Original Article

Pharmacological treatment of neuropsychiatric symptoms of dementia: a network meta-analysis protocol

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Background: Neuropsychiatric symptoms (NPS) of dementia are a common issue in dementia patients which can lead to poor medical and functional outcomes. Pharmacological interventions are its treatment of choice. However, whether to use pharmacological treatments in this population and which drug should be preferred remain controversial. We therefore aimed to compare and rank pharmacological interventions for NPS according to their efficacy and acceptability profiles by quantifying information from randomized controlled trials (RCTs).

Methods: We will include all RCTs reported as double-blind and comparing one active drug with another or with placebo that compare cholinesterase inhibitors (ChEIs), N-methyl-D-aspartic acid (NMDA) receptor modulators, antipsychotics, antidepressants, and mood stabilisers. Studies will be retrieved by searching electronic databases, including Cochrane Central Register of Controlled Trials, PubMed, MEDLINE, Clinicaltrial.govs, EMBASE, and with no date or language restrictions. The primary outcomes were efficacy (change in overall symptoms) and acceptability (all-cause discontinuation). The network meta-analysis (NMA) will be conducted in R software within a Bayesian framework. The quality of evidence will be evaluated using the Cochrane risk of bias tool, and the GRADE approach. We will conduct subgroup analyses to assess the robustness of our findings.

Results: The results of this study will be published in a peer-reviewed journal.

Conclusions: This systematic review will synthesize the available evidence on the comparative efficacy of different pharmacological approaches in the management of overall NPS, agitation, psychosis, apathy and depressive symptoms in dementia patients. The results of the present NMA will influence evidence-based treatment decisions for clinicians.

Keywords: Dementia; pharmacological; neuropsychiatric symptoms (NPS); randomized controlled trial

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Introduction

In the 21st century, dementia is reckoned as the greatest global challenge for health. About 47 million people were living with dementia in 2015 (1), with Alzheimer disease (AD), dementia with Lewy bodies (DLB), and vascular dementia (VaD) in most cases. Dementia is a disease that include a variety of symptoms and signs, characterized by cognitive, neuropsychiatric, and functional symptoms. Neuropsychiatric symptoms (NPS) which are common and always can dominate disease presentation. It involves agitation, delusions, hallucinations, mood and sleep changes, anxiety, apathy, and wandering, occur in approximately 80% of patients with dementia (2). Although many different symptoms exist, NPS present as three main syndromes—agitation, psychosis, and mood disorders (3)—and these syndromes frequently co-exist (4). Symptoms have been shown to persist or recur over time which can cause significant distress to both patients and care givers.

Since the pathogenesis of NPS is quite complex, a "one size fits all" solution may not exist. The firmer understanding of the underlying etiology is required to develop rational therapeutic approaches for NPS. For example, there is evidence for alterations in monoaminergic, noradrenergic, gamma amino butyric acid (GABA) neurotransmission dysfunction in AD (5,6). A growing body of evidence shows agitation in dementia is related to cholinergic neurotransmission deficits and D2/D3 receptor availability in the striatum (4). Clinicians should differentiate these disparate symptom clusters which have different biological and psychosocial triggers since the appreciation of such complexity is vital to determine the appropriate treatment (7).

Management of NPS has relied on the use of both pharmacological and non-pharmacological therapies. Although non-pharmacological strategies, such as cognitive stimulation, psychological treatments, exercise and music, are recommend as the preferred first line treatment approach, pharmacological agents are widely used, especially when NPS are causing extreme distress or high risk to the patient and/or others. There are multiple classes of pharmacological agents in use for NPS, including antipsychotics, antidepressants, anticonvulsants, cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartic acid (NMDA) receptor modulators.

Many of the interventions for NPS have had recent meta-analyses confirming their efficacy. These include ChEIs (8,9), memantine (10-12), atypical antipsychotics (13), antidepressants (14), anticonvulsants (15), herbal medicine (16) and the various forms of non-pharmacological interventions. In 2018, a Cochrane systematic review evaluated the available evidence does not provide strong support for the efficacy of antidepressants for treating depression in dementia (14). However, antidepressants maybe useful to alleviate agitation in dementia (17). Globally, agitation and aggression are disturbing for individuals with dementia, and present a major management challenge for clinicians. Atypical antipsychotics as one of the most widely prescribed pharmacological treatments for these symptoms have a modest but significant beneficial effect in the short-term treatment of aggression. Nevertheless, results from randomized controlled trials (RCTs) on the efficacy and safety of these agents are conflicting (18).

