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Original Study

Combination Therapy Showed Limited Superiority Over Monotherapy for Alzheimer Disease: A Meta-analysis of 14 Randomized Trials

Kelvin K.F. Tsoi PhD [a,b], Joyce Y.C. Chan MPH [a], Nelson W.Y. Leung[a], Hoyee W. Hirai MSc [a,b], Samuel Y.S. Wong MD [a], Timothy C.Y. Kwok MD, PhD [c,*]

[a] Jockey Club School of Public Health and Primary Care, Hong Kong
[b] Stanley Ho Big Data Decision Analytics Research Centre, Hong Kong
[c] Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong

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Combination
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A B S T R A C T

Background: Acetylcholinesterase inhibitor (AChEI) and memantine are recognized drug treatments with limited clinical efficacy. Combination therapy for patients with Alzheimer disease (AD) was suggested, but the additional benefit of combination therapy is still controversial.
Aim: To evaluate the additional benefit of combination therapy over monotherapy with either AChEI or memantine.
Methods: Prospective randomized controlled trials were searched from the OVID databases. The trials were eligible if study subjects were diagnosed with AD, and were randomized to compare combination therapy with monotherapy. Any clinical assessment measured using validated scales on cognitive function, activities of daily living, behavioral problems, and global changes were the primary outcomes, and any reported adverse events were the secondary outcomes. Quality of studies and risk of bias were evaluated.
Results: Fourteen randomized trials were identified between 2004 and 2015 from the United States, Canada, Germany, Japan, China, and Korea. A total of 5019 patients with AD were randomly assigned to receive combination therapy of AChEI and memantine or monotherapy with AChEI or memantine. Combination therapy showed no significant benefit on cognitive function (mean difference [MD] of MMSE = 0.06, 95% CI −0.52 to 0.65), activities of daily living (MD of ADCS-ADL = −0.15, 95% CI −1.08 to 0.78), neuropsychiatric symptoms and behavioral problems (MD of NPI = −1.85, 95% CI −4.83 to 1.13), and global changes (MD of CIBIC-plus = 0.01, 95% CI −0.25 to 0.28). In subgroup analyses, combination therapy can improve cognitive function more than memantine alone; and it can significantly relieve neuropsychiatric symptoms and behavioral problems when concomitantly used with donepezil. No additional adverse event was reported in the combination therapy.
Conclusion: Combination therapy only showed the benefit on neuropsychiatric symptoms and behavioral problems in moderate-to-severe AD, but no other superiority in terms of cognitive function, activities of daily living, and global changes. Although reported adverse events were comparable, the additional cost for combination therapy may be unnecessary.

Alzheimer disease (AD) is the most common type of dementia that afflicts millions of the older age population worldwide. AD is characterized by deterioration in cognition and functional ability, and with behavioral and neuropsychiatric disturbances. The acetylcholinesterase inhibitors (AChEI), including donepezil, rivastigmine, and galantamine, have been approved by the US Food and Drug Administration (FDA) for the treatment of AD. Memantine targets the NMDAR (N-methyl-D-aspartate receptor) and is available for the treatment of moderate-to-severe AD, but the clinical evidence for treating mild AD is lacking.[1] Two clinical trials using memantine as an add-on therapy on stable doses of AChEI were conducted for the treatment of AD with conflicting results.[2,3]

The authors declare no conflicts of interest.

* Address correspondence to Timothy C.Y. Kwok, MD, PhD, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, 9/F, Shatin, Hong Kong.
E-mail address: tkwok@cuhk.edu.hk (T.C.Y. Kwok).

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Combining the use of memantine and AChEIs for the treatment of AD is still controversial. The National Institute for Clinical Excellence[4] did not recommend the combined use of memantine and AChEIs for AD due to the lack of evidence for added benefits when compared with monotherapy.[4] The German Institute for Quality and Efficiency in Healthcare concluded that there is no proof of benefit from memantine treatment for patients with AD, either as a monotherapy or in combination with other antidementia drugs.[5] However, the FDA approved the use of a fixed-dose combination of memantine hydrochloride extended-release and donepezil hydrochloride (ie, Namzaric) for moderate-to-severe AD in 2014.[6]

Several meta-analyses have been conducted to make definitive conclusion on the effectiveness of combination therapy,[7–9] although these studies were usually lacked a completed literature search, and misinterpretation of measurement scale.[10] The findings of these meta-analyses were inconclusive. As combination therapy can be a potential treatment strategy to improve treatment efficacy for people with AD, we aimed to perform a meta-analysis with a comprehensive and updated literature search to address limitations from previous studies. We also compared the effectiveness of combination therapy with different types of monotherapy (memantine or AChEIs) among the elder patients with AD.

