chronic obstructive pulmonary disease, response rate, Bristol Activities of Daily Living Scale, Standardized Mini-Mental State Examination, Neuropsychiatric Inventory, DEMQOL-Proxy, General Health Questionnaire 12

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### Introduction

Alzheimer's disease (AD) entails the accumulation of amyloid- $\beta_{1-42}$  (the major constituent of neuritic plaques) into oligomeric and fibrillar assemblies; thus, AD is characterized by debilitating memory impairment and considerable neural degeneration.<sup>1,2</sup> It affects approximately 30.6 million individuals worldwide, with a growing incidence in older people.<sup>3-6</sup> In China, the incidence is 1.5% to 3.5%, with an annual incidence of 5 to 9 per 1,000 inhabitants. Each year, 2.3 million new patients are diagnosed with AD, imposing a great burden on families, elevating the societal healthcare costs of the growing older population, and reducing the quality of life and survival of affected patients.<sup>7-11</sup>

Although its pharmacological mechanism has not yet been fully elucidated, donepezil (DO) is a cholinesterase inhibitor that is extensively metabolized by glucuronidation, CYP2D6, and CYP3A4; it yields four main metabolites and multiple minor metabolites, and has been widely applied in the management of AD.<sup>12,13</sup> Memantine (1-amino-3,5-dimethyladamantane) is an amantadine derivative that functions

as a voltage-dependent non-competitive (open-channel) antagonist for the glutamatergic N-methyl-D-aspartate receptor, thereby preventing pathogenic  $\text{Ca}^{2+}$  influx caused by stimulation with glutamate; it may have neuroprotective properties, may improve cognition, and may influence memory and learning.<sup>4,14</sup> Several studies regarding DO or memantine treatment for patients with AD have focused on patients who have mild-to-moderate disease.<sup>10,11,13</sup> However, the results of recent randomized, controlled trials involving patients with moderate-to-severe AD showed that DO treatment led to modest improvements in terms of cognition and physical function; notably, the finding that donepezil plus memantine (DM) was more effective than single-drug treatment with DO has not been replicated in European populations.<sup>3,15</sup>

Chronic obstructive pulmonary disease (COPD) is associated with an abnormal inflammatory response; its prevalence varies from 20% to 30% in patients with AD, increasing with AD severity.<sup>16,17</sup> In addition, concomitant COPD in patients with AD may reduce adherence to therapy, worsening patient outcomes.<sup>18,19</sup> Thus far, there is limited evidence to guide the

difficult treatment decisions for patients with concomitant COPD and AD.<sup>19</sup> Furthermore, it remains unclear whether DM is superior to DO with regard to efficacy and safety in Asian patients who have a concomitant diagnosis of moderate-to-severe AD and mild-to-moderate COPD (AD-COPD). The aim of this study was to assess the clinical outcomes of DM and DO in Asian patients with AD-COPD.

## Materials and methods

### *Study population and medical treatment*

This retrospective study was approved by the Medical Ethics Committees of the Third Affiliated Hospital of Southern Medical University, and an exemption from the requirement for informed patient consent was obtained from the Investigational Ethics Review Board. Patients who had been diagnosed with AD-COPD from June 2012 to May 2016 were included in the study. All included patients had received stable treatment with DO (Ratiopharm GmbH, Ulm, Germany; Anatomical Therapeutic Chemical Classification, N06DA02; drug specification, 10 mg) at a dose of 10 mg per day for at least 6 months plus memantine (PharOS Ltd., Metamorfossi Attikis, Greece; Anatomical Therapeutic Chemical Classification, N06DX01; drug specification, 10 mg) initiated at 10 mg per day for 1 month, followed by 20 mg per day for at least 5 months; alternatively, they had received single-drug treatment with DO. Baseline information was collected, including age, sex, smoking status, body mass index, residence status, and primary and secondary endpoints. The primary and secondary endpoints were measured at 1, 2, 3, 4, 5, 6, 9, and 12 months. Standard guidelines were used for all treatment cohorts. Analyses of AD were restricted to diagnoses made in our hospital's neurology clinics to maximize diagnostic specificity. Patients were included if they met the

