Treatment effects of pharmacotherapy and non-pharmacotherapy of Alzheimer dementia: A systematic review overview and updated network meta-analysis.

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Protocol

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Abstract

Introduction: Many existing systematic reviews and meta-analyses summarize the evidence of pharmacotherapies (PTs) and non-pharmacotherapies (NPTs) for wide range of available interventions for the management of Alzheimer dementia (AD). However, a succinct summary and efficacy comparison across the different types of treatments and interventions is lacking. We aim to identify the treatment or treatments with the highest efficacy of current pharmacological and non-pharmacological treatments for AD.

Methods and analysis: Systematic reviews of randomized controlled trials (RCTs) will be selected according to the following criteria: conducted in elderly patients aged 60 years or older with AD, applied pairwise meta-analysis (PMA) or network meta-analysis (NMA) for pooled relative treatment effects for at least one pair of PTs and NPTs, and at least one of following outcomes was provided for patients/caregivers: cognitive function status, behavior, quality of life. The summary characteristics for each RCT will include the general design, participants, intervention, outcome measurements, duration of therapy and adverse events. The risk of bias will be assessed using Risk of Bias in Systematic Reviews (ROBIS) checklist and the risk of bias of individual RCTs will be assessed using the Revised Cochrane risk-of-bias tool.

Ethics and Dissemination: Ethical approval will not be required because this study is based solely on published literature that meets accepted ethical standards, and there will be no concerns about privacy. Dissemination of the evidence obtained will include publication in a peer-reviewed international journal to improve clinical practices on the basis of robust scientific evidence.

PROSPERO registration number: CRD42021228245

Article Summary

Strengths and Limitations

- This is an umbrella systematic review protocol to summarize the evidence for pharmacological and non-pharmacological treatments for Alzheimer dementia.
- The protocol has been developed according to the published PRISMA-P guidelines.
- We aim to identify the treatment or treatments with the highest efficacy of current pharmacological and non-pharmacological treatments for AD based on cognitive function status, behaviors, and quality of life for both patients and caregivers.
- The main limitation of this study is the limited sample size for non-pharmacotherapies (NPTs) and the substantial variation in characteristics of the interventions. The authors of the primary studies reported different conceptual frameworks for the interventions which could be broad with quite general descriptions.

Background

Dementia is an age-related neurodegenerative condition with increased prevalence in older populations. The World Health Organization (WHO) estimated there were more than 50 million people with dementia, with approximately 60 percent originating from low and middle-income countries[1]. Almost 600,000 individuals were reported with dementia in Thailand in 2015, a number anticipated to exceed one million by 2030[2]. The familial, societal and economic burdens associated with this condition is significant with a recent survey indicating 86% of dementia caregivers in Thailand were from an informal household source with the bulk of associated care costs characterized as indirect due to lost productivity of unpaid caregivers[2].

Multiple systematic reviews with pairwise meta-analysis (PMA) and network meta-analysis (NMA)[3–8], including several Cochrane Collaborations, have identified pharmacological treatments (PT) to maintain or reduce the rate of decline in cognitive function in older adults with early-stage dementia. Several reviews [5 8 9] have recommended the use of acetylcholinesterase inhibitors (AChEI) such as donepezil, rivastigmine, and galantamine, in addition to memantine, an uncompetitive antagonist of N-methyl-D-aspartate (NMDA) glutamate receptors, in moderate to severe dementia. In addition, herbal remedies have included huperzine A[10], ginkgo biloba leaf (EGb761)[11], and traditional Chinese medicines[12] that have demonstrated clinical benefits on cognitive function similar to AChEI. However, reported adverse effects and the high risk of contraindications associated with PTs[13], have led to increasing acceptance of non-pharmacological treatments (NPT) for limiting dementia progression. The most common NPTs include cognitive stimulation (CST), cognitive rehabilitation (CR), music therapy (MT), computerized cognitive training (CCT), and non-invasive brain stimulation (repetitive trans magnetic stimulation (rTMS)) have been associated with improved cognitive function and associated behaviors such as decreased agitation and depressed mood [14–19].

Currently, no disease-modifying treatment has proven fully effective in controlling the symptoms of Alzheimer's dementia (AD). Despite focused research efforts on the preclinical and early stage of AD, and the development of new disease-modifying treatments to reduce the pathophysiological changes associated with AD[20] (i.e. amyloid deposition, phosphorylation and protein aggregation), no significant clinical effect has been achieved, to date[21]. Caring for people with AD and dementia requires the involvement of a large number of healthcare professionals (eg. psychologists, occupational therapists, etc.) and caregivers to provide a comprehensive and individualized management plan. NPTs tend to be non-invasive, safe and with few side effects with an aim to maintain cognitive function for as long as possible as the disease progresses, thus reducing disability and improving patients and caregivers' quality of life.