Method

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[11]

Search Strategy

Literature searches were performed in MEDLINE, EMBASE, AMED (Allied and Complementary Medicine), AJG Journal Club, and all EBM (Evidence-based Medicine) Reviews from the Cochrane Center from the earliest available dates stated in the individual databases to December 2015. Each medication, including memantine, donepezil, galantamine, and rivastigmine, was separately searched with general keywords including Cholinesterase inhibitor, Alzheimer, dementia, and trial. Randomized controlled trials that compared effectiveness between combination therapy and monotherapy for AD were manually identified after the title or abstract preview of all search records. As Google Scholar searches literature with a combined ranking algorithm on citation count and keyword relevancy, our literature search was also extended to Google Scholar. The selection was limited to peer-reviewed articles. Manual searches were extended to the bibliographies of review articles and included research studies.

Inclusion and Exclusion Criteria

Randomized controlled trials were included if they met the following inclusion criteria: (1) patients were diagnosed with AD, according to the National Institute of Neurologic and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria[12]; (2) compared the effectiveness of combination therapy of AChEIs and memantine with monotherapy of memantine, donepezil, galantamine or rivastigmine; (3) studies measured the change in scores of assessment scales from baseline to the study endpoints, or reported any adverse events. Studies were excluded if (1) study participants only had mild cognitive impairment; (2) study design was not randomized controlled trial; (3) full text of the study was not available in the databases; (4) study reported insufficient details to derive the study outcomes.

Study Outcomes

The primary outcomes of this study were the mean difference (MD) in scores of clinical assessment scales in 4 domains, including cognitive function, activities of daily living, neuropsychiatric symptoms and behavior, and global changes. In each domain, we selected the assessment scales that were most commonly mentioned in the included studies. Mini-mental state examination (MMSE),[13] Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL),[14] Neuropsychiatric Inventory (NPI),[15] and Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus)[16] were selected, respectively (Table 1). Sensitivity analyses were extended to other types of measuring scales in each domain to confirm the result consistency. The secondary outcomes were the reported adverse events.

Data Extraction

Two investigators (JYC, NWL) independently assessed the relevancy of search results, and abstracted the demographic details of individual studies into a data extraction form, including year of publication, study location, number of participants included, mean age, percentage of males, recruitment site, type of dementia, type and dosage of medication, treatment duration, and all clinical assessment scales. When discrepancies were found regarding inclusion of studies or data extraction, the third investigator (KKT) would make the definitive decision for study eligibility and data extraction.

Risk of Bias and Study Quality

Potential sources of bias were evaluated by Cochrane risk of bias,[17] which evaluates the adequate sequence generation, subject allocation and concealment, blinding of participants and outcome assessment, outcome data completely addressed, selective outcome reporting, and other bias. The quality of each eligible trial was also assessed according to the methodology section of CONSORT statement (Consolidated Standards of Reporting Trials).[18] An 8-point scale was designed for the evaluation of study quality, including (1) method of subject allocation, (2) randomization procedures with concealed allocation, (3) mechanism used to implement the random allocation sequence, such as computer-generated allocation, (4) eligibility criteria for subjects and settings for data collection, (5) interventions for each group with sufficient details, (6) prespecified primary and secondary outcome measures, (7) estimation of required sample size, and (8)

Table 1
Components of the Selected Outcome Measurement

Outcome Measurement	Score Range	Interpretation of High Score	Domains
MMSE*	0–30	Better cognitive function	Cognitive function (eg, Orientation, Memory, Language, and Visuospatial)
ADCS-ADL†	0–78	Better ability for daily living	Activities of daily living (eg, using household appliances, choosing clothes, bathing, and toileting)
NPI	0–144	More behavioral problems	Neuropsychiatric and behavioral symptoms (eg, delusions, hallucinations, dysphoria, and anxiety)
CIBIC-plus	1–7	Poorer in terms of overall status	Clinical impression of global changes (Cognition, Function, and Behavior), ranged from 1 (marked improvement) to 7 (marked worsening)

*Standardized MMSE was included.
†Two versions of ADCS-ADL with 19 or 23 items were included.

method of blinding appropriately described. Some of these quality parameters have also included in the risk of bias evaluation such as the adequate sequence generation, subject allocation and concealment, and blinding methods.