following criteria: age 65 to 80 years and fulfillment of standardized clinical criteria for probable or possible moderate or severe AD;<sup>20,21</sup> a diagnosis of COPD, consistent with the Global Initiative for COPD guidelines and at least one International Classification of Disease, Ninth Revision code (i.e., codes 491, 492, 496) or at least one International Classification of Disease, Tenth Revision code (i.e., codes J41–J44); a forced expiratory volume in 1 second >50%; a diagnosis of AD within 3 months after the onset of stroke;<sup>10</sup> and the ability to cooperate with the examination and treatment. Patients were excluded if they met any of the following criteria: development of other types of dementia or cognitive dysfunction caused by other special factors; previous use of cholinesterase inhibitors or N-methyl-D-aspartate receptor antagonists; substantial coexisting neurological or psychiatric diseases; suicidal tendencies; premature treatment discontinuation; differential dropout; unhealed wounds or planned surgeries; imprecision regarding effect estimates; incomplete medical records; refusal to participate; dependence on alcohol or drugs; psychotropic substance abuse; concurrent tumor, epilepsy, and/or severe or unstable medical conditions; severe visual or hearing impairment; life expectancy <2 years; history of asthma, pulmonary resection, uncontrolled diabetes mellitus, or hypertension; COPD exacerbation; and/or enrollment in an ongoing randomized controlled trial. In addition to analyses of the therapeutic drugs, routine treatment options were offered for each of the patients in each cohort. No patient received any drug that could modify cognitive function or alertness during the follow-up period.

### *Outcome measures*

The primary endpoint was scores on the SMMSE (0–30, with higher scores indicative of better cognitive function)

throughout the study period.<sup>21</sup> The secondary endpoints were scores on the Bristol Activities of Daily Living Scale (BADLS; 0–60, with higher scores indicative of greater impairment),<sup>22</sup> the Neuropsychiatric Inventory (NPI; 0–144, with higher scores indicative of elevated behavioral and psychological symptoms),<sup>23</sup> the dementia quality of life (DEMQOL)-Proxy (31–134, with higher scores indicative of better patient health-related quality of life),<sup>24</sup> and the General Health Questionnaire 12 (GHQ-12; 0–12, with higher scores indicative of elevated psychological symptoms in non-professional caregivers), throughout the study period.<sup>25</sup> All evaluations were performed by the chief physicians in our hospital for all included patients.

### Statistical analysis

A sample size of 310 patients was determined to provide adequate power to compare the primary endpoint between groups. Descriptive statistics were used to summarize baseline characteristics. SMMSE and BADLS scores were obtained for a limited number of timepoints. The chi-squared test or Mann–Whitney U test was used to assess interactions of categorical variables between treatment effect and baseline characteristics. Logistic regression models were adjusted for age, sex, smoking status, body mass index, residence status, and other factors; these models were then used to determine associations between drug treatments (DM and DO) and AD-COPD. Student's t-test was used for analyses of continuous variables. All statistical analyses, including sample size calculations, were performed using SPSS Statistics, version 24.0 (IBM Corp., Armonk, NY, USA). Differences with  $p < 0.05$  were considered statistically significant.

