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Review Article

Time to Treatment Initiation in People With Alzheimer Disease: A Meta-Analysis of Randomized Controlled Trials

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A B S T R A C T

Background: Alzheimer disease (AD) is a global health problem which afflicts millions of old age population worldwide. Acetylcholinesterase inhibitors and memantine are recognized drug treatments with limited clinical efficacy. It is uncertain if earlier initiation of these drugs will result in better outcomes in the longer term.

Aim: To evaluate the benefit of early treatment among people with AD.

Methods: Prospective randomized controlled trials were systematically searched from the OVID databases. The trials were eligible if study participants diagnosed with AD and were randomized to have early or late treatment. Any clinical assessment scales on cognitive function, physical function, behavioral problems, and the overall clinical status were the primary outcomes, and any reported adverse events were the secondary outcomes.

Results: Ten randomized trials were identified between 2000 and 2010. A total of 3092 participants with AD with mean age 75.8 years were randomly assigned to receive early treatment or treatment delayed by placebo intervention for around 6 months. Compared with late treatment, early AD drug treatment showed no significant benefit on cognitive function [mean difference (MD) of Alzheimer's Disease Assessment Scale- Cognitive Subscale = −0.49, 95% CI = −1.67 to 0.69], physical function (MD of Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory = 0.47, 95% CI = −1.44 to 2.39), behavioral problems (MD of Neuropsychiatric Inventory = −0.26, 95% CI = −2.70 to 2.18), and clinical status (MD of Clinician's Interview-Based Impression of Change plus Caregiver Input = 0.02, 95% CI = −0.23 to 0.27). Nausea was the most common adverse events in acetylcholinesterase inhibitor users, while memantine did not result in more side effects than the placebo group. For both drugs, early treatment had comparable adverse events when compared with late treatment.

Conclusions: Earlier AD drug treatment by around 6 months did not result in significant difference in cognitive function, physical function, behavioral problems, and clinical status. This study included relative high proportion of early AD with the follow-up less than 2 years. Future studies can be conducted to further investigate the long-term findings.

There is controversy about the rationale of early detection of dementia.[1] One of the potential benefits of early detection is early initiation of drug treatment for Alzheimer disease (AD), the major cause of dementia in old age. A recent updated systematic review of Food and Drug Administration-approved medications for the treatment of AD combined the results from 48 randomized, placebo-controlled trials of acetylcholinesterase inhibitors (AChEIs) and 10 trials of memantine.[2] AChEIs showed improvement in cognitive function in the short term, but the pooled reduction on the Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-Cog) was small. Memantine showed a similar benefit to that observed in AChEIs on cognitive function in people with moderate dementia. Although the cognitive improvement with AD drugs was small, they resulted in significant delay of the demand for nursing home placement.[3] On the other hand, the benefits of AD drug treatment should be

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balanced by side effects, particularly with AChEIs.[4–7] Some randomized controlled trials had shown comparable outcomes in participants with AD even when drug treatment was delayed.[8–25] However, these studies were limited by relatively small sample size and yielded conflicting results. On the basis of existing literature, we perform this systematic review and meta-analysis to evaluate the benefit or disadvantage of early initiation of treatment in people with dementia.

Methods

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 Cochrane Center to identify prospective randomized controlled trials that compared the time of starting AChEIs or memantine in participants with AD. Search was conducted with general keywords including dementia, acetylcholinesterase, AChEI, donepezil, galantamine, rivastigmine, memantine, and open-label, and was limited by randomized controlled trials. The trials were manually identified after the title and abstract preview of all search records. Studies, which randomly assigned participants with AD, to receive treatment or placebo before the treatment, were eligible for this systematic review. Participants, started with placebo and then treatment, were defined as the group with "late treatment," and those who received treatment along the follow-up period were defined as the group with "early treatment (Figure 1)." The selection was limited to peer-reviewed articles published in English abstracts before May 30, 2014 and from the earliest available dates stated in the individual databases. Manual searches were extended to the bibliographies of review articles and included studies. First or corresponding author was contacted if the study outcomes were not clearly reported.