Data Synthesis and Statistical Analysis

MD with 95% confidence interval (95% CI) was used to evaluate the change of assessment scores between combination therapy and monotherapy. Risk difference with 95% CI was used to compare the adverse events. Meta-analyses were performed to combine the effect sizes with Review Manager (Version 5.3; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Statistical heterogeneity among the trials was assessed, and $P < .1$ was considered as statistical significance. Level of heterogeneity was assessed by I^2, which describes the percentage of total variation across studies due to heterogeneity rather than chance alone. We used a random-effects model for the trials with statistically significant heterogeneity; or otherwise, Mantel-Haenszel fixed-effects model was applied.[19] Forest plots were used to graphically present the combined results. Subgroup analyses were performed according to (1) type of medication in monotherapy, (2) dosage of memantine in combination therapy, (3) type of AChEIs used in combination therapy, (4) study duration, and (5) severity of AD. Sensitivity analyses were performed to include more studies with other types of measurement scales (eg, ADAS-cog or Severe Impairment Battery [SIB] for MMSE). Standardized mean difference (SMD) was used to confirm the result consistency. The secondary outcomes were the reported adverse events.

Results

Literature Search and Study Selection

A total of 4429 abstracts were identified from the databases and other 56 potential studies were further extracted from the bibliographies of review articles or Google Scholar. All titles and abstracts were screened. A total of 262 studies were relevant to evaluate effectiveness of dementia medication, but 248 of them were excluded for the following reasons: studies did not evaluate combination therapy (n = 211), studies did not randomize participants to the treatment groups (n = 18), studies were systematic reviews (n = 14), 1 study only included patients with mild cognitive impairment (MCI), 3 studies lacked adequate original data, and 1 randomized controlled trial did not randomize the use of memantine (Figure 1). The definitive analysis in this study included 14 randomized controlled trials published between 2004 and 2015 for individuals with AD from United States, Canada, Germany, Japan, China, and Korea.

Characteristics of Individual Trials

The 14 eligible trials consisted of 5019 patients with AD, and 42% of them were men (Table 2). Two studies included 2 groups of patients