## Results

### Patient characteristics

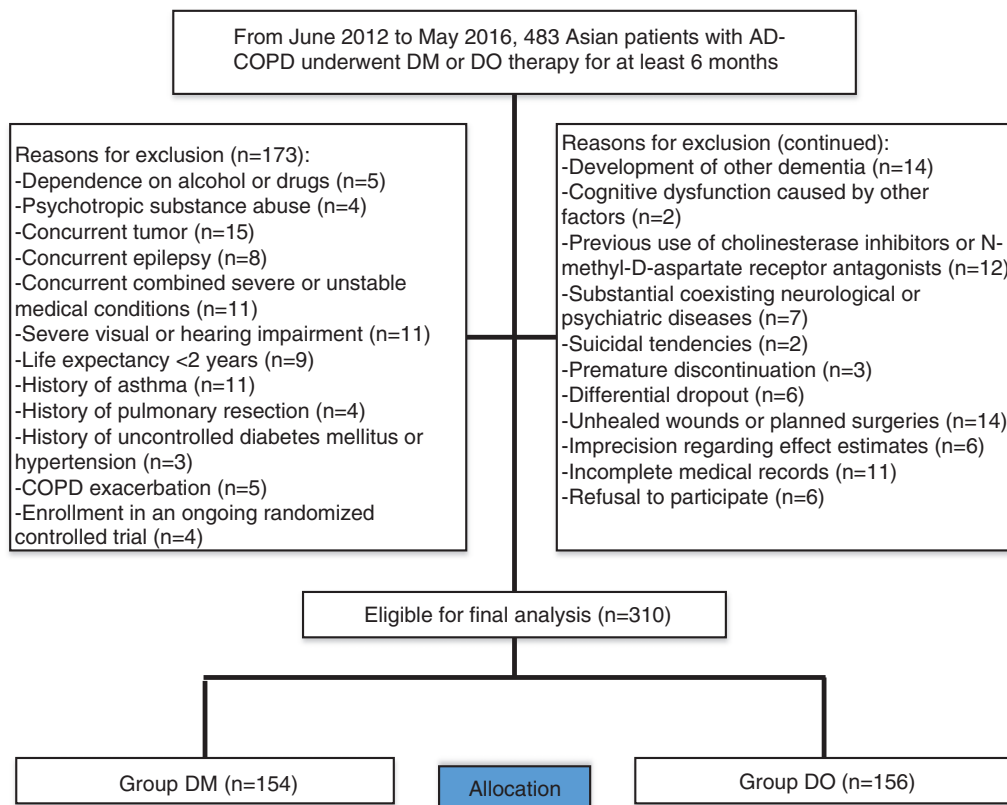
In total, 483 patients had been diagnosed with AD-COPD in the First Hospital of Hebei Medical University between June 2012 and May 2016. Of these, 173 patients were excluded because they met one or more exclusion criteria, resulting in 310 patients with AD-COPD (DM-treated cohort,  $n = 154$ ; DO-treated cohort,  $n = 156$ ) who eligible for inclusion in the study (Figure 1). The mean duration at the primary analysis date was 12 months (interquartile ratio, 11.2–14.5 months). The median patient age was 74 years. No significant differences were detected in baseline characteristics between groups, as shown in Table 1.

### Primary endpoint

The between-group differences in SMMSE scores are presented in Table 2 and Figure 2. Significant between-group heterogeneity was not detected in outcomes over time. The benefits of treatment with DM were greater than those of treatment with DO in terms of SMMSE score at final follow-up ( $15.4 \pm 4.6$  vs.  $13.3 \pm 5.2$ ;  $p = 0.015$ ). The effect of treatment with DM on the primary endpoint measures was appreciably influenced by the severity of AD.

### Secondary endpoints

Compared with the DO-treated cohort, the DM-treated cohort had a significantly lower mean score on the BADLS ( $18.3 \pm 8.5$  vs.  $19.7 \pm 9.6$ ;  $p = 0.027$ ). Additionally, the NPI score significantly differed between patients who received DM and those who received DO ( $18.6 \pm 8.7$  vs.  $21.1 \pm 11.3$ ;  $p = 0.011$ ), such that a greater treatment benefit was provided by DM. The DEMQOL-Proxy and GHQ-12 scores also



**Figure 1.** Flow diagram demonstrating the identification of Asian patients diagnosed with a concomitant diagnosis of moderate-to-severe Alzheimer's disease and mild-to-moderate chronic obstructive pulmonary disease (AD-COPD) from June 2012 to May 2016. This analysis was performed to assess the clinical outcomes of donepezil plus memantine (DM) and donepezil (DO) alone using scores on the Standardized Mini-Mental State Examination (SMMSE) as the primary endpoint and scores on the caregiver-rated Bristol Activities of Daily Living Scale (BADLS) as a secondary endpoint.