Network meta-analysis (NMA) as a statistical method of synthesizing information from a network of trials relying on the combination of direct and indirect evidence gives a higher degree of precision in the estimation of efficacy and acceptability/tolerability of multiple drugs (19,20). One of the most attractive features of NMA is the ranking of interventions using rank probabilities, which in itself is highly relevant for treatment decision-making in clinical practice. Recently, a network meta of 146 RCTs comprising 44,873 patients with BPSD which also included nonpharmacological therapies concluded that pharmacological therapies, especially antipsychotics, showed the significant to modest efficacy (21). However, in majority of network meta-analyses focused only on the overall change in NPS or on the comparison of medications which came from only one drug class defined by the therapeutic use or the pathology they are intended to treat This is, to our knowledge, the first systematic review and NMA studying the effect of a diverse class of medications in different type of NPS, such as agitation, psychosis, apathy and depressive symptoms.

The objective of this systematic review and NMA is to answer important questions that will afford more and better options for clinicians and patients about evidence-based components to alleviate NPS. We therefore aimed to use this NMA method to assess which pharmacological therapies are most suitable to treat NPS in various domains of efficacy and safety.

Methods

Overview

The conduct of our systematic review will develop

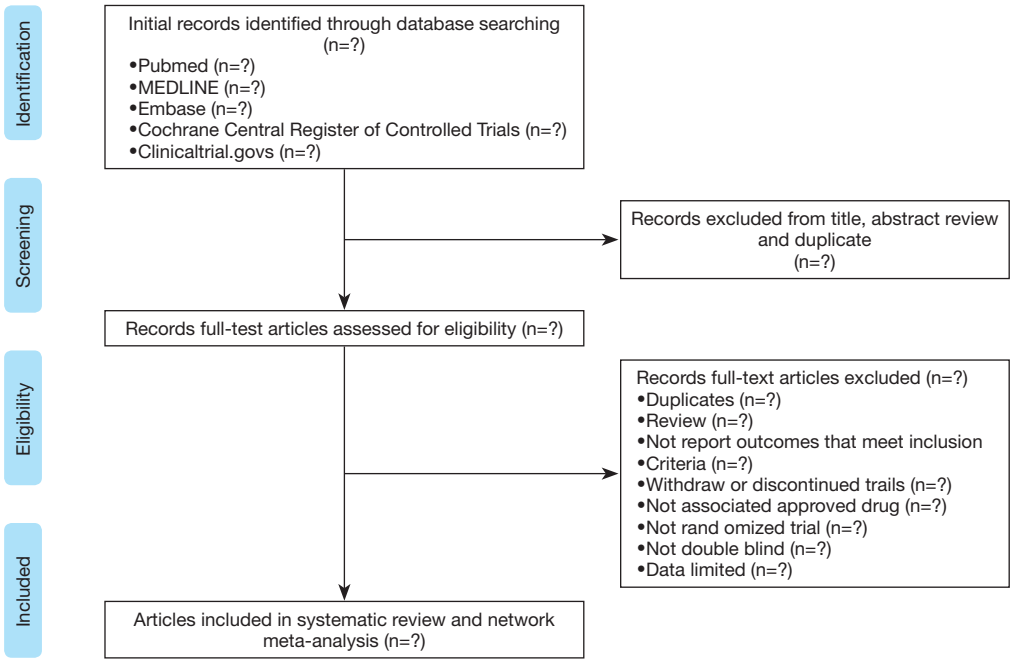

Figure 1 Proposed flow diagram to depict the search process.

according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) extension statement for reporting of systematic reviews incorporating NMA of healthcare interventions (22-24). This systematic review and NMA is registered (CRD42019132231) with the International Prospective Register of Systematic Reviews (PROSPERO).