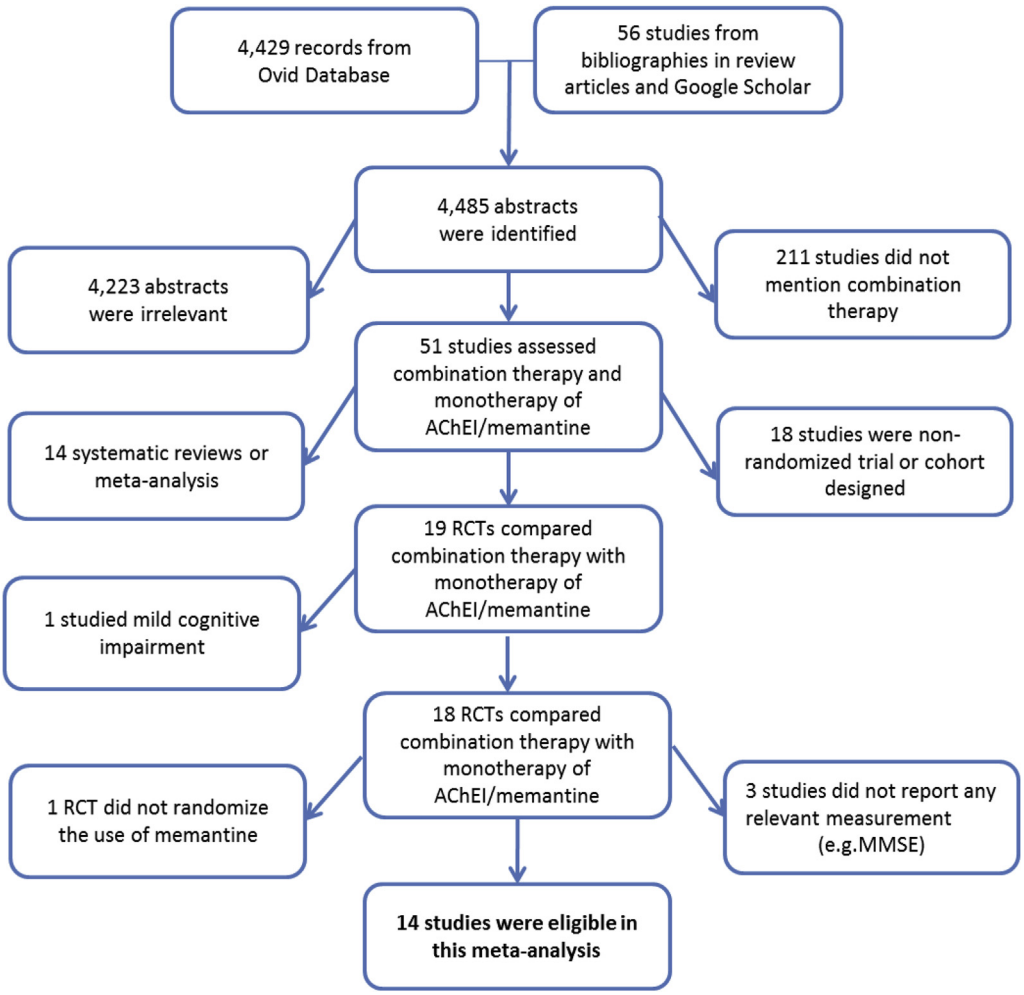

Fig. 1. Summary of the literature search.

Table 2
Characteristics of Randomized Controlled Trials Included in this Systematic Review

Study, Year	Country	Baseline MMSE	Sample Size	Male, %	Mean Age	Combination Therapy		Monotherapy		Duration of Treatment	Quality Scores (max = 8)
						Memantine Dosage/Day	Name of AChEI (Dosage/Day)	Name of Medication (Dosage/Day)	With Placebo		
Araki 2014	Japan	NA	37	58	78	20 mg	Donepezil (NA)	Donepezil (NA)	No	24 weeks	6
Choi 2011	Korea	16.9	171	21	75	20 mg	Rivastigmine Patch (9.2 mg)	Rivastigmine Patch (9.2 mg)	No	16 weeks	7
Doody 2012	US	11.9	1434	39	74	≤20 mg ≤20 mg	Donepezil (23 mg) Donepezil (10 mg)	Donepezil (23 mg) Donepezil (10 mg)	No No	24 weeks	5
Dysken 2014	US	20.8	282	97	79	20 mg	Donepezil/Rivastigmine/ Galantamine (NA)	Donepezil/Rivastigmine/ Galantamine (NA)	Yes	mean 2.3 yrs range 6 mo–4 y	5
Farlow 2010	US	16.9	261	42	77	NA	Rivastigmine patch (4.6 mg)	Rivastigmine patch (4.6 mg)	Yes	25 weeks	4
Feldman 2006	US	9.9	403	35	76	20 mg	Donepezil (5–10 mg)	Donepezil (5–10 mg)	Yes	24 weeks	4
Grossberg 2013	US	10.9	676	28	76	28 mg	Donepezil (8 mg)* or Rivastigmine (13.5 mg)* or Galantamine (6.8 mg)*	Donepezil (7.8 mg)* or Rivastigmine (13.5 mg)* or Galantamine (6.8 mg)*	Yes	24 weeks	8
Herrmann 2013	Canada	12	369	42	75	20 mg	Donepezil/Rivastigmine/ Galantamine (NA)	Donepezil/Rivastigmine/ Galantamine (NA)	Yes	24 weeks	7
Howard 2012	US	9.1	295	35	77	20 mg 20 mg	Donepezil (10 mg) Donepezil (10 mg)	Memantine (20 mg) Donepezil (10 mg)	No No	52 weeks	7
Peter 2015	Germany	22.2	135	64	72	20 mg	Galantamine (24 mg)	Galantamine (24 mg)	No	52 weeks	7
Porsteinsson 2008	US	16.7	433	48	75	20 mg	Donepezil (9.5 mg)* or Rivastigmine (9.2 mg)* or Galantamine (9.7 mg)*	Donepezil (9.5 mg)* or Rivastigmine (9.2 mg)* or Galantamine (9.7 mg)*	Yes	24 weeks	6
Shao 2015	China	15.3	88	48	73	20 mg	Donepezil (10 mg) or Rivastigmine (6 mg) or Galantamine (12 mg)	Memantine (20 mg)	Yes	24 weeks	4
Tariot 2004	US	9.9	403	35	76	20 mg	Donepezil (5–10 mg)	Donepezil (5–10 mg)	Yes	24 weeks	7
Zheng 2011	China	14.9	32	100	86	20 mg	Donepezil (10 mg)	Donepezil (10 mg)	No	16 weeks	4

