Cochrane Library

Cochrane Database of Systematic Reviews

Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia (Protocol)

Mühlbauer V, Luijendijk H, Dichter MN, Möhler R, Zuidema SU, Köpke S

Mühlbauer V, Luijendijk H, Dichter MN, Möhler R, Zuidema SU, Köpke S.
Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia.
Cochrane Database of Systematic Reviews 2019, Issue 4. Art. No.: CD013304.
DOI: 10.1002/14651858.CD013304.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia

Viktoria Mühlbauer[1], Hendrika Luijendijk[2], Martin N Dichter[3], Ralph Möhler[4], Sytse U Zuidema[2], Sascha Köpke[5]

[1]Geriatric Research Unit, AGAPLESION Bethesda Hospital, University of Ulm, Ulm, Germany. [2]Department of General Practice and Elderly Care Medicine, University of Groningen, University Medical Center Groningen, Groningen, Netherlands. [3]German Center for Neurodegenerative Diseases (DZNE), Witten, Germany. [4]Department of Health Services Research and Nursing Science, School of Public Health, Bielefeld University, Bielefeld, Germany. [5]Nursing Research Group, Institute of Social Medicine and Epidemiology, University of Lübeck, Lübeck, Germany

Contact address: Sascha Köpke, Nursing Research Group, Institute of Social Medicine and Epidemiology, University of Lübeck, Ratzeburger Allee 160, Lübeck, D-23538, Germany. sascha.koepke@uksh.de.

Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: New, published in Issue 4, 2019.

Citation: Mühlbauer V, Luijendijk H, Dichter MN, Möhler R, Zuidema SU, Köpke S. Antipsychotics for agitation and psychosis in people with Alzheimer's disease and vascular dementia. *Cochrane Database of Systematic Reviews* 2019, Issue 4. Art. No.: CD013304. DOI: 10.1002/14651858.CD013304.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of antipsychotics for the treatment of agitation and psychosis in people with Alzheimer's disease and vascular dementia.

BACKGROUND

Description of the condition

Dementia is a clinical syndrome characterised by cognitive, neuropsychiatric, and functional symptoms. It involves cognitive deterioration, disturbances in language, psychological and psychiatric changes, and impairments in activities of daily living (ADL). Five percent of people aged over 65 years and 20% of those over 80 years have dementia. In 2015, an estimated 47 million people were living with dementia worldwide. The total number of people with dementia will most likely continue to rise as the age of the population increases. Alzheimer's disease is the most common type of dementia (Livingston 2017).

Neuropsychiatric symptoms, also known as behavioural and psychological symptoms of dementia (BPSD), or challenging behaviour are common features of dementia. About 90% of people with dementia experience agitation, psychosis, or other neuropsychiatric symptoms such as anxiety, depression, and apathy at some time during the course of the disease (Borsje 2018). Symptoms often co-occur. Agitation is difficult to define simply (Cummings 2015). It covers unsettled verbal, vocal, or motor activity that is or is not accompanied by aggression (Cohen-Mansfield 1996). Common symptoms include restlessness, wandering, verbal insults, and shouting. Agitation is often measured with the Cohen-Mansfield Agitation Inventory (CMAI), a scale that covers many different types of agitation. In clinical practice, simpler definitions are also used.

Psychosis in dementia is characterised by delusions and halluci-

nations. Simple delusions about theft or abandonment are typical symptoms in Alzheimer's disease (Murray 2014). Prevalence of psychosis in Alzheimer's disease varies from 25% to 50% and depends on the stage of the disease: the prevalence is lower in the early stage of the disease, and rises as the disease progresses (Murray 2014).

Agitation and psychosis are distressing for people with dementia and their carers, and make it more difficult to care for the patient (Gilley 1991; Livingston 2014; Schmidt 2012). The symptoms are associated with greater functional impairment and poorer quality of life (Morris 2015; Scarmeas 2005; Wetzels 2010). They frequently trigger placement in residential care or use of psychotropic drugs and are associated with higher care costs (Testad 2010; Toot 2017).