Despite the increasing evidence of the benefits associated with PTs and NPTs, published comparisons between both have been limited. In addition, implementation of real-world evidence remains challenging given the financial and resource limitations in the majority of healthcare settings. As such, this study will

provide an overview and efficacy comparisons between individual PTs and NPTs for the treatment of AD characterized by cognitive function status, behaviors, and quality of life (QoL) for both patients and caregivers. A NMA will be applied to update and estimate treatment effects for all regimens, ranking each against the outcomes indicated. The findings from this umbrella review will provide a platform for future research design and cost effectiveness comparisons of pharmacological and non-pharmacological dementia treatments in real practice settings, where resources are limited.

Research question:

Do the effects of PTs and NPTs differ in the outcomes for Alzheimer dementia patients?

Patient and public involvement

No patients were involved in the design of this study. We will disseminate plain language summaries to relevant patient groups.

Objective

- To estimate and summarize relative treatment effects between individual PTs and NPTs
- To rank PT and NPT according to improved cognitive function status, behaviors, and QoL for patients and caregivers

Methods And Design

This overview study and NMA update will be conducted in accordance with PRISMA guidelines for network meta-analysis and the protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in February 2021 (registration number CRD42021228245)

Study selection process

Type of study

Systematic reviews of randomized controlled trials (RCTs) will be selected according to the following criteria:

- Conducted in elderly patients aged 60 years or older with AD
- Reported PMA or NMA for pooled relative treatment effects for at least one pair of PTs or NPTs
- Provided at least one of the following outcomes for patients/caregivers: cognitive function status, rate of falls, behavior, QoL.

Individual RCTs included in selected systematic reviews will be re-selected based on the following criteria:

- Undertaken in elderly patients aged 60 years or older with AD
- Compared relative treatment effect of at least one pair of PTs or NPTs
- Provided at least one of the following outcomes for patients/caregivers: cognitive function status, rate of falls, behavior, QoL.

The individual RCTs will be excluded where insufficient data is available for pooling following 2-3 attempts to contact the corresponding author.

Type of Participants

We will include any RCT that included elderly participants aged 60 years or older diagnosed as AD using their country's standard AD diagnostic criteria, e.g., Diagnostic and Statistical Manual of Mental Disorders (DSM) IV[22] or DSM-5[23] (American Psychiatric Association (APA)), the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association, and/or National Institute on Aging (NIA) and the Alzheimer's Association criteria[24], and/or the International Working Group, and neuropsychological tests to diagnose AD. We will use the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment/Clinical Dementia Rating Scale for additional screening.

Intervention

Interventions of interest include any comparison between individual NPTs and usual/standard care or PTs and placebo or head-to-head comparison between PTs and PTs:

9. NPTs

The most common NPTs include CST, CR, MT, CCT, and non-invasive brain stimulation (rTMS) and the following will be considered:

1. CST
2. CR
3. Reminiscence therapy (RMT)
4. CCT
5. Physical activity (PA)
    1. Aerobic only
    2. Non-aerobic
    3. Combination or multicomponent
    4. High intensity functional exercise

6. Functional-based analysis intervention (behavioral management)
7. Occupational therapy- fall prevention program
8. Care-giver interventions
9. Massage
10. Recreation therapy
11. MT
12. Aromatherapy
13. Psychological therapy
14. Social intervention
15. Multisensory stimulation (MSS or Snoezelen)
16. Light therapy
17. Art therapy
18. Therapeutic touch
19. Multicomponent therapy (SONAS)
20. Acupuncture
21. Non-invasive brain stimulation (rTMS, transcranial direct current stimulation (tDCS))
22. Animal assisted therapy (AAT)
23. Usual/ standard care
24. PTs
    1. Cognitive enhancer
        1. Cholinesterase inhibiter (ChEIs); donepezil, galantimine, rivastigmine
        2. NMDA receptor antagonists; memantine
        3. Herbs; Huperzia serrate, Gingo biloba extract (EGB 761) Yokukansan (TJ-54), Panax Ginseng, saffron (crocus sativus L.)
        4. Melatonin
25. Placebo

Outcome measure

The outcomes of interest include cognitive function, behavioral and psychological symptoms of dementia (BPSD), QoL, functional status and rate of falls. Cognitive function assessed in the original studies mainly using the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment-Scale Cognitive (ADAS-Cog), Montreal Cognitive Assessment (MoCA), Global Cognitive Functions (e.g., Clock drawing test), Clinical Global Impression of Change (CGIC), Clinician's Interview-Based Impression of Change (CIBIC), self or caregiver reported functions (caregiver input), Clinical Dementia Rating (CDR). The BPSD were evaluated by neuropsychiatric inventory (NPI), brief psychiatric rating scales and other

behavior assessment tools. QoL and functional status were measured by EQ5D, Barthel or modified Barthel index. Rate of falls was the number of reported falls. A fall was defined as “a person unintentionally coming to rest on the ground, floor or other level.” The secondary outcomes include caregiver burden and QoL measured by Zarit burden inventory scale (ZBI) and EQ5D, respectively.