NA, not available.
*Mean dosage.

for different types of monotherapy,[20,21] so a total of 16 patient cohorts were used in this analysis. The mean age of participants was from 72 to 86 years, and baseline average MMSE ranged from 9 to 21. Seven trials measured participants with moderate-to-severe AD, and 7 trials measured participants with mild-to-moderate AD. In combination therapy with memantine, donepezil was used in 7 trials.[2,20–25] Rivastigmine was used in 3 trials,[24,26,27] and galantamine was used in 2 trials.[24,28] In monotherapy, memantine was used in 2 trials; donepezil was used in 6 trials; rivastigmine was used in 2 trials and galantamine was used in 1 trial. However, 4 trials did not report the types of AChEIs.[3,29–31] Eight trials used placebo with monotherapy for treatment blinding. The durations of medication ranged from 16 to 52 weeks in general, and 1 study showed the average duration was up to 2.3 years.[29] The qualities of included trials were good; 7 (53.8%) trials were scored ≥6 of 8. Cochrane's risks of bias were assessed, and the overall risk of bias was low. Two open-labeled trials[26,27] induced high risk of bias due to unsuccessful blinding.

Comparison Between Combination Therapy and Monotherapy

Nine trials compared the change of cognitive function (MMSE) between combination therapy and monotherapy. Heterogeneity was significantly found across the studies, so the results were combined with a random-effect model and showed that cognitive function between combination therapy and monotherapy were comparable (MD = 0.06, 95% CI −0.52 to 0.65) (Figure 2a). Eleven trials compared the change of activities of daily living with ADCS-ADL. The results from a random-effect model showed no difference between combination therapy and monotherapy (MD = −0.15, 95% CI −1.08 to 0.78) (Figure 2b). Seven trials compared the change of neuropsychiatric symptoms and behavior with NPI. The combined result showed no statistically significant difference between combination therapy and monotherapy (MD = −1.85, 95% CI −4.83 to 1.31) (Figure 2c). Four trials compared global changes with CIBIC-plus. The combined result showed almost identical between both intervention groups (MD = 0.01, 95% CI −0.25 to 0.28) (Figure 2d).

Subgroup Analysis Across Different Outcomes

Analyses for different types of medication in monotherapy were demonstrated in the main results (Figure 2). Only 2 trials showed the MMSE of combination therapy not being statistically significantly better than monotherapy with memantine for cognitive improvement (MD = 0.54, 95% CI −0.19 to 1.28). In other subgroups, most trials used memantine at 20 mg or below in the combination therapy, and compared monotherapy for approximately 24 weeks. No significant benefit with combination therapy was observed (Table 3). Combination therapy showed no superiority over monotherapy in patients with mild-to-moderate AD, but it showed significant advantage in NPI (MD = −2.70, 95% CI −4.82 to −0.58) in patients with higher dose of memantine (28 mg). With different types of AChEI in monotherapy, combination therapy also showed significant reduction in NPI (MD = −6.01, 95% CI −10.9 to −1.12) than the monotherapy with donepezil.

Sensitivity Analysis With SMD

When the SMD was used to compare combination therapy with monotherapy, 3 more trials with SIB were included for cognitive evaluation. The conclusion remained unchanged and cognitive function between combination therapy and monotherapy were comparable (SMD = 0.05, 95% CI −0.07 to 0.18) (Appendix 1). Same conclusions were found in activities of daily living (SMD = −0.15, 95% CI −0.40 to 0.09), neuropsychiatric symptoms and behavior (SMD = −0.17, 95% CI −0.41 to 0.07), and global changes (SMD = 0.02, 95% CI −0.20 to 0.24).

Adverse Events

Eleven of 14 trials reported the number of adverse events, including fall, urinary tract infection, nausea, weight lost, dizziness, urinary incontinence, upper respiratory infection, diarrhea, influenza, agitation, anxiety, depression, vomiting, and state of confusion (Appendix 2). When the results on adverse events were combined by