**Table 1.** Baseline patient characteristics between groups.

Variable	DM (n = 154)	DO (n = 156)	p-value
Age (years)	74.4 ± 9.4	74.5 ± 9.5	0.315 <sup>ns,a</sup>
Sex			0.842 <sup>ns,b</sup>
Female	49	48	
Male	105	108	
Smoking status (years)			0.641 <sup>ns,c</sup>
≤10	24	29	
11–20	36	34	
21–30	43	45	
31–40	32	28	
41–60	13	15	
>60	6	5	

(continued)

**Table 1.** Continued.

Variable	DM (n = 154)	DO (n = 156)	p-value
Body mass index (kg/m <sup>2</sup> )			0.538 <sup>ns,c</sup>
≤ 18.5	55	61	
> 18.5	99	95	
Residence status, No.			0.927 <sup>ns,c</sup>
With caregiver	25	26	
With a relative/friend	12	11	
Alone	54	50	
In assisted living facility	13	15	
In senior residence	26	23	
In skilled nursing facility	11	14	
In intermediate nursing facility	7	5	
Other	6	7	
SMMSE score <sup>#</sup>			
Mean	8.7 ± 2.1	8.8 ± 2.7	0.276 <sup>ns,a</sup>
Distribution, No.			0.748 <sup>ns,c</sup>
5–9, indicating severe AD	98	102	
10–13, indicating moderate AD	56	54	
BADLS score <sup>###</sup>	27.1 ± 9.2	27.4 ± 8.8	0.153 <sup>ns,a</sup>
NPI score <sup>####</sup>	23.4 ± 13.4	23.6 ± 14.2	0.341 <sup>ns,a</sup>
DEMQL-Proxy score <sup>\$</sup>	98.8 ± 12.3	99.1 ± 13.9	0.108 <sup>ns,a</sup>
GHQ-12 score <sup>\$\$</sup>	6.2 ± 2.7	6.1 ± 3.0	0.101 <sup>ns,a</sup>

<sup>ns</sup>Not statistically significant. <sup>a</sup>Analyzed by independent-samples t-test. <sup>b</sup>Analyzed by chi-squared test. <sup>c</sup>Analyzed by Mann–Whitney test. DM: Donepezil plus memantine; DO: donepezil; SMMSE: Standardized Mini-Mental State Examination; AD: Alzheimer's disease; BADLS: Bristol Activities of Daily Living Scale; NPI: Neuropsychiatric Inventory; GHQ-12: General Health Questionnaire 12.

<sup>#</sup>Range 5–13, with higher scores indicative of better cognitive function.

<sup>###</sup>Range 0–60, with higher scores indicative of greater functional impairment.

<sup>####</sup>Range 0–144, with lower scores indicative of better behavior.

<sup>\$</sup>Range 31–134, with higher scores indicative of better patient health-related quality of life.

<sup>\$\$</sup>Range 0–12, with higher scores indicative of elevated psychological symptoms in informal caregivers.

revealed significant treatment benefits for patients who received DM, compared with patients who received DO ( $p=0.014$  and  $p=0.036$ , respectively; Table 2, Figure 3).

### Adverse events

Adverse events included gastrointestinal discomfort (nausea, vomiting, diarrhea, and anorexia), hallucinations, confusion, dizziness, headache, and tiredness. Gastrointestinal adverse events occurred in 33 of 154 patients (21.4%) receiving DM, compared with 19 of 156 (12.2%) patients receiving DO ( $p=0.029$ ). No serious adverse events were noted. There was no

evidence that the incidence of adverse events differed between groups, with respect to baseline data. No significant differences were detected in terms of psychiatric events, metabolic/nutritional events, nervous system events, general events, cardiovascular events, or skin events. Detailed information regarding adverse events is presented in Table 3.

### Discussion

The present study showed that treatment with DM significantly improved cognitive function scores and exhibited a favorable

**Table 2.** Estimate of treatment differences in coprimary and secondary outcome measures at final follow-up.

Variable	DM (n=154)	DO (n=156)	p-value
SMMSE score <sup>#</sup>	15.4 ± 4.6	13.3 ± 5.2	0.015 <sup>*,a</sup>
BADLS score <sup>###</sup>	18.3 ± 8.5	19.7 ± 9.6	0.027 <sup>*,a</sup>
NPI score <sup>####</sup>	18.6 ± 8.7	21.1 ± 11.3	0.011 <sup>*,a</sup>
DEMQOL-Proxy score <sup>§</sup>	112.7 ± 11.4	104.8 ± 10.6	0.014 <sup>*,a</sup>
GHQ-12 score <sup>§§</sup>	3.6 ± 2.1	4.3 ± 2.5	0.036 <sup>*,a</sup>

\*Statistically significant. <sup>a</sup>Analyzed by independent-samples t-test. DM: Donepezil plus memantine; DO: Donepezil; SMMSE: Standardized Mini-Mental State Examination; BADLS: Bristol Activities of Daily Living Scale; NPI: Neuropsychiatric Inventory; GHQ-12: General Health Questionnaire 12.