Agitation and psychosis can occur as a result of other causes (superimposed on dementia). Therefore, a comprehensive assessment of possible precipitating factors such as pain or delirium should be performed to rule out other treatable causes before hypothesising that agitation and psychosis are due to the dementia syndrome and considering the use of antipsychotics.

Description of the intervention

Antipsychotics, also known as neuroleptics, are widely used to treat agitation and psychosis in dementia. Antipsychotic use in Western European nursing home residents ranges from 12% to 59% (Janus 2016). Factors influencing antipsychotic use in people with dementia in nursing homes are nurses' job satisfaction and their belief in positive treatment effects (Janus 2017).

Antipsychotics can be classified into two subgroups: typical (conventional, first-generation) and atypical (second-generation) agents. Examples for typical agents are haloperidol, chlorpromazine, or levomepromazine; atypical agents include risperidone, olanzapine, quetiapine, clozapine, or aripiprazole. Haloperidol is the most commonly used typical antipsychotic and risperidone the most commonly used atypical antipsychotic for agitation and psychosis in dementia (Yohanna 2017). The US Food and Drug Administration (FDA) has not approved any antipsychotics for use in people with dementia; in the EU, only risperidone is licensed for short-term use for aggression in this patient population (Tampi 2016; Almutairi 2018).

Despite the wide use of antipsychotics for agitation and psychosis in dementia, their benefit is uncertain because some trials have yielded negative results and effectiveness may be outweighed by harms (Schneider 2006). Antipsychotics have various severe adverse effects such extrapyramidal symptoms (EPS), somnolence, and (further) cognitive decline (Ballard 2005; Kirchner 2001). Less frequent but serious adverse events (SAE) are malignant neuroleptic syndrome, strokes, falls, and pneumonia (Banerjee 2010; Knol 2008; Lonergan 2002).

Regulatory agencies issued the first warnings concerning the use of antipsychotics in people with dementia in the mid-2000s due to an increased risk of death (EMA 2008; Kuehn 2005; MHRA 2009; Schneider 2005) and stroke (MHRA 2009) in this population .

Cohort studies have also shown an association between use of atypical and typical antipsychotics and an increased risk of mortality in older people (Arai 2016; Kales 2007; Kales 2012). However, it has also been postulated that this might be caused by "confounding by indication" as many cohort studies included people with terminal illness and delirium, which might explain the co-occurrence of the use of typical antipsychotics and deaths in these studies. This could also explain why mortality is highest during the first month of use (Luijendijk 2016).

Overprescribing of antipsychotics in people with dementia has become a major problem. Antipsychotic drugs are often prescribed inappropriately (unclear indication, presence of contraindications, or chronic use longer than necessary or advocated) and with little monitoring (Furniss 1998; Renom-Guiteras 2018). The use of antipsychotics in people with dementia has also provoked much debate due to the potential for SAEs. In addition, some consider the use of antipsychotics to be simply a chemical restraint, suggesting that the sedative adverse effects of antipsychotics are used to calm people down rather than treating agitation and psychosis specifically or searching for and remedying the triggers for these behaviours (Hughes 2008). Furthermore, it has been shown that antipsychotics could be successfully discontinued in people with dementia and psychosis or agitation (Van Leeuwen 2018).

How the intervention might work

Almost all typical antipsychotics are antagonists at the dopamine receptor. Atypical antipsychotics also act as antagonists on muscarinic, serotonergic, adrenergic, and histaminergic receptors. These effects are considered to reduce agitation and psychosis. D2-receptor blockade is responsible for many adverse drug reactions, including motor EPS. Atypical antipsychotics have been marketed on the premise that they offer a better adverse effect profile than conventional antipsychotics, in particular fewer severe EPS (Pierre