Inclusion and Exclusion Criteria

All randomized trials were included if they met the following inclusion criteria: (1) participants were diagnosed with AD, according to the National Institute of Neurologic and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria,[26] the Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria,[27] a Mini-Mental State Examination (MMSE) score,[28] or the standard 11-item cognitive subscale of the ADAS)[29]; (2) same treatment was used along the follow-up period in both groups with early or late treatment; (3) placebo was used before the start of treatment in the group with late treatment; and (4) studies measured the change in assessment scales from baseline to the study endpoints, or reported any adverse events. Studies were excluded if they are (1) not a randomized controlled trial; (2) not English written in the full-text of manuscript; or (3) crossover study design with early stop of dementia treatment.

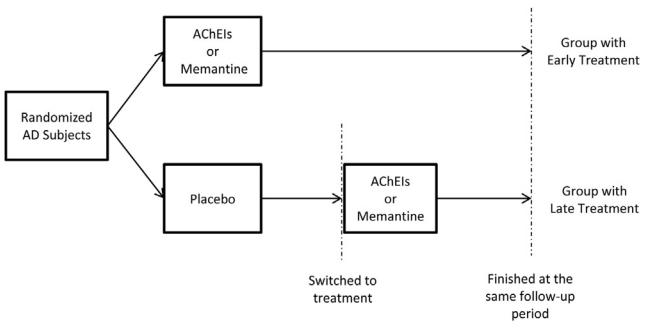

Fig. 1. Schematic diagram of the eligible study design in this systematic review.

Table 1
Clinical Assessment Scales in Different Domains for Dementia

Scale	Range of Scale	Interpretation
Cognitive function		
MMSE	0–30	Higher scores indicate better cognition
ADAS-Cog	0–70	Lower scores indicate better cognition
SIB	0–100	Higher scores indicate better cognition
Physical function (eg, using household appliances, choosing clothes, bathing, and toileting)		
ADCS-ADL	0–78	Higher scores indicate better function
Behavioral problems (eg, delusions, hallucinations, dysphoria, and anxiety)		
NPI	0–120	Higher scores indicate greater behavioral impairment
Overall clinical status on cognition, function, and behavior		
CIBIC-Plus	1–7	1 = very much improved, 4 = no change, 7 = very much worse

ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; CIBIC-Plus, Clinician's Interview-Based Impression of Change plus Caregiver Input; NPI, Neuropsychiatric Inventory.

Study Outcomes

The primary outcomes of this study were the change in clinical assessment scales in 4 domains, including cognitive function, physical function, behavioral problems, and the overall clinical status. For cognitive function, MMSE, the ADAS-Cog, or the Severe Impairment Battery (SIB)[30] was used. For physical function, the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory was used.[31] For behavioral problems, the Neuropsychiatric Inventory was used.[32] For clinical status, the Clinician's Interview-Based Impression of Change plus Caregiver Input was used.[33] The ranges and interpretation of each assessment scale were presented in Table 1. The secondary outcomes were the reported adverse events, including nausea, diarrhea, fall, vomiting, headache, respiratory infection, urinary infection, depression, agitation, dizziness, and insomnia.

Data Extraction

Two investigators (K.T., H.H.) independently assessed the relevancy of search results, and abstracted the data into a data extraction form. This form was used to record the demographic details of individual papers, including year of publication, study location, number of participants, mean age, type of dementia, MMSE at baseline, type of treatment used, and all clinical assessment scales. When discrepancies were found regarding inclusion of studies and data extraction, the third investigator (T.K.) would make the definitive decision for trial eligibility and data extraction.

Risk of Bias and Study Quality

Potential sources of bias were evaluated by Cochrane Risk of Bias,[34] which evaluates the adequate sequence generation, participant 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 the CONSORT statement (Consolidated Standards of Reporting Trials).[35] An 8-point scale was designed for the evaluation of study quality, including (1) method of participant 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 participants 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) method of blinding appropriately described.