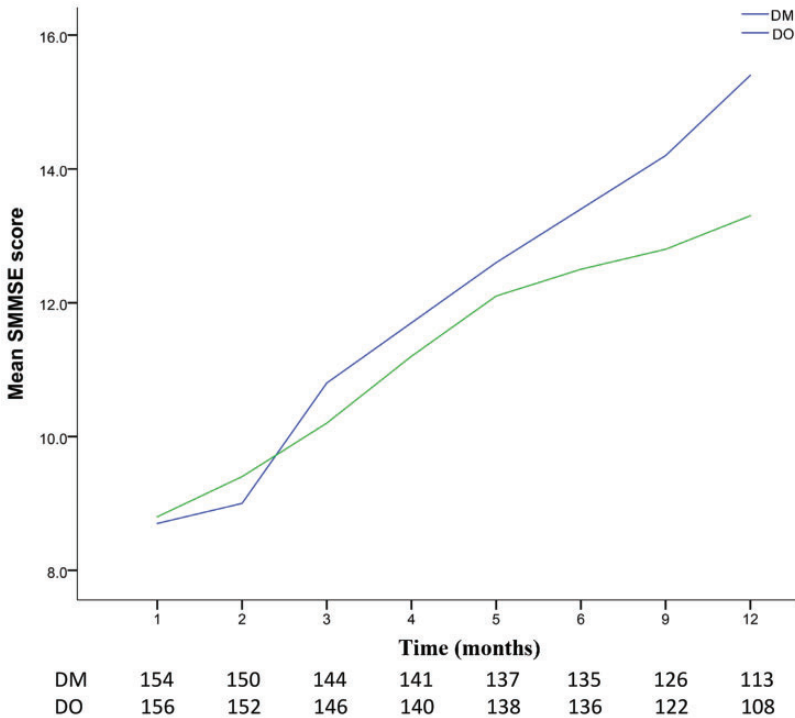
<sup>#</sup>Range 5–13, with higher scores indicative of better cognitive function.

<sup>###</sup>Range 0–60, with higher scores indicative of greater functional impairment.