Search strategy and study selection

Searches for published double blind RCTs will be undertaken in the following electronic databases: EMBASE, MEDLINE, PubMed, the Cochrane Central Register of Controlled Trials, with no language restriction. The initial search strategy for PubMed is shown in Supplementary. Based on the requirements of each database, the search strategy for other databases will be adapted. Grey literature source will be searched included study registries (e.g., ClinicalTrials.gov). Additionally, the reference lists of included studies and relevant reviews will be scanned.

All studies extracted from electronic databases will be imported into EndNote. Duplicate studies will be removed by using the 'Find Duplicates' tool in EndNote. We will obtain the full text of articles whose title and abstract appear to meet the inclusion criteria. Two authors will select studies independent of each other. If consensus cannot be reached by the first two authors after they review their selection, the third reviewer will participate in the discussion and make the decision. A flow diagram will be included in the study of which the proposed structure is shown in *Figure 1*.

Criteria for selecting studies for this review

Types of participants

Studies that include elderly people, both males and females, either inpatients or outpatients, who meet the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III, III-R, IV, V, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or clinical diagnosis criteria for a primary diagnosis of AD, DLB, Parkinsonism dementia (PDD), VaD, Mix AD. There will be no restriction on the severity or stage of the symptoms. We will exclude: trials with too short-term follow-up (less than 4 weeks), or with an overall sample size of less than 20 patients, or trials that recruited fewer than 10 participants per group.

Interventions

We will include studies with pharmacological interventions, including but not limited to: (I) ChEIs such as donepezil, galantamine and rivastigmine; (II) NMDAR antagonist:

memantine; (III) antidepressants such as citalopram, escitalopram, or trazodone; (IV) antipsychotics such as risperidone, aripiprazole, quetiapine, or olanzapine; (V) anticonvulsants such as carbamazepine, or valproate.

Only study arms randomising patients to drugs within the licensed dose will be included. Although meta-analytic methods considering the effect of drug dose would ideally be limited to fixed dose trials, we aware that some studies allow clinicians to decrease or increase doses based on side effects or clinical response in clinical practice. Consequently, both flexible-dose and fixed-dose designs will be allowed in this meta-analysis (25). Studies with non-pharmacological interventions, including psychological interventions such as cognitive behavioral therapy, problem-solving therapy, or psychodynamic therapy; and procedural interventions such as transcranial magnetic stimulation, transcranial direct-current stimulation or bright light therapy will be excluded.

Types of studies

We will only include double blind RCTs of any design (cluster, factorial, parallel, cross-over and stepped wedge), which aimed to demonstrate the superiority of a treatment to another and will not include equivalence trials. We will include both published and unpublished research. No language restrictions should be included. Narrative reviews, letters, editorials and studies without objective data to be evaluated will be excluded.

Types of outcome measures

Primary outcomes

We considered the mean overall change in overall NPS and all-cause discontinuation from baseline to endpoint for our primary analyses. To measure improvement in NPS, Neuropsychiatric Inventory (NPI), the Brief Psychiatric Rating Scale (BPRS), the Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) Rating Scale, or any other validated scale for the assessment of overall NPS symptomatology were used by the study investigators (17). When the outcomes had been measured with more than one rating scale, we used a predefined hierarchy, based on frequency of use in dementia, and consistency of use across included trials (see *Table 1* for the details about hierarchy of scales). All-cause discontinuation was used as a measure for the acceptability of treatments since it encompasses efficacy and tolerability.

Secondary outcomes

The secondary outcomes were discontinuation due to adverse events, adverse events and serious adverse events (study defined), as well as change in positive symptoms, negative symptoms, aggressive behavior, psychosis, apathy, and depressive symptoms, measured by means of published rating scales. We extracted outcome data as close to 12 weeks as possible for all analyses. The minimum duration of follow-up will be 4 weeks. Outcomes will be classified into short-term results (4–12 weeks), and long-term results (>12 weeks).