Search strategy

Relevant systematic reviews and meta-analyses will be identified by a single reviewer (CB) from PubMed and Scopus from initiation to January 2021. The search terms and strategies are based on patients (P), interventions/ comparators (I/C), outcomes (O), and study design (S) as follows:

P: “Alzheimer dementia; I/C: donepezil, rivastigmine, galantamine, memantine, huperzine-A, EGb761, Yokukansan (TJ-54), “cognitive stimulation therapy”, “cognitive rehabilitation”, “music therapy”, “physical activity”, “non-invasive brain stimulation”, “non-pharmacological therapy”; O: cognitive, behaviors, function, “quality of life”; S: meta-analysis.

Searches will be updated every 3 months until December 2021.

Data extraction

Data will be extracted independently by two reviewers (CB and WT). Data for systematic reviews will be extracted including systematic review characteristics (pairwise or network meta-analysis), number of RCTs included, number of interventions/comparators, type of outcomes, methods used for pooling relative treatment effects (standardized/unstandardized mean difference (SMD/UMD) for continuous outcomes; ORs, RRs for dichotomous outcomes). The following data will be extracted from individual RCTs: patient characteristics (e.g., age, percentage female, body mass index, diabetes, hypertension, cardiovascular disease status etc.), intervention/comparator, type of outcomes and tool/scale used to determine outcome measures. In addition, data for pooling will be extracted including the number of patients, mean and standard deviation (SD) by intervention groups for continuous outcomes, contingency data of intervention and dichotomous outcomes.

Risk of bias and quality assessment

Risk of bias will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist [25] by two independent reviewers (CB and TA), disagreement will be resolved by a third reviewer (AT). Four domains will be considered including study eligibility criteria, methods used to identify and/or select studies, data collection and appraisal of studies, and synthesis/findings. The result will be graded as low or high risk of bias if there is sufficient information to assess, otherwise, it will be graded as unclear.

Risk of bias of individual RCTs will be assessed using the Revised Cochrane risk-of-bias tool for randomized trials considering the five domains of randomization, deviation from the intended intervention, missing outcome data, outcome measurements, and selection of the reported results. Each domain will be rated as low, some concerns, and high risk according to the risk-of-bias tool algorithm. The

RCT will be judged as high risk of bias if at least one domain is rated high risk; low risk of bias if all domains are rated as low risk; otherwise, the RCT will be judged as some concerns. Any disagreement will be resolved by consensus or judgment of a third reviewer (AT).

Data Synthesis

A two-stage NMA will be performed as follows: Relative treatment effects (e.g., SMD, UMD, ln ORs/ln RR) along with variance estimates for individual RCTs. Relative treatment effects will be pooled across RCTs using a consistency model and all possible relative treatment comparisons estimated. Consistency assumptions will be assessed using design-treatment interaction methods with a loop-specific approach to identify inconsistencies, where present. Patient characteristics associated with specific loops will be explored and treatment efficacy ranked for each outcome using surface under cumulative ranking curves (SUCRA). Adjusted funnel plots will assess publication bias.

We will perform subgroup analysis to explore source/s of heterogeneity and inconsistency, and will focus on factors including extreme elderly patients (age 85 years or older), stage of disease as defined by the functional assessment staging test (FAST) criteria[26], etc. In addition, a sensitivity analysis will be performed by excluding studies with high risk of bias, very old age, low/high effect size/variance (e.g., 25^{th} or 75^{th} percentile) to determine the robustness of the findings. All analyses will be performed using STATA 16.

Discussion

Currently, a comprehensive review of the comparison of pharmacological and non-pharmacological treatments to determine the most efficacious and cost-effective options for AD patients is lacking. Despite evidence supporting small to medium ranged benefits of pharmacological treatments, the majority of people with dementia have limited choice of therapies due to costs and associated intolerability of medications. In addition, non-pharmacological treatments require multidisciplinary specialized teams which are often limited in real world clinical settings. This umbrella review and network meta-analysis will fill the knowledge gap with findings to guide evidence-based decision-making in AD treatment strategies to support recommended AD management, not only for patients but also for family caregivers.

Declarations

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Competing of interest none declared

Ethics and dissemination

Ethical approval will not be required because this study is based solely on published literature that meets accepted ethical standards, and there will be no concerns regarding privacy. The evidence obtained will be disseminated through peer-reviewed publication to inform clinical practices with scientific evidence.

Author statement CB and AT are co-first authors and contributed equally to the protocol. GMK provided input on the design and drafting of the protocol. WT and TA are the co-corresponding authors. All authors read and approved the final protocol.

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