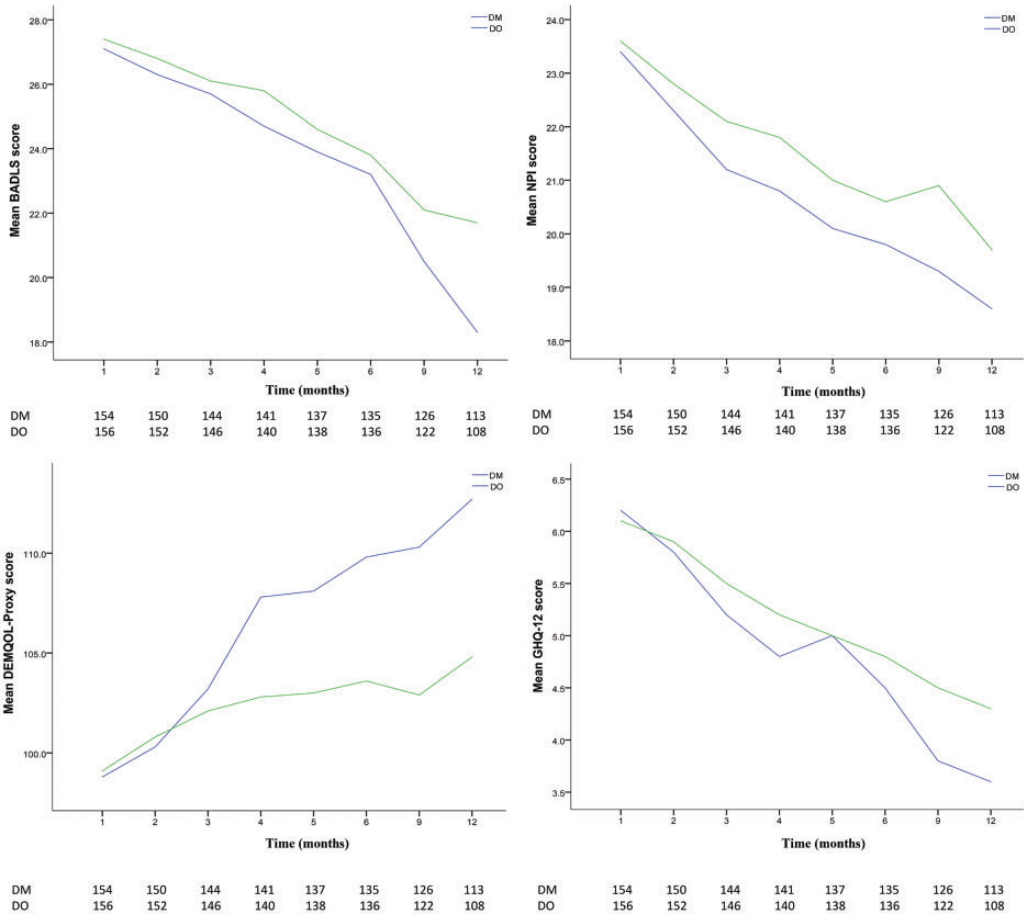
<sup>####</sup>Range 0–144, with lower scores indicative of a better behavior.

<sup>§</sup>Range 31–134, with higher scores indicative of better patient health-related quality of life.

<sup>§§</sup>Range 0–12, with higher scores indicative of elevated psychological symptoms in informal caregivers.



**Figure 2.** Mean scores on the Standardized Mini-Mental State Examination (SMMSE) range from 8 to 16, with higher scores indicative of better cognitive function.



**Figure 3.** Mean Scores on the Bristol Activities of Daily Living Scale (BADLS), Neuropsychiatric Inventory (NPI), DEMQOL-Proxy score, and General Health Questionnaire 12 (GHQ-12). BADLS scores range from 0 to 60, with higher scores indicative of greater functional impairment; NPI scores range from 0 to 144, with lower scores indicative of better behavior; DEMQOL-Proxy scores range from 31 to 134, with higher scores indicative of better patient health-related quality of life; GHQ-12 scores range from 0 to 12, with higher scores indicative of elevated psychological symptoms in informal caregivers.

safety profile, compared with treatment with DO, in Asian patients with AD-COPD. Although the proportion of patients who discontinued drug treatment owing to adverse events was higher in the DM-treated cohort, most of these events were of acceptable severity. Early separation of the SMMSE and BADLS curves was consistent with the effect of DM, rather than confounding post-treatment factors. This finding suggested that the inhibitory effect

of DM on the progression of AD-COPD may persist beyond the treatment period.

Our findings are considerably important given the heterogeneous results among studies regarding the SMMSE in Asian patients with AD-COPD. There is a growing body of evidence suggesting that aging elicits a multifaceted disorder or impairment in cerebral microcirculation, which is important in the pathological evolution of age-related AD.<sup>26,27</sup> During long-term



**Table 3.** Major adverse events.

Variable	DM (n=154)	DO (n=156)	p-value
Patients with AEs	78	67	0.174 <sup>a</sup>
Gastrointestinal system events <sup>#</sup>			0.008 <sup>*,a</sup>
Diarrhea	22	5	
Vomiting	14	10	
Nausea	11	9	
Anorexia	5	12	
Psychiatric events			0.989 <sup>a</sup>
Insomnia	9	8	
Anxiety	8	7	
Nightmares	15	11	
Confused state	11	9	
Metabolic/nutritional events			0.973 <sup>a</sup>
Anorexia	15	11	
Weight reduction	21	17	
Appetite reduction	7	5	
Nervous system events			0.998 <sup>a</sup>
Dizziness	16	14	
Syncope	11	9	
Somnolence	12	11	
Aphasia	8	7	
General events			0.781 <sup>a</sup>
Trauma	12	10	
Asthenia	8	8	
Gait disturbance	7	4	
Cardiovascular events			0.846 <sup>a</sup>
Hypotension	12	11	
Hypertension	17	14	
Skin events			0.537 <sup>a</sup>
Peripheral edema	7	5	
Ecchymosis	5	6	