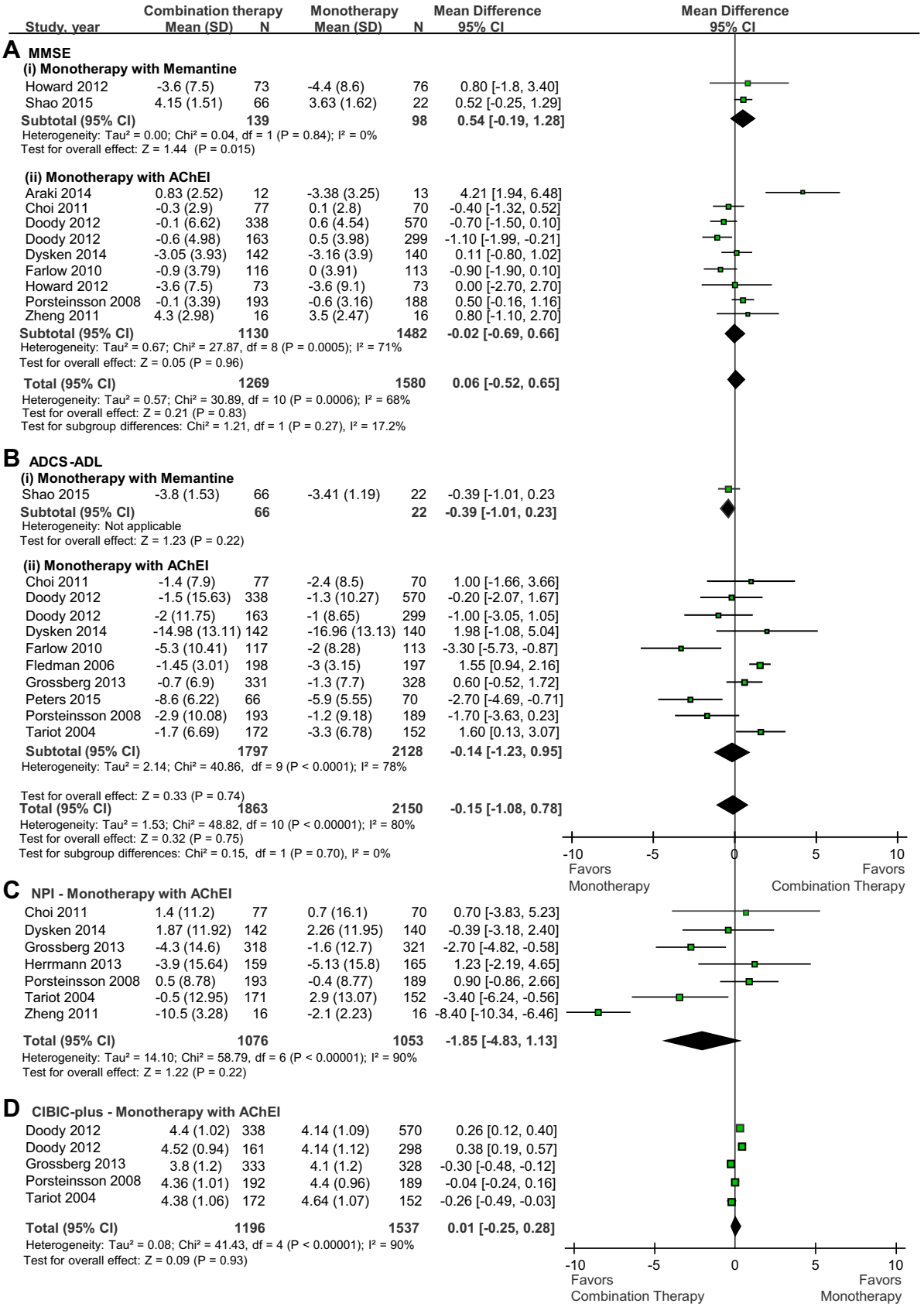

Fig. 2. Forest plots to compare combination therapy and monotherapy. MMSE, mini mental state examination; ADCS-ADL, Alzheimer's Disease Cooperative Study - activities of daily living; NPI, neuropsychiatric inventory; CIBIC-plus, clinical interview-based impression of change, plus carer interview.