Data extraction

The following information will be collected from each included study: study citation, year of publication, diagnostic criteria, study design, sample size, length of follow-up, location, funding/sponsor (industry), intervention, treatment duration, study size. Characteristics of study participants, including gender distribution, mean and range of age, number randomized into each group and number of dropouts, screening tools/neuropsychological assessments/outcomes, mean (and SD) MMSE score at baseline, and severity of dementia at baseline. Characteristics of interventions including mean and maximum doses, formulation, route of administration, treatment duration. Outcome measures should be based on an intention-to-treat (ITT) as far as possible. To obtain the missing information, the research team will search for companion papers (by author searching and citation searching).

Risk of bias in individual studies

Study quality will be critically appraised using the Cochrane Collaboration 'risk of bias' tool, as a reference, by two reviewers (26). The following five domains will be considered: sequence generation, allocation concealment, blinding of study participants, blinding of personnel and outcomes assessors, selective outcome reporting, and other sources of bias. Overall bias will be summarized as "low risk", "high risk", or "unclear" risk of bias. Any disagreements will be resolved via discussion with another member of the review group.

Analysis

Assessment of heterogeneity and consistency

NMA allows the synthesis of direct and indirect estimates for the relative treatment effects for the same health condition and inherits all issues present in a standard pairwise meta-analysis that increased complexity which

Table 1 Hierarchy of scales

Outcome	Description
Change in overall symptoms	We extracted scales that measured overall symptoms of NPS with the following hierarchy: NPI total change, BEHAVE-AD total change, BPRS total change, and other published rating scale of overall symptoms of BPSD
Positive symptoms	We extracted scales or subscales that measured positive symptoms with the following hierarchy: BEHAVE-AD positive, BPRS positive change, CMAI change
Negative symptoms	We extracted scales or subscales that measured negative symptoms with the following hierarchy: BEHAVE-AD negative, BPRS negative change
Depressive symptoms	We extracted scales or subscales that measured negative symptoms with the following hierarchy: NPI depression change, BPRS depression and anxiety subscore change, then CDSS change, HAM-D change, MADRS
Apathy	We extracted scales or subscales that measured negative symptoms with the following hierarchy: NPI-apathy, AES
Aggressive behavior	We extracted scales or subscales that measured aggressive behavior with the following hierarchy: NPI-agitation, BEHAVE-AD aggressiveness, NBRS agitation score, CMAI
Psychosis	We extracted scales or subscales that measured psychosis symptoms with the following hierarchy: BPRS psychosis, BEHAVE-AD psychosis, NPI psychosis, NPI delusion
Adverse events	Number of patients who had adverse events
Serious adverse events	Number of patients who had serious adverse events according the authors' original definition
All-cause discontinuation	Number of patients who withdraw from individual arm before end of study for whatever reason. Zero dropouts would only be put if it was clearly stated that there had been no dropouts
Discontinuation due to adverse events	Number of participants who withdraw from individual arm before the end of a study due to adverse events

NPI, Neuropsychiatric Inventory; BEHAVE-AD, The Behavioral Pathology in Alzheimer's Disease Rating Scale; CMAI, Cohen-Mansfield Agitation Inventory; CDSS, Calgary Depression Scale for Schizophrenia; HAM-D, Hamilton Depression Rating Scale; AES, Apathy Evaluation Scale; BPRS, Brief Psychiatric Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; NBRS, Neurobehavioral Rating Scale.

may generate inconsistency in the model. To deal with these challenges, NMA adopts some assumptions that should be carefully considered: homogeneity, similarity and consistency.

The homogeneity assumptions also apply to pairwise meta-analyses (27-29) which is defined as there must be no relevant heterogeneity between comparable trials (30,31). Heterogeneity is variability in estimates within the same contrast which will be estimated in pairwise meta-analyses. To avoid the obvious sources of potential heterogeneity of effect we will investigate the distribution of clinical and methodological variables across treatment comparisons. Heterogeneity will be assessed statistically within each pairwise comparison using the I^2 statistic along a 95% CI.

The assumptions of heterogeneity and consistency underlie NMA which need to be carefully evaluated. The study population characteristics across all eligible trials, describing some important variables, such as patient characteristics, setting, sponsorship, and outcome definitions, will be generated. We will present the available evidence in the network diagram for each outcome. Furthermore, subgroup or network meta-regression will be conducted for the primary outcomes to explore whether treatment effects are robust (32).

