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Efficacy and Safety of Antidepressant Therapies for Alzheimer's Disease with Depression: A Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - International Medical University.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 June 2023 and was last updated on 17 June 2023.

INTRODUCTION

Review question / Objective 1. What are the therapeutic benefits of antidepressant interventions in Alzheimer's disease with depression? 2. What are the potential harms of antidepressant interventions in Alzheimer's disease with depression?.

Rationale Alzheimer disease is a progressive and debilitating disease which exhibit cognition and functional decline with neuropsychiatric disturbances or behavioral and psychological symptoms of dementia (BPSD). Neuropsychiatric disturbances such as depression, anxiety psychosis, agitation, aggression, disinhibition, and sleep disturbances exist in 90% of AD patients. Depression is one of the most common NPDs or BPSDs in AD. (1) It was estimated that 25% of AD patients have major depression as a neuropsychiatric consequence and in some studies, it is stated as 10%-60% of AD patients. For some patients, depression can be the first symptom before the diagnosis of AD and moreover, depression is found to be more common in mild-moderate than severe AD patients. In addition, depression is a major cause of disability in AD in activities of daily living (ADL).

Pharmacologic treatments used for treatment of depression in AD generally include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOIs), noradrenaline and serotonin reupdate inhibitors. Non-pharmacologic interventions also exist for treatment of depression which are known as behavioural interventions such as music therapy, art/music therapy, aromatherapy, animal-assisted/pet therapy, activity therapies, massage/touch therapies, and multisensory environment such as snoezelen.

Recent Cochrane review in 2018 which included 8 randomized controlled trials (RTCs) suggested that no difference was found between anti-depressants and placebo at 12 weeks of treatment. According to Dudas, small trials found positive results whereas larger and more recent trials were found to have negative results and as a result, there is little evidence of the efficacy of antidepressants for

treatment of depression in dementia. As a result of this emerged evidence, the most recent guidelines suggested that antidepressant should not be routinely offered as a first-line treatment for people with mild-moderate depression in dementia. In the RCT done by Benerjee, it was stated that this indifference in the results could be partly due to the heterogeneity of depression in people with dementia and suggested to investigate the antidepressant efficacy in subgroups of depression in dementia. Zhuo et al did a network meta-analysis of drugs for depression related to Parkinsonism.

The aim of this study is to answer the comparative effectiveness of multiple available interventions for the treatment of AD with depression by performing a network meta-analysis. Network meta-analysis can estimate the comparative effectiveness of interventions from direct comparisons as well as from indirect comparisons and hence this can allow the ranking of treatment. We believe that the current study will provide an updated information for the selection of pharmacotherapeutic intervention in management of AD with depression.

Condition being studied In general, depression is associated with adrenergic neuronal loss in locus coeruleus as well as loss of serotonergic nuclei in central nervous system. Anti-depressants in general act by regulating the relevant neurotransmitter systems in treatment of depression, for instance selective serotonin reuptake inhibition or monoamine oxidase enzyme inhibition.

Treatment of cognition for AD usually includes parasympathomimetic agents, NMDA antagonists, anti-amyloid, anti-tau agents. However, treatment of the neuropsychiatric disturbances including depression is also a major treatment of AD. Ineffective management of depression in AD can lead to other consequences such as aggression, exacerbation of cognitive and functional impairment, greater likelihood of being discharged from an assisted-living facility, earlier entry to nursing home, increased stress and depression in caregivers, greater care-giver burden, reduced quality of life and increased mortality or suicide. In general, 22%–47% of community-dwelling persons with dementia are prescribed with antidepressants agents.

METHODS

Search strategy An extensive electronic search of the multiple databases will be done to identify relevant studies available from inception to Dec 2022. To do so, appropriate MeSH terms with suitable Boolean operators will be used. The following is an example of study search using key words and Boolean operators in PubMed. ((((alzheimer[MeSH Terms])) OR (alzheimer disease[MeSH Terms])) AND (depression[MeSH Terms])) AND ((clinical trials, randomized[MeSH Terms]) OR (randomized controlled trial[MeSH Terms])).

Participant or population Alzheimer's disease with depression, any age, gender.

Intervention Anti-depressant treatment.

Comparator alternative anti-depressant treatment or placebo.

Study designs to be included randomized controlled trials.

Eligibility criteria Studies published in English language only will be included. Studies must report at least one outcome related to changes in depression scores.

Information sources We will search the following databases to identify relevant RCTs:

1. Ovid MEDLINE
2. EBSCOhost
3. The Cochrane Library (CENTRAL)
4. ScienceDirect
5. Scopus sources
6. PubMed

We will also search the following clinical trials registries:

1. ClinicalTrials.gov (http://www.clinicaltrials.gov/)
2. WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx)
3. EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/).

Main outcome(s) Studies must report the changes in the depression score using at least one of the outcomes:

a) Cornell scale for depression in dementia (CSDD score)
b) Hamilton depression rating scale (HRDS score)
c) Montgomery Asberg Depression Rating Scale
d) Geriatric Depression Scale
e) Psychogeriatric depression rating scale-activities of daily living subscale PGDRS-ADL.

Additional outcome(s) Any reported adverse effects or serious adverse effects.

Data management Two investigators will independently screen the titles/abstracts of

citations from the database search and retrieve full text of all potentially relevant articles. If studies have duplicated publications, maximum amount of data will be extracted from the available publications. Additionally, manual-search in the references of the relevant reviews/ included studies. The two investigators then independently check the full-text articles for eligibility based on the inclusion criteria. Any discrepancy will be solved with the third investigator.
After initial screening, piloted data extraction will be carried out by two investigators. The piloted data extraction sheet will contain the following information from each included study.
o Authors, country, publication year and the study participants' characteristics,
o Details of the intervention & control regimens (dosage, route of administration, frequency, duration)
o Study outcomes and method of outcome measurements
o Follow-up time points of the outcome(s)
o Any reported adverse effects.

Quality assessment / Risk of bias analysis The methodological quality of the studies will be assessed using the Cochrane risk of bias tool 1.0, described elsewhere. Methodological quality assessment will be carried out by the two independent investigators and any discrepancy will be solved by discussion with the third investigator.

Strategy of data synthesis The clinical trialists or the investigators will be contacted to verify the key characteristics and any missing data in the published trials whenever possible.
The efficacy of different therapeutic agents of antidepressant therapies will be compared by pairwise meta- analysis. Relative risk and 95% confidence level will be measured for dichotomous outcomes and mean difference, or standard mean difference will be measure for continuous outcomes. Heterogeneity will be assessed using the χ^2 test and the I^2 statistic. The I2 value of 25% will consider as low heterogeneity, 50% as the moderate heterogeneity, and more than 75% as a high heterogeneity. A two-tailed P value of less than 0.05 will be considered statistically significant. A funnel plot will be done to detect the publication bias.

Subgroup analysis Subgroup analysis will be done according to the duration of treatment, drugs, age, gender, disease severity, and/or comorbidities if data permits.

Sensitivity analysis Sensitivity analysis will be done either by excluding the studies with high risk of bias, high heterogeneity or by leave one out analysis method.

Language restriction English only.

Country(ies) involved Malaysia.

Keywords Alzheimer's Disease, depression, meta-analysis, network meta-analysis.

Contributions of each author
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