\*Statistically significant. <sup>a</sup>Analyzed by chi-squared test. <sup>#</sup>Patients affected (DM, n=33 versus DO, n=19, p=0.029). DM: Donepezil plus memantine; DO: Donepezil; AE: Adverse event.

follow-up in the present study, DM continued to maintain superiority in terms of the primary endpoint, and the between-group significant differences tended to increase over time. These findings are consistent with those of previous studies.<sup>28-30</sup> Although such combination drug interventions are recommended by most experts, there is currently no evidence from high-quality clinical trials that these interventions improve cognitive function outcomes in Asian patients with AD-COPD. Most patients receive a traditional regimen of

DO or memantine alone, rather than in combination;<sup>31</sup> nevertheless, the prognosis for these patients with AD-COPD is considered poor because of the limited efficacy of single-drug treatment.<sup>30,32</sup> Despite the growing number of single-drug options for treatment of patients with AD-COPD, limited improvement has been observed in terms of primary endpoints.<sup>16,17</sup> Historically, DO or memantine is regarded as the standard of care for patients with AD-COPD.<sup>16,19,33</sup> A prior study of patients with AD-COPD revealed that treatment with DM was

associated with a significant benefit in the primary endpoint, compared with treatment with DO.<sup>34</sup> Our findings are supported by those of previous studies involving Asian patients with AD-COPD who were not previously treated with DO or memantine; those results demonstrated the superiority of DM over DO in terms of SMMSE and BADLS scores.<sup>7,30</sup> A previous study by Graham et al.,<sup>34</sup> which randomly assigned patients to receive either DM or DO treatment, reported that DM was associated with a significant improvement in SMMSE and BADLS scores at 6 months, along with improved quality of life. Together with the findings by Grossberg et al.,<sup>6</sup> these results suggest that in previously untreated patients, treatment with DM provides substantial clinical benefits.

Safety analyses demonstrated that both DM and DO treatment regimens were well tolerated in an Asian population and had similar rates of adverse events.<sup>10</sup> DM, which has been assessed in previous clinical trials,<sup>10,29</sup> was validated as a treatment for AD-COPD. A multicenter randomized controlled trial demonstrated that the incidence of DM-related adverse events was 25%, which was comparable with the incidence of 18% observed for DO-related adverse events.<sup>11</sup> Historical data suggest that treatment with DM contributes to improvements in learning memory and overall brain function.<sup>10,34</sup> Although they are rare, reports of gastrointestinal adverse events in patients treated with DM suggest that this regimen can result in severe gastrointestinal adverse events with fatal outcomes.<sup>33,34</sup> Patients receiving DM should be monitored closely throughout the treatment period.

The study should be interpreted in light of several key limitations. First, because of the retrospective nature of study and the problems inherent in this methodology, patient- and institution-related confounders could not be avoided. Furthermore, all

potential confounding variables were not addressed in the present analyses. Second, these potential confounding variables (i.e., short duration of DM or DO treatment, poor recording of adverse events related to drug treatment, less stringent definitions of AD-COPD, limited assessment of behavior and quality-of-life outcomes, and limited direct comparisons of different protocols) may have weakened the ability of this study to yield reliable conclusions. Despite these limitations, this analysis revealed important long-term follow-up results.

In conclusion, we hypothesized that treatment with DM or DO could stabilize or slow declines in cognition and function, based on the results of prior studies. The present analysis revealed that, for Asian patients with AD-COPD, treatment with DM significantly improved cognitive function scores, compared with treatment with DO. Additional analyses (i.e., prospective multi-center studies) are needed to clarify the outcomes and safety of DM, relative to DO, and should further explore the inhibitory effects and underlying mechanisms of DM, as well as the appropriate administration dosage in patients with AD-COPD.

### **Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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