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Original Study

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

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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 = 0.11, 95% CI −0.40 to 0.61), activities of daily living (MD of ADCS-ADL = −0.15, 95% CI −1.07 to 0.77), 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 relief neuropsychiatric symptoms and behavioral problems among the subjects of moderate-to-severe AD. 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 moderate-to-severe AD with conflicting results.[2,3]

The authors declare no conflicts of interest.

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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.