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SYSTEMATIC REVIEW AND META–ANALYSIS

Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis

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AIMS

To determine the most efficacious and acceptable treatments of agitation in dementia.

METHODS

MEDLINE, EMBASE, PsycINFO, CENTRAL and clinicaltrials.gov were searched up to 7 February 2017. Two independent reviewers selected randomized controlled trials (RCTs) of treatments to alleviate agitation in people with all-types dementia. Data were extracted using standardized forms and study quality was assessed using the revised Cochrane Risk of Bias Tool for RCTs. Data were pooled using meta-analysis. The primary outcome, efficacy, was 8-week response rates defined as a 50% reduction in baseline agitation score. The secondary outcome was treatment acceptability defined as treatment continuation for 8 weeks.

RESULTS

Thirty-six RCTs comprising 5585 participants (30.9% male; mean ± standard deviation age, 81.8 ± 4.9 years) were included. Dextromethorphan/quinidine [odds ratio (OR) 3.04; 95% confidence interval (CI), 1.63–5.66], risperidone (OR 1.96; 95% CI, 1.49–2.59) and selective serotonin reuptake inhibitors as a class (OR 1.61; 95% CI, 1.02–2.53) were found to be significantly more efficacious than placebo. Haloperidol appeared less efficacious than nearly all comparators. Most treatments had noninferior treatment continuation compared to placebo, except oxcarbazepine, which was inferior. Findings were supported by subgroup and sensitivity analyses.

CONCLUSIONS

Risperidone, serotonin reuptake inhibitors as a class and dextromethorphan/quinidine demonstrated evidence of efficacy for agitation in dementia, although findings for dextromethorphan/quinidine were based on a single RCT. Our findings do not support prescribing haloperidol due to lack of efficacy, or oxcarbazepine due to lack of acceptability. The decision to prescribe should be based on comprehensive consideration of the benefits and risks, including those not evaluated in this meta-analysis.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Agitation is highly prevalent in people with dementia.
- Clinical practice guidelines recommend that pharmacological treatments may be prescribed at the lowest possible dose for the shortest possible time in conjunction with nonpharmacological measures, if agitation causes severe distress or an immediate risk of harm. However, the role of pharmacological treatments remains controversial because of uncertainty in relation to efficacy and concerns regarding safety.

WHAT THIS STUDY ADDS

- Dextromethorphan/quinidine and risperidone are statistically significantly more efficacious than placebo. However, compared to placebo, haloperidol fails to demonstrate efficacy and oxcarbazepine has inferior acceptability.
- Selective serotonin reuptake inhibitors are not significantly more efficacious than placebo when analysed individually but are significantly more efficacious than placebo when considered as a class.

Introduction

The number of people living with dementia is estimated to double every 20 years, reaching more than 131 million worldwide by 2050 [1]. Almost all people living with dementia experience one or more behavioural or psychological symptoms of dementia (BPSD) during the course of their illness [2, 3]. A recent systematic review reported that 18–87% of people with BPSD exhibit agitation [4]. Agitation is an inappropriate verbal, vocal or motor activity which is considered to be aggressive, excessively repetitive or contradictory to social standard [5]. Agitation has a high incidence (19–80% of people with dementia develop agitation over a 3-month period) and is moderately persistent (21–77% of people continue to experience agitation over a 3-month period) [4]. Agitation impairs daily functioning, prolongs hospitalization, reduces time to institutionalization and is associated with higher mortality [2, 6, 7]. Family caregivers of people with agitation also experience increased physical, psychological, and financial burden [2, 8].

Clinical practice guidelines recommend nonpharmacological approaches as first line for managing agitation in dementia [9–13]. However, if agitation causes severe distress or an immediate risk of harm, pharmacological treatments may be prescribed to complement non-pharmacological approaches [10, 12, 13]. The use of medications for alleviating agitation is limited by uncertainty in relation to their efficacy and concerns regarding their safety. Although there is no medication currently approved by the US Food and Drug Administration (FDA) for treating agitation in people living with dementia, randomized controlled trials (RCTs) have evaluated various psychotherapeutic interventions including, but not limited to, antipsychotics, antidepressants, anticonvulsants, and cholinesterase inhibitors to use for this indication [2, 14]. Nevertheless, most of the studies have been placebo controlled, while a few have been head-to-head comparisons of different medications [15]. Previous meta-analyses have only combined studies with the same pair of medications [16–19].

Network meta-analysis (NMA) is a method that facilitates indirect comparisons of all treatments with common comparators in a single framework. Accordingly, all direct and indirect evidence can be combined and compared simultaneously, resulting in the better precision of estimates [20]. In the field of psychiatric disorders, NMA has been employed to assess pharmacological treatments for schizophrenia [21, 22] and depression [23, 24], providing not only clearer recommendations for medication usage but provisions for future research. Therefore, the aim of this study was to conduct a systematic review and NMA of RCTs to determine the most efficacious and acceptable pharmacological treatments of agitation in dementia.