If the comparable studies are differently designed, or direct and indirect estimates of an effect size are divergent, inconsistency will be raised (28). To check the consistency assumption we will use global inconsistency test and node splitting test in the inconsistency model (33,34). We will first assess the consistency assumption globally of which approaches consider the potential for inconsistency in the network as a whole. Then we will assess the consistency assumption locally by separating the direct from the indirect evidence for every comparison to assesses whether two

kinds of evidence on a specific node are in agreement. Both global and local assessments will be performed under the random-effects model using the R software, or Stata version 14.0. A two-sided P value of less than 0·05 was regarded as statistically significant.

Pairwise meta-analyses

The standardized mean difference (SMD) was calculated as the effect size for continuous outcomes. Dichotomous outcomes will be analyzed by calculating the OR. A random-effects meta-analysis will be conducted for all outcomes and comparisons to estimate each summary treatment effect and its 95% CI (35-37). The I^2 statistic will be used to assess heterogeneity in each pairwise meta-analysis as we mentioned before. In the presence of I^2 value greater than 50% in a particular intervention, will be considered as substantial heterogeneity. Subgrouping meta-analysis will be conducted for the primary outcome by the severity of dementia, or treatment duration, with or without NPS, and type of dementia.

Network meta-analyses

A Bayesian NMA with consistency model will be carried out to compare all interventions using direct and indirect data. In the Bayesian analysis, three Markov chains will be run simultaneously and each chain will have at least 50,000 simulations and at least the first 10,000 simulations will be discarded as burn-in. The trace plots will be used to test the convergence of the simulations. We will conduct a random effects NMA to synthesise all evidence for each outcome, and estimate the ranking probabilities for all interventions. To rank the various treatments for each outcome, the surface under the cumulative ranking curve (SUCRA) and the mean ranks will be used. Results of SUCRA will be graphically showed in the form of rankograms or league tables. Small-study effects will be assessed using comparison-adjusted funnel plots.

Subgroup analyses

To determine whether the results were affected by study characteristics, we performed subgroup network meta-analyses for primary outcomes according to the following variables: treatment duration, severity of dementia, and sample size. If necessary, we will conduct meta-regression analyses to determine whether study-level covariates will be considered as significant moderators. Due to the different biological characteristics of different types of dementias, subgroup analysis will be done to test the effects of study drugs on AD, VaD, DLB or PDD.

Assessment of quality of evidence

The quality of evidence contributing to network estimates of the main outcomes will be assessed (41). We will perform quality assessment on the basis of study limitations, imprecision, inconsistency and indirectness and using the GRADE approach to assessing the certainty of the evidence. Evidence obtained from each well-designed RCT is at high quality and, because of residual confounding, evidence will be downgraded according to the assessments of these domains (39).

Results

The results of this study will be published in a peer-reviewed journal.

Discussion

To date, there have been a variety of pharmaceuticals used for the treatment of NPS. And there are a great lot of systematic reviews comparing effectiveness of pairs of interventions in patients with NPS. However, these systematic reviews focus only on direct pairwise comparisons. We hope that we can integrate direct and indirect evidence about the effectiveness of pharmaceuticals for NPS and provide new and informative evaluations of present competing therapies. An important strength of this systematic review is that we have planned to focus our review upon separate symptoms of different important aspects of NPS which typically under diverse etiology.

Our previous work that combined evidence from 32 trials, with change in NPI, overall symptoms, as the primary outcome, indicated a benefit in NPS for AD patients from ChEIs and atypical antipsychotics (40). We also made a NMA of which result did not show a significant improvement in NPS among ChEIs and memantine for AD (41). Based on the previous work, this systematic review and NMA will summarize the existing evidence to compare pharmacological strategies for the treatment of NPS in terms of efficacy and safety. To our awareness, this will be the first network encompasses seven (different) domains of NPS, i.e., overall NPS, positive symptoms, negative symptoms, depressive symptoms, apathy, aggressive behavior, psychosis. We will publish the findings of our review in a clinical specialty journal and report evidence networks collating completed studies to establish the

current state of the evidence. The results of the present NMA may find the rational therapeutic approaches for NPS in view of a firmer understanding of the underlying etiologies and have the potential to provide further direction in the treatment of NPS.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-611). JTY serves as an unpaid Associate Editor-in-Chief of *Annals of Translational Medicine* from Jun 2019 to May 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study does not require ethical approval because individual patient data will not be included. There are no ethical concerns nor informed consent required.