Table 3
Subgroup Analyses Across the Study Outcomes

	MMSE		ADCS-ADL		NPI		CIBIC-plus	
	No. of Trials	MD [95% CI]	No. of Trials	MD [95% CI]	No. of Trials	MD [95% CI]	No. of Trials	MD [95% CI]
Type of medication in monotherapy								
Memantine	2	0.54 [−0.19 to 1.28]	1	−0.39 [−1.01 to 0.23]	0	NA	0	NA
AChEIs	9	−0.02 [−0.69 to 0.66]	10	0.17 [−0.85 to 1.18]	7	−1.85 [−4.83 to 1.13]	5	0.01 [−0.25 to 0.28]
Dosage of memantine in combination therapy								
≤20 mg	10	0.20 [−0.32 to 0.72]	9	0.02 [−1.01 to 1.05]	6	−1.67 [−5.32 to 1.98]	2	0.30 [0.19–0.42]
28 mg	0	NA	1	0.60 [−0.47 to 1.67]	1	**−2.70 [−4.82 to −0.58]**	1	**−0.30 [−0.48 to −0.12]**
Type of AChEI*								
Donepezil	7	−0.13 [−0.58 to 0.32]	5	0.45 [−0.66 to 1.57]	2	**−6.01 [−10.91 to −1.12]**	3	0.14 [−0.20 to 0.47]
Rivastigmine	3	−0.35 [−0.91 to 0.21]	3	−0.74 [−2.82 to 1.34]	1	0.70 [−3.83 to 5.23]	0	NA
Galantamine	3	0.73 [−0.15 to 1.61]	2	−1.50 [−3.39 to 0.38]	0	NA	0	NA
Study duration								
16 weeks	2	−0.10 [−1.12 to 0.92]	1	1.00 [−1.66 to 3.66]	2	−4.09 [−12.99 to 4.82]	0	NA
24–25 weeks	6	0.10 [−0.80 to 1.00]	8	−0.10 [−1.09 to 0.89]	4	−1.01 [−3.37 to 1.34]	5	0.01 [−0.25 to 0.28]
≥52 weeks	3	0.17 [−0.65 to 0.99]	2	−0.51 [−5.09 to 4.07]	1	−0.39 [−3.18 to 2.40]	0	NA
Severity of AD								
Mild to moderate	6	0.09 [−0.39 to 0.57]	6	−0.99 [−2.31 to 0.33]	4	−1.90 [−7.08 to 3.29]	1	−0.04 [−0.24 to 0.16]
Moderate to severe	5	0.37 [−1.11 to 1.85]	5	0.78 [−0.08 to 1.64]	3	−1.85 [−4.83 to 1.13]	4	0.02 [−0.31 to 0.36]
Overall	11	0.06 [−0.52 to 0.65]	11	−0.15 [−1.07 to 0.77]	7	−1.85 [−4.83 to 1.13]	5	0.01 [−0.25 to 0.28]

P values ≤ .05 are in boldface type; NA, not available.
*The type of AChEIs used in the following studies was not specified: Porsteinsson 2008, Grossberg 2013, Herrmann 2013, and Dysken 2014. Shao 2015 has been divided into 3 groups according to the type of AChEI used in MMSE and ADCS-ADL.

meta-analyses, no statistically significant difference between combination therapy and monotherapy was observed.

Discussion

This meta-analysis with comprehensive and updated literatures compared combination therapy with monotherapy in 5019 patients with AD. Combination therapy only showed the benefit on neuropsychiatric symptoms and behavioral problems in moderate-to-severe AD, but no other superiority in terms of cognitive function, activities of daily living, and global changes. When the patients with mild-to-moderate AD are included, the combination therapy showed no superiority over monotherapy in terms of cognitive function, activities of daily living, neuropsychiatric symptoms and behavior, and global changes. The occurrence of adverse events was comparable between combination therapy and monotherapy.

The major findings of this study are totally opposite to those of previous meta-analyses[7–9] (Table 4). In 2012, Muayqil and Camicioli[7] found that combination therapy has small but significant improvement in cognition, functional outcomes and the neuropsychiatric inventory than monotherapy. Unfortunately, this study misinterpreted the scale of CIBIC-plus.[10] Another systematic review by Farrimond and her colleagues[8] revealed a small benefit at 6 months of adding memantine to AChEIs on cognitive function for patients with moderate-to-serve AD, but no benefit on global function. Another more recent meta-analysis by Matsunaga and his colleagues[9] concluded that the effects of combination therapy were more effective than memantine alone for patients with moderate-to-severe AD. The results of previous studies are possible to be overestimated if their literature search was incomplete. When we compared the date of literature search in the previous meta-analyses with the date of existing literature in our study, we found that 2 open-labeled trials[23,27] were excluded in the study by Farrimond et al[8]; 5 articles[23,25–28] were missed in the study by Muayqil and Camicioli[7]; and 7 articles[20,22,23,25,27,28,31] were missed in the study by Matsunaga and colleagues.[9]

This study focused on only 1 instrument for each domain of cognitive function, activities of daily living, neuropsychiatric symptoms, and global changes. Although SMD is a method that combines the instrument with different scales, we believe that the interpretation of SMD is far more difficult than the MD, and it is possible that the instruments may have a certain levels of diagnostic variation.[32] Therefore, we only use MD to report an instrument that is the most frequently used in the domain. To ensure the validity of results, we also conducted the analyses with SMD and the conclusions remained the same.