Methods

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for NMA [25]. The study protocol was registered on PROSPERO (CRD42017056722).

Participants and interventions

Our systematic review focused on people with all types of dementia who developed agitation and required a pharmacological intervention [5]. For inclusion in the review, studies needed to include participants with dementia diagnosed according to standardised criteria including, but not limited to, the Diagnostic and Statistical Manual of Mental Disorders (DSM), and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) criteria [26, 27]. Since there is no gold standard definition of agitation in dementia, studies that judged clinically significant agitation according to: (i) the discretion of clinicians that pharmacological treatment of agitation was required; or (ii) a cut-off value on rating scales indicating at least moderate agitation were considered [28]. Interventions of interest were any medications investigated for alleviating agitation.

Search strategy and selection criteria

MEDLINE, EMBASE, PsycINFO, Cochrane central register of controlled trials (CENTRAL), and clinicaltrial.gov were searched for literature pertinent to pharmacological treatments for alleviating agitation in dementia, from inception to 7 February 2017. Search terms included "dementia", "agitation", along with other related terms and the Cochrane highly sensitive search strategies for identifying randomized trials [29]. We also reviewed the reference lists of previous

relevant systematic reviews to identify additional studies. Full details of search strategies are provided in Appendix S1.

To be eligible for inclusion in the review, studies needed to: (1) be RCTs, (2) compare medications for alleviating agitation in dementia with either placebo or other medications, and (3) assess agitation using standardized rating scales including one of the following: the Cohen-Mansfield Agitation Inventory (CMAI), the Neuropsychiatric Inventory–Agitation subscale score (NPI-A), the Behavioural Pathology in Alzheimer's Disease rating scale–Aggression/agitation subscale score (BEHAVE-AD-A) or the Neurobehavioral Rating Scale–Agitation subscale score (NBRS-A). The CMAI was a reliable instrument intentionally designed to assess agitated behaviours in people with dementia [30, 31], while the NPI-A, BEHAVE-AD-A and NBRS-A performed satisfactorily and equally well in detecting agitation associated with dementia [32].

Outcome measures

The primary outcome was the 8-week response rates. This was defined as the proportion of people with dementia who had a 50% reduction in the baseline score on the specific agitation rating scale [24, 32]. We used a validated imputation method to estimate the number of people with dementia responding to treatment [33–35]. The agitation rating scales used for computing the 8-week response rates were selected using the following hierarchy: CMAI, NPI-A, BEHAVE-AD-A, NBRS-A. In main analyses, imputed number of responders from all the rating scales were pooled simultaneously. The robustness of these findings was extensively investigated in sensitivity analyses. If 8-week data were not available, data ranging from 4 to 12 weeks were used as an alternative [28]. The secondary outcome was treatment acceptability (dropout rates), defined as the number of people with dementia who discontinued the intervention early for any reason during the first 8 weeks of treatment (range 4–12 weeks) [35].

Data extraction and quality assessment

Data from all eligible studies were extracted using a structured data collection tool. For each of the included studies, the following information was extracted: country, study design, setting [community, nursing home (a facility with a domestic-styled environment that provides 24-h functional support and care for persons who require assistance with activities daily living and have identified health needs [36]) or hospital], type of dementia, type of BPSD, intervention, route of administration, dose, treatment duration, concomitant medication, study size, age, sex, mini-mental state examination score, defined outcome, agitation score, number of dropouts, and study sponsorship.

The quality of the included studies was assessed using the revised Cochrane Risk of Bias Tool for Randomised Trials (RoB version 2.0) [37]. This tool examined five major domains of bias: (i) bias arising from the randomisation process; (ii) bias due to deviations from intended interventions; (iii) bias due to missing outcome data; (iv) bias in measurement of the outcome; and (v) bias in selection of the reported result. The overall risk of bias in each study was categorised as low risk of bias, some concerns or high risk of bias.

Two reviewers (K.K. and R.S.) independently selected articles, extracted data and conducted the quality assessment. Any discrepancies between the two reviewers were discussed with the other investigators (I.T., J.S.B., S.H. and N.C.) until consensus was reached.

Statistical analysis

For the main analyses, we performed head-to-head comparisons between individual medications for both primary and secondary outcomes. A pairwise meta-analysis using a random-effects model was applied to calculate pooled odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) for studies comparing the same interventions [38]. Heterogeneity in each direct comparison was quantified using the I^2 statistics [38]. All calculations were based on an intention-to-treat basis, assuming the worst-case scenario, where missing participants were considered non-responders [39].

NMA was performed within a frequentist framework, where consistency and inconsistency models were formulated [40, 41]. The comparisons of treatments were graphically summarized as a network map. Nodes represented each treatment, while links between the nodes indicated the available direct comparisons between pairs of treatments [42]. Direct and indirect evidence from any pair of interventions were combined to generate mixed treatment effect sizes as pooled ORs with corresponding 95% CI. To assess whether the direct and indirect estimates were consistent (an assumption of multiple-treatments meta-analysis) we employed a design-by-treatment interaction model [43]. The surface under the cumulative ranking area (SUCRA) was applied to determine the hierarchy of interventions [42, 44]. Furthermore, the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) framework was implemented to evaluate the quality of all primary treatment effect estimates [45].

Prespecified subgroup analyses were conducted for groups of people with dementia who may have a different treatment response. Subgroup analyses were conducted by restricting the analyses to studies in which participants had an average age >65 years. Subgroup analyses were also performed for community, nursing home, and hospital settings.

Prespecified sensitivity analyses were carried out to enhance the robustness of the pooled outcomes as follows: (i) using a fixed-effect model to perform pairwise meta-analysis; (ii) using different cut-off values indicating response to interventions (30% and 70% reduction from baseline agitation scores); (iii) using different pooling strategies (pooling agitation scores from all rating scales as standardized mean differences, and pooling agitation scores from individual rating scales as mean differences); (iv) excluding studies with a high risk of bias; and (v) excluding studies receiving funds from for-profit organizations. We also carried out additional sensitivity analysis by grouping specific medications into therapeutic classes: (i) second generation antipsychotics (**risperidone**, **quetiapine**, **olanzapine** and **aripiprazole**); (ii) selective serotonin reuptake inhibitors (SSRIs; **citalopram**, **fluoxetine**, **fluvoxamine** and **sertraline**); (iii) anticonvulsants (**oxcarbazepine**, **topiramate** and **valproate**); and (iv) cholinesterase

inhibitors (**donepezil**, **galantamine** and **rivastigmine**). The remaining medications could not be categorized and were treated as individual medications in the network.

A comparison-adjusted funnel plot was performed to detect any small-study effects [46]. All statistical analyses were executed with STATA (version 13.0, StataCorp, College Station, TX, USA).

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [47], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [48].

Results

Description of included studies

We identified 6855 records through database searching from which 37 studies were included in this systematic review [49–85]. One of these eligible studies did not report baseline NPI-A scores required to calculate 8-week response rates and therefore this study was excluded [49]. This meant that 36 studies with 5585 participants were included in network meta-analysis. The PRISMA flow diagram outlining the study selection is shown in Figure 1. Of the 5585 participants, the mean [standard deviation (SD)] age was 81.8 (4.9) years; the mean (SD) baseline mini-mental state examination score was 10.0 (5.2); and 1727 (30.9%) were male. Studies were conducted in the USA (17 of 36 studies), Europe (12 of 36 studies),

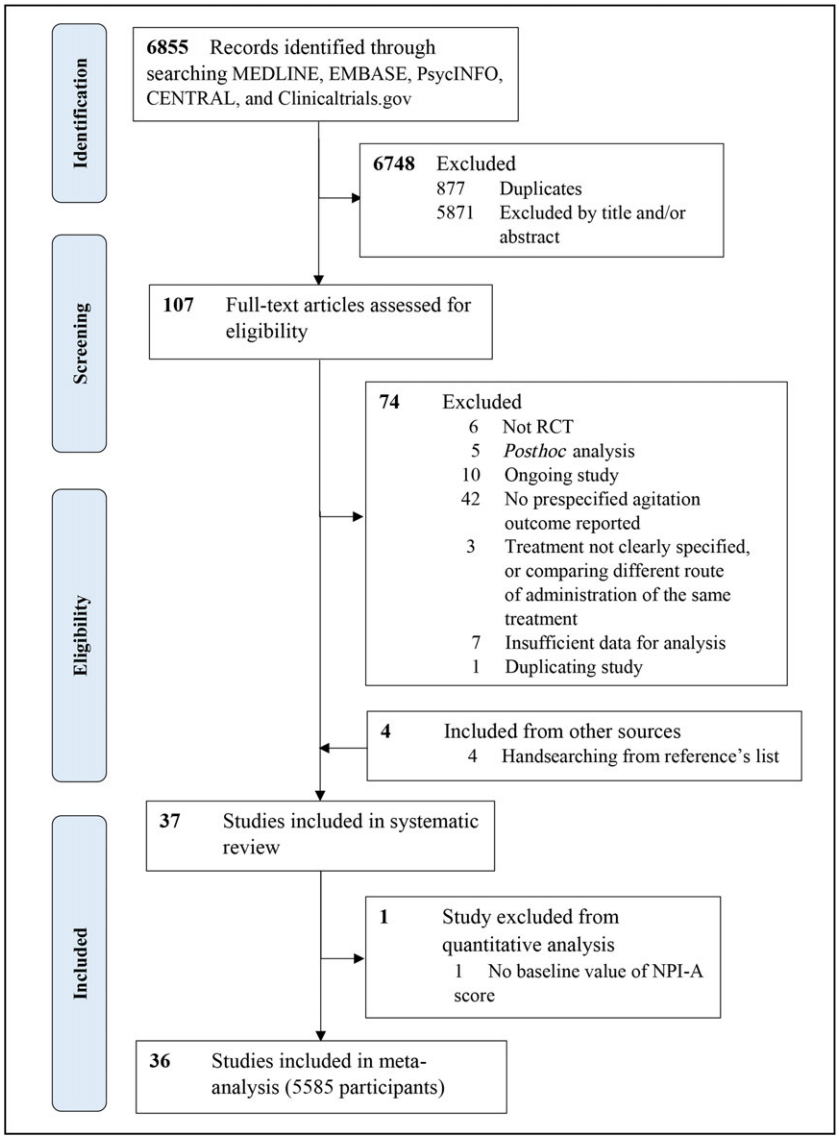

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram: the diagram demonstrates the process of review, inclusion and exclusion of studies. RCT, randomized controlled trial; NPI-A, Neuropsychiatric Inventory–Agitation subscale score

and Asia and Oceania (seven of 30 studies). The major type of dementia was Alzheimer's disease with significant symptoms of agitation. The CMAI was the most frequently used scale to assess agitation (25 of 36 studies), followed by NPI-A (11 of 36 studies), NBRS (two of 36 studies), and BEHAVE-AD (one of 36 studies). Multiple agitation rating scales were reported in two studies [52, 59]. The mean (SD) of study duration was 9.3 (3.8) weeks. Characteristics of all included studies are summarized in Appendix S2.

Quality assessment

The risk of bias assessment is presented in Appendix S3. Most studies had a low risk of bias (38.9%), followed by some concerns (33.3%) and high risk (27.8%). Overall, 19.4% studies were deemed to have high risk of bias because there was no evidence clarifying that outcome assessors were blinded.

Network map

Network maps of main analyses are presented in Figure 2 (and Appendix S4). Overall, risperidone was investigated in the highest number of comparisons (11 of 36 studies), followed by **haloperidol** (seven of 36 studies), valproate (five of 36 studies), and quetiapine (four of 36 studies). There were three studies for yokukansan; two studies for aripiprazole, citalopram, olanzapine, rivastigmine, sertraline and

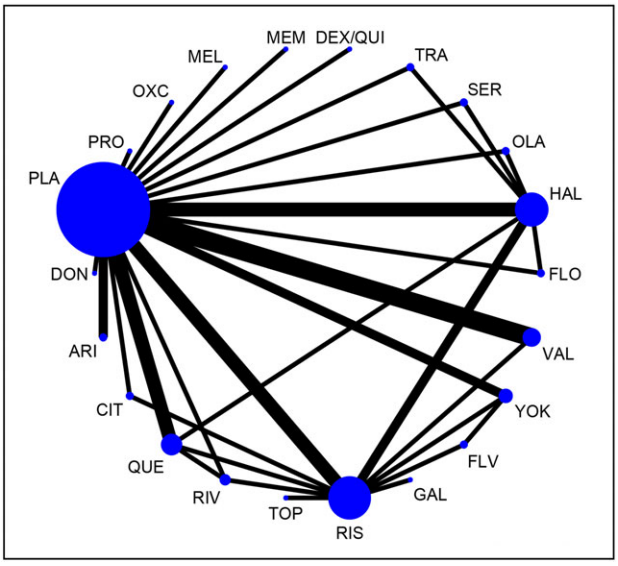

Figure 2

Network map of treatment comparisons for both primary and secondary outcomes: Nodes represented each treatment, while links between the nodes indicated the available direct comparisons between pairs of treatments. The size of the nodes corresponds to the number of studies investigating the treatments. The thickness of the lines corresponds to the number of studies assessing the comparisons. ARI, aripiprazole; CIT, citalopram; DEX/QUI, dextromethorphan/quinidine; DON, donepezil; FLO, fluoxetine; FLV, fluvoxamine; GAL, galantamine; HAL, haloperidol; MEL, melatonin; MEM, memantine; OLA, olanzapine; OXC, oxcarbazepine; PLA, placebo; PRO, propranolol; QUE, quetiapine; RIS, risperidone; RIV, rivastigmine; SER, sertraline; TOP, topiramate; TRA, trazodone; VAL, valproate; YOK, yokukansan

trazodone; and one study for **dextromethorphan/quinidine**, donepezil, fluoxetine, fluvoxamine, galantamine, **melatonin**, **memantine**, oxcarbazepine, **propranolol** and topiramate. No global inconsistency was found in any network (Appendix S5).

Primary and secondary outcomes

Results from the NMA were generally consistent with those from the pairwise meta-analysis (Appendix S6). In the main analyses, our NMA (Figure 3 and Appendix S7) showed that only two medications had statistically significant higher response rates than placebo: dextromethorphan/quinidine (OR 3.04; 95% CI, 1.69 to 5.46), and risperidone (OR 1.88; 95% CI, 1.46–2.43). Both dextromethorphan/quinidine and risperidone further had superior efficacy to haloperidol and quetiapine. Haloperidol was the second most investigated medication but failed to demonstrate higher efficacy than placebo (OR 0.86; 95% CI, 0.54–1.37). Haloperidol was also less efficacious compared to nearly all medications in the network. No individual SSRI had a significantly greater efficacy than placebo. In terms of efficacy rankings from the SUCRA analysis (Appendix S8), donepezil ranked first, followed by galantamine, dextromethorphan/quinidine and then risperidone. However, neither donepezil nor galantamine demonstrated statistically significant results in any comparison.

Nonsignificant differences in treatment acceptability were observed for nearly all medications compared to placebo, except for oxcarbazepine (OR 3.73; 95% CI, 1.06–13.16). Oxcarbazepine also had inferior acceptability than donepezil and haloperidol. With regard to acceptability rankings from the SUCRA analysis, memantine ranked first, followed by fluvoxamine, citalopram and propranolol. However, none of these medications showed statistically significant results in any comparison.

When applying GRADE, the majority of comparisons were rated as moderate (43.3%, 100 of 231 comparisons). For the rest, 26.8% (62 of 231 comparisons), 28.1% (65 of 231 comparisons) and 1.7% (four of 231 comparisons) had high, low and very low quality, respectively (Appendix S9).

Subgroup analyses

Prespecified subgroup analysis according to age was not performed because all included studies recruited participants aged ≥65 years. For subgroup analyses in different settings, significant results were observed in the nursing-home setting, where risperidone (OR 2.24; 95% CI, 1.16–4.33) was more efficacious than placebo. This finding was consistent with the main analysis (Appendix S10). There was insufficient power to conduct subgroup analyses for studies conducted in the community and hospital settings.

Sensitivity analyses and small-study effects assessment

Results from the sensitivity analyses are reported in Appendix S11. For pairwise meta-analysis, similar outcomes were obtained using either random- or fixed-effect models. For NMA, the findings in relation to response rates were still robust when altering the cut-off value from 50% to 30% and 70% reduction from baseline agitation scores. Furthermore, similar estimates were attained when pooling agitation scores

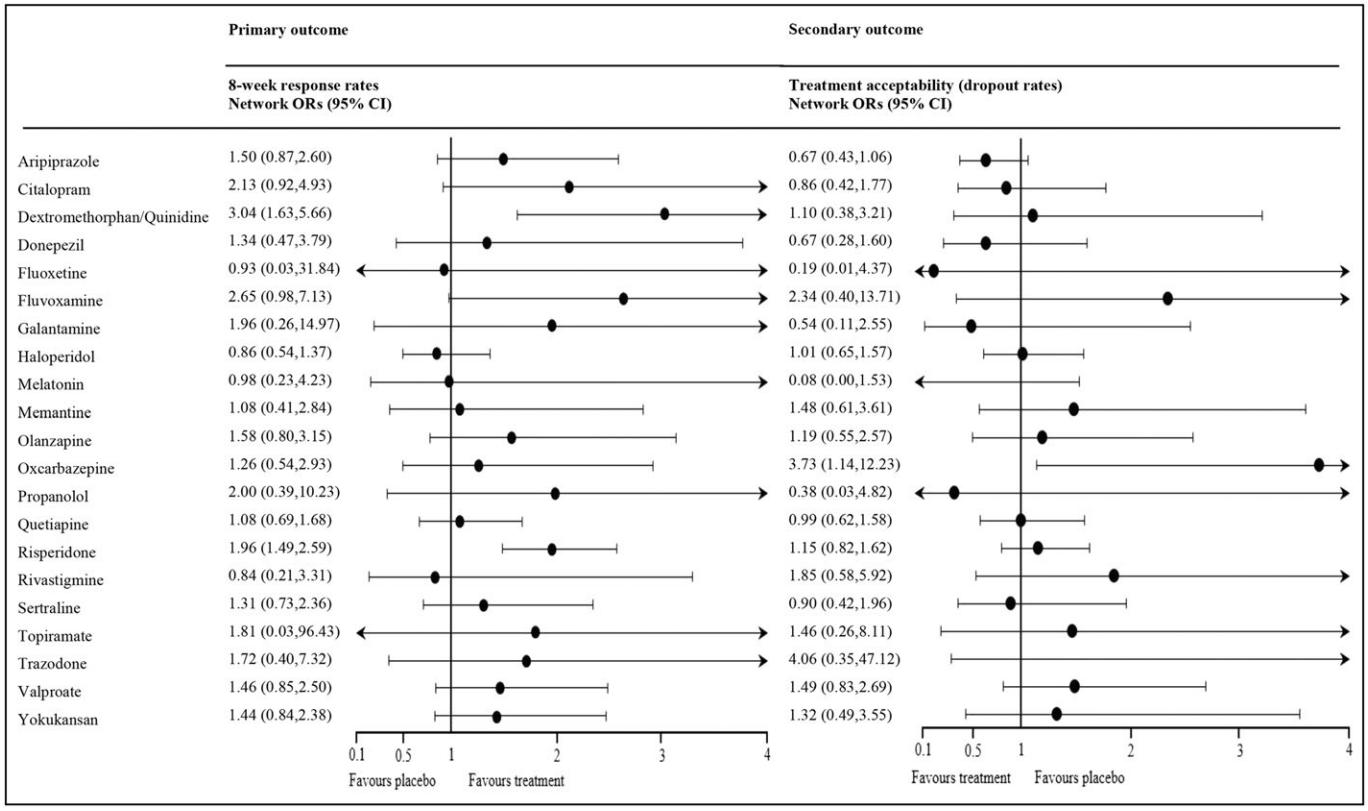

Figure 3

Plots of network meta-analysis results for primary outcome (8-week response rates) and secondary outcome (treatment acceptability, dropout rates) when each of medications compared to placebo. OR, odds ratio; CI, confidence interval

as standardized mean differences and mean differences, and when excluding studies with high risk of bias. The results were not significant in the sensitivity analysis that excluded studies funded by for-profit organizations. Additional sensitivity analysis based on therapeutic drug classes provided similar results to the main analysis, except that SSRIs demonstrated a significantly higher response rate than placebo (OR 1.61; 95% CI, 1.02–2.53). Comparison-adjusted funnel plots of the main analyses showed no evidence of asymmetry (Appendix S12).

Discussion

Our research applied pairwise meta-analysis and NMA to compare efficacy and acceptability of different medications used to alleviate agitation in dementia. Dextromethorphan/quinidine, risperidone and SSRIs as a class were found to have significantly higher response rates than placebo and the other medications considered in this review. Conversely, haloperidol was appeared to have lower response rates than placebo, and the other medications. In terms of acceptability, only oxcarbazepine was significantly inferior to placebo and other medications.

According to a longitudinal observational study published by Hendriks *et al*. (2015) [86], residents of Dutch nursing homes with dementia were most likely to be prescribed antipsychotics (27–46%) for relieving agitation, followed by anxiolytics (29–33%) and antidepressants (2–11%), respectively. The findings from this *real-world study* of prescribing are consistent with evidence for efficacy from our meta-analysis. We found that second generation antipsychotics, especially risperidone, were efficacious and acceptable for agitation in dementia compared to placebo. Differences exist between jurisdictions on approval of medications for this indication, which may reflect the limited evidence from systematic reviews. For example, no medication is approved by the US FDA for this indication while risperidone is approved by the European Medicines Agency for persistent aggression in patients with moderate to severe Alzheimer's dementia. Efficacy and acceptability findings from our review, however, should also be interpreted in conjunction with other safety and effectiveness data.

Antipsychotics have been the most investigated drug class for alleviating agitation. Previous research has suggested that risperidone, olanzapine and haloperidol are more efficacious than placebo [2, 87]. However, our findings do not support the superiority of olanzapine and haloperidol over placebo for relieving agitation in dementia, which may be related to our approach of analysing all of the data rather than focusing on specific subgroups. In the case of olanzapine, the direct RCT specific to agitation reported significantly higher efficacy of low-dose olanzapine (5 and 10 mg day^{-1}) over

placebo, but the efficacy reduced with a higher dose [75]. Street *et al*. speculated that the inverse correlation of efficacy and olanzapine dose may be multifactorial and related to age-related pharmacokinetic and pharmacodynamic changes [75]. To discern the overall efficacy of olanzapine, our analyses considered all doses of olanzapine (5–15 mg day^{-1}) and found that olanzapine had a nonsignificantly higher response rate than placebo. In the case of haloperidol, the previous meta-analysis of this treatment revealed that it had a slight benefit for the aggressive domain of agitation only [19]. Our review generated further evidence to suggest that haloperidol lacks efficacy because haloperidol showed inferior response rates to placebo and many other medications. Only risperidone had a higher response rate with similar acceptability compared to placebo with moderate network GRADE quality. Although risperidone is associated with a range of adverse events (i.e. extrapyramidal symptoms, somnolence, peripheral oedema, and cerebrovascular events) [2, 18], and an FDA black-box warning (i.e. associated with a significant 1.7-fold increase in mortality compared to placebo) [88], many clinical practice guidelines have still recommended short-term use of this medication [10, 11, 13, 89]. Evidence from our review supports the short-term efficacy of risperidone in the people with dementia whose agitation is prominent, causes harm and distress to themselves or others, and has not been relieved after implementing nonpharmacological interventions. Nevertheless, the decision to prescribe risperidone would need to be based on existing knowledge of its adverse event profile. The clinical studies included in our review may not have had sufficient power or duration to detect important adverse events, and clinical trial participants may not have been representative of all people with dementia in routine clinical practice.

Several studies have been conducted to investigate whether SSRIs are an equally efficacious and safer alternative to second generation antipsychotics [16, 52, 61]. Several clinical practice guidelines have also recommended citalopram as the medication of choice for agitation in dementia [11, 13, 89]. The most recent RCT has suggested that citalopram (30 mg day^{-1}) provides significant improvement in agitation over placebo [52]. In this RCT, citalopram improved the majority of agitation-related outcomes but did not significantly improve NPI-A compared to placebo. Even when we analysed the outcome that favoured citalopram over placebo (CMAI) in our main analysis, citalopram did not demonstrate higher response rates than placebo or any second-generation antipsychotics. SSRIs only showed significantly superior efficacy to placebo when considered as a class in the sensitivity analysis, suggesting that SSRIs have the potential to be more efficacious than placebo but current available evidence is insufficient to recommend one SSRI over another. According to our acceptability analysis, and the broader literature, it is unclear whether SSRIs have a favourable safety profile. In addition to a range of common side effects (i.e. sexual dysfunction, sleep disturbances and weight gain [90, 91]), SSRIs may increase the risk of falls to a similar extent as the older tricyclic antidepressants [92], and people with dementia are at already increased risk of falls [93]. Clinicians should consider these safety concerns when deciding whether or not to prescribe SSRIs for this indication. Nevertheless, in the *real-world* clinical practice when pharmacological treatment is deemed necessary and there are very limited usable medications, SSRIs could be an additional acceptable alternative when the risks and benefits are individualized to patient's characteristics.

Dextromethorphan/quinidine is a new drug combination and its use for agitation in dementia has been evaluated in few studies. It is hypothesized that dextromethorphan reduces agitation by diminishing glutamate, and serotonin actions, while activating **sigma-1 receptors**. Quinidine, a cytochrome P450 2D6 inhibitor, has a role to promote plasma concentration, and brain penetration of dextromethorphan [94]. According to a 10-week phase-2 clinical trial [51], this combination (AVP-923) was reported to provide a meaningful improvement in agitation, and was generally well tolerated, which is consistent with our findings. The most common adverse events include falls, diarrhoea, urinary tract infection and dizziness. In contrast, incidence of prolonged QT interval, a previous safety concern associated with quinidine, was found to be not clinically different from placebo. This may be because this combination (AVP-923) contains much lower dose of quinidine (10 mg), compared to other formulations for cardiac arrhythmias (200–300 mg) [94]. Even if this drug combination shows short-term efficacy and similar acceptability compared to placebo with high network GRADE quality, supporting evidence is still very limited. Although not statistically significant, the rate of serious adverse events in the RCT by Cummings *et al*. was almost twice as high in the dextromethorphan/quinidine treated group than in the placebo-treated group (7.9% vs 4.7%) [51]. Moreover, only 5.5% of participants in this RCT were residents of nursing homes. This is important because pharmacological treatments for agitation in dementia are often prescribed in this setting, and residents of nursing homes may be particularly susceptible to adverse events. Together with a small number of participants included in this study, more high-quality research is needed before dextromethorphan/quinidine can be recommended for this indication. Clinicians should consider the known individual adverse event profiles of dextromethorphan and quinidine before prescribing this combination to people with dementia.

Strengths and limitations

The studies included in our analyses investigate various types of dementia, and broad BPSD with agitation being one. The consistent findings across these diverse populations can be considered a strength because it reflects real world presentation of people with dementia who may have multiple presentations of BPSD concomitantly rather than agitation alone. However, our study was not able to investigate the relative effectiveness and safety of medicines for agitation by dementia type. To the best of our knowledge, this study is the first systematic review and NMA addressing this issue. Not only do the majority of included studies have a low risk of bias, but more than two-thirds of the synthesized network evidence were of moderate to high quality. Importantly, the results were considerably robust across analyses.

Our study also has limitations. First, different doses were used between and within studies, and our comparisons of efficacy and acceptability across studies were the overall results from all reported doses. Second, we assessed treatment

acceptability rather than the adverse event profile of each medication. Medications with similar acceptability to placebo are not necessarily safe or without adverse events. Therefore, it is important to note that people living with dementia using these medications should be monitored for adverse events, and clinicians should interpret the findings of our review in light of existing knowledge of the adverse event profile of specific medications from clinical and observational research. Third, this study considers only prespecified agitation-specific rating scales on the outcome measurements. While this approach promotes standardization of the outcome measurements, some potentially usable information from the studies using different rating scales may have not been included in the analysis. Soto *et al*. (2014) suggested that a global rating of change for agitation outcomes should be considered in addition to the agitation-specific quantitative measures to optimize the outcome measurements [28]. Fourth, in terms of availability of literature, there are enough studies examining risperidone, haloperidol and valproate to power this NMA. In contrast, a paucity of evidence is found for the other medications. There might have been more studies eligible to be included in our analysis, but we were unable to contact the authors of these studies for clarification [95–100]. Provided that these studies had been eligible and included in our analysis, it is possible that some of the findings may have been different. Besides, high-quality RCTs are required to strengthen the existing evidence. Finally, the generalizability of efficacy and acceptability data from short-term clinical trials, most conducted in nursing-home settings, with strict inclusion and exclusion criteria and protocols, to usual care may be limited.

Conclusion

In summary, our analyses of RCT data suggest that prescribing of haloperidol and oxcarbazepine should be discouraged for treating agitation due to lack of efficacy, and acceptability, respectively. Risperidone and dextromethorphan/quinidine have demonstrated efficacy and short-term acceptability, although the results of dextromethorphan/quinidine are based on one RCT only. SSRIs also show a promising efficacy as a class. The clinical decision to prescribe short-term pharmacological therapy for severe agitation in a person living with dementia can be informed by this analysis of the relative benefits and risks of pharmacological treatments in RCTs, as well as by data from other study types and understanding of individual patient factors.

Competing Interests

There are no competing interests to declare.

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Contributors

K.K., R.S., I.T., J.S.B. and N.C. were responsible for the study concept and design. All authors, acquired, analysed, or interpreted the data. K.K., N.C., J.S.B. and S.N.H. drafted the manuscript. All authors critically revised the manuscript for important intellectual content. N.C. supervised the study.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

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Appendix S1 Search strategies
Table S1 Search strategies
Figure S1 Flow diagram and references of all included studies

Appendix S2 Characteristics of all included studies
Table S2 Characteristics of all included studies in this systematic review (37 studies)
Table S3 Description of interventions of all included studies in this systematic review (37 studies)
Appendix S3 Risk of bias assessments
Table S4 Risk of bias summary: review authors' judgement on risk of bias domains for studies included in meta-analysis (36 studies)
Figure S2 Risk of bias graph: review authors' judgement on risk of bias domains, presented as percentages of studies included in meta-analysis (36 studies)
Appendix S4 Networks of treatment comparisons
Figure S3 Networks map of treatment comparisons for primary and secondary outcomes
Appendix S5 Assessments of inconsistency for each outcome network
Table S5 Evaluation of the global inconsistency in networks using 'design-by-treatment' interaction model for each outcome
Appendix S6 Results of meta-analysis of direct comparisons between treatment options
Table S6 Pairwise meta-analysis for all outcomes by using random-effect model
Appendix S7 Results of network meta-analysis
Figure S4 Network estimated odds ratios (95% confidence intervals) of treatment options on primary outcome, 8-week response rates
Figure S5 Network estimated odd ratios (95% confidence intervals) of treatment options on secondary outcome, treatment acceptability
Table S7 Results of network meta-analysis focusing on when interventions compared to placebo for both primary outcome, 8-week response rates, and secondary outcome, treatment acceptability
Appendix S8 Treatment ranking and surface under the cumulative ranking curves (SUCRA)
Figure S6 SUCRA ranking curve for primary outcome, 8-week response rates
Figure S7 SUCRA ranking curve for secondary outcome, treatment acceptability
Appendix S9 Evaluation of the quality of evidence using GRADE framework for primary outcome
Table S8 Treatment effects and quality ratings for primary outcome, 8-week response rates, according to GRADE framework
Appendix S10 Subgroup analyses
Table S9 Subgroup analysis according to different study settings (community, nursing home and hospital) for primary outcome, 8-week response rates
Appendix S11 Sensitivity analyses
Table S10 Sensitivity analysis of pairwise meta-analysis for all outcomes, using fixed-effect model
Table S11 Sensitivity analysis according to different cut-off values indicating response to interventions (30% and 70% reduction from baseline score) and different pooling strategy (standardised mean difference) for primary outcome, 8-week response rates
Table S12 Sensitivity analysis according to different agitation rating scales (CMAI, NPI-A, BEHAVE-AD-A* and NBRS-A*) for primary outcome, 8-week response rates
Table S13 Sensitivity analysis according to excluding studies with high risk of bias and excluding studies receiving fund from for-profit organization for primary outcome, 8-week response rates
Table S14 Sensitivity analysis based on pharmacological drug classes for primary outcome, 8-week response rates
Appendix S12 Comparison-adjusted funnel plots for each outcome from the network meta-analysis
Figure S8 Comparison-adjusted funnel plot for the network of primary outcome, 8-week response rates
Figure S9 Comparison-adjusted funnel plot for the network of secondary outcome, treatment acceptability
Appendix S13 References