References

1. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673-734.
2. Mathys M. Pharmacologic management of behavioral and psychological symptoms of major neurocognitive disorder. Ment Health Clin 2018;8:284-93.
3. Aalten P, de Vugt ME, Lousberg R, et al. Behavioral problems in dementia: a factor analysis of the neuropsychiatric inventory. Dement Geriatr Cogn Disord 2003;15:99-105.
4. Nowrangi MA, Lyketsos CG, Rosenberg PB. Principles and management of neuropsychiatric symptoms in Alzheimer's dementia. Alzheimers Res Ther 2015;7:12.
5. Lai MK, Tsang SW, Esiri MM, et al. Differential involvement of hippocampal serotonin1A receptors and re-uptake sites in non-cognitive behaviors of Alzheimer's disease. Psychopharmacology (Berl) 2011;213:431-9.
6. Rodriguez JJ, Noristani HN, Verkhratsky A. The serotonergic system in ageing and Alzheimer's disease. Prog Neurobiol 2012;99:15-41.
7. De Deyn PP, Katz IR, Brodaty H, et al. Management of agitation, aggression, and psychosis associated with dementia: a pooled analysis including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. Clin Neurol Neurosurg 2005;107:497-508.
8. Campbell N, Ayub A, Boustani MA, et al. Impact of cholinesterase inhibitors on behavioral and psychological symptoms of Alzheimer's disease: a meta-analysis. Clin Interv Aging 2008;3:719-28.
9. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2018;6:CD001190.
10. Kishi T, Matsunaga S, Iwata N. The effects of memantine on behavioral disturbances in patients with Alzheimer's disease: a meta-analysis. Neuropsychiatr Dis Treat 2017;13:1909-28.
11. Thancharoen O, Limwattananon C, Waleekhachonloet O, et al. Ginkgo biloba Extract (EGb761), Cholinesterase Inhibitors, and Memantine for the Treatment of Mild-to-Moderate Alzheimer's Disease: A Network Meta-Analysis. Drugs Aging 2019;36:435-52.
12. Meng YH, Wang PP, Song YX, et al. Cholinesterase inhibitors and memantine for Parkinson's disease dementia and Lewy body dementia: A meta-analysis. Exp Ther Med 2019;17:1611-24.
13. Yunusa I, Alsumali A, Garba AE, et al. Assessment of Reported Comparative Effectiveness and Safety of