Four trials fulfilled the inclusion criteria, but were finally excluded from the analysis (ie, 4 of 17 potential studies). Hager and his colleagues[33] conducted a study to investigate the efficacy of galantamine, with a subgroup analysis of concurrent prescription of memantine. As the use of memantine was not randomized and the original data could

Table 4
Comparison With Previous Meta-Analyses

Study Name	Farrimond	Muayqil*	Matsunaga	This Study
Literature search until	May 2011	May 2012	Oct 2014	Dec 2015
No. of included trials	3	3	7	14
No. of individuals included	1317	971	2182	5019
Results (95% CI)†				
Cognition	**−0.29 (−0.45 to −0.14)[1&2]**	**0.49 (0.38–0.64)[2&3]**	−0.13 (−0.26 to 0.01)[1]	0.11 (−0.40 to 0.61)[3]
Function	−0.04 (−0.21 to 0.13)[4]	**0.28 (0.16–0.47)[4]**	**−0.10 (−0.19 to −0.01)[4&5]**	−0.15 (−1.07 to 0.77)[4]
Behavior	**−0.17 (−0.32 to −0.03)[6]**	**4.18 (2.24–5.50)[6]**	**−0.13 (−0.24 to −0.02)[6]**	−1.85 (−4.83 to 1.13)[6]
Global changes	**−0.20 (−0.31 to −0.09)[7]**	NA	**−0.15 (−0.28 to −0.01)[7]**	0.01 (−0.25 to 0.28)[7]

Note: bold values are statistically significant ($P < .05$).
*Muaygil and Camicioli's study was combined from different levels of AD by meta-analysis, but the results were reported with some important errors.[7]
†Superscript numbers correspond to the following: 1. ADAS-Cog; 2. SIB; 3. MMSE; 4. ADCS-ADL; 5. BADLS; 6. NPI; 7. CIBIC-Plus.

not be extracted, this study was finally excluded. The results of another 2 studies were not supported with adequate details for analysis.[34,35] In addition, only an abstract was found to compare the effects of memantine among patients with moderate-to-severe AD who were receiving donepezil.[36] We attempted to search for the full text using the contact details of the corresponding author but received no response from the author.

This meta-analysis included only randomized controlled trials, which should have the minimal risk of selection bias, but there are still several limitations. First, different types of AChEIs were included in this study. Treatment variation may cause different effectiveness on combination therapy. Although subgroup analysis on the types of AChEIs was performed, the conclusions were still limited by small sample size. Second, we selected only the most frequently used instrument in the domains for cognitive function, activities of daily living, neuropsychiatric symptoms and behavior, and global changes. This was to avoid the problems associated with result interpretation across various instruments. However, there was still a certain degree of variation on the versions selected in each study (eg, ADCS-ADL with 19 items and ADCS-ADL with 23 items). The longer version covered more complex measurement for activities of daily living. Such variation was not adjusted in this study. Third, some studies included patients who had high baseline of MMSE (17 to 21). Treatment effectiveness may not have been detected in the patients with early AD. As the progression of cognitive decline was low, treatment for 6 months may also not show a significant impact on cognitive and physical deterioration. Finally, some unpublished studies might have been missed through the literature search. Publication bias could never be avoided.

The present medication for AD is unable to cure the disease. The use of AChEIs and/or memantine mainly targeted at symptoms associated with AD,[1] but taking medication to relieve the symptoms of AD is still controversial. In fact, other kinds of interventions, such as cognitive stimulation, are also shown to be effective in enhancing cognitive functioning of patients with AD.[37–39] Therefore, future studies can compare intervention with medication along different levels of AD patients.

In conclusion, combination therapy showed only the benefit on neuropsychiatric symptoms and behavioral problems, but no other superiority in terms of cognitive function, activities of daily living, and global changes, especially for those with mild-to-moderate AD are included. Although no additional adverse event was observed in combination therapy, the cost of treatment would be higher than that of monotherapy. Because AD is not curable with existing available medications, long-term treatment with combination therapy may cause a financial burden on the existing health care system, due to the aging population.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jamda.2016.05.015.

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