Atypical Antipsychotics in the Treatment of Behavioral and Psychological Symptoms of Dementia: A Network Meta-analysis. JAMA Netw Open 2019;2:e190828.
14. Dudas R, Malouf R, McCleery J, et al. Antidepressants for treating depression in dementia. Cochrane Database Syst Rev 2018;8:Cd003944.
15. Lonergan E, Luxenberg J. Valproate preparations for agitation in dementia. Cochrane Database Syst Rev 2009;(3):CD003945.
16. Hyde AJ, May BH, Dong L, et al. Herbal medicine for management of the behavioural and psychological symptoms of dementia (BPSD): A systematic review and meta-analysis. J Psychopharmacol 2017;31:169-83.
17. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ 2015;350:h369.
18. Kongpakwattana K, Sawangjit R, Tawankanjanachot I, et al. Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis. Br J Clin Pharmacol 2018;84:1445-56.
19. Mavridis D, Giannatsi M, Cipriani A, et al. A primer on network meta-analysis with emphasis on mental health. Evid Based Ment Health 2015;18:40-6.
20. Cipriani A, Higgins JP, Geddes JR, et al. Conceptual and technical challenges in network meta-analysis. Ann Intern Med 2013;159:130-7.
21. Jin B, Liu H. Comparative efficacy and safety of therapy for the behavioral and psychological symptoms of dementia: a systemic review and Bayesian network meta-analysis. J Neurol 2019;266:2363-75.
22. Cornell JE. The PRISMA extension for network meta-analysis: bringing clarity and guidance to the reporting of systematic reviews incorporating network meta-analyses. Ann Intern Med 2015;162:797-8.
23. Hutton B, Catala-Lopez F, Moher D. The PRISMA statement extension for systematic reviews incorporating network meta-analysis: PRISMA-NMA. Med Clin (Barc) 2016;147:262-6.
24. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777-84.
25. Furukawa TA, Salanti G, Atkinson LZ, et al. Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis. BMJ Open 2016;6:e010919.
26. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev 2019;10:ED000142.
27. Song F, Loke YK, Walsh T, et al. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ 2009;338:b1147.
28. Tonin FS, Rotta I, Mendes AM, et al. Network meta-analysis: a technique to gather evidence from direct and indirect comparisons. Pharm Pract (Granada) 2017;15:943.
29. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009;172:137-59.
30. Nikolakopoulou A, Mavridis D, Salanti G. Planning future studies based on the precision of network meta-analysis results. Stat Med 2016;35:978-1000.
31. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Res Synth Methods 2012;3:80-97.
32. Rochwerg B, Brignardello-Petersen R, Guyatt G. Network meta-analysis in health care decision making. Med J Aust 2018;209:151-4.
33. Gartlehner G, Moore CG. Direct versus indirect comparisons: a summary of the evidence. Int J Technol Assess Health Care 2008;24:170-7.
34. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess 2005;9:1-134, iii-iv.
35. Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. Res Synth Methods 2016;7:55-79.
36. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. Stat Med 2001;20:3875-89.
37. Copas J. A simple confidence interval for meta-analysis. K. Sidik and J. N. Jonkman, Statistics in Medicine 2002; 21:3153-3159. Stat Med 2003;22:2667-8.
38. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. PLoS One 2014;9:e99682.
39. Zhang Y, Coello PA, Guyatt GH, et al. GRADE guidelines: 20. Assessing the certainty of evidence in

the importance of outcomes or values and preferences-inconsistency, imprecision, and other domains. J Clin Epidemiol 2019;111:83-93.
40. Wang J, Yu JT, Wang HF, et al. Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2015;86:101-9.
41. Dou KX, Tan MS, Tan CC, et al. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. Alzheimers Res Ther 2018;10:126.

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Supplementary

#12 Search (#1 and #9 and #10 and #11)

#11 Search (behav* or depress* or delusion* or aggress* or adjustment* or mood* or disinhibition* or motor* or night-time* or irritability* or affective*)

#10 Search (#7 or #8)

#9 Search (#2 or #3 or #4 or #5 or #6)

#8 Search (dementia or Alzheimer disease or vascular dementia or dementia in Parkinson's disease or frontotemporal dementia or Lewy body disease)

#7 Search dementia[MeSH Terms]

#6 Search Anticonvulsants[MeSH Terms]

#5 Search Antidepressive Agents[MeSH Terms]

#4 Search antipsychotic agents[MeSH Terms]

#3 Search (Antipsychoti* or Anti-psychotic* or Neurolepic* or Neurolept* or Antidepress* or Anti-depress*)

#2 Search (Memantine or Anticonvulsants or Benzodiazepines or Lithium or Carbamazepine or Valproate or Anticonvulsants or Trazodone or Citalopram or Fluoxetine or Antidepressive Agents or Setraline or Antidepressants or Antidepressive Agents or Aripiprazole or Quetiapine or Olanzapine or Clozapine or Acetophenazine or Chlorpromazine or Thiothixene or Thioridazine or Trichlorfon or Rivastigmine or Galantamine or Donepezil or Aripiprazole or Pimozide or Droperidol or Flupenthixol or Methotrimeprazine or Haloperidol or Olanzapine or Risperidone or Butyrophenones or Phenothiazines or Antipsychotic Agents or Memantine or Cholinesterase Inhibitors)

#1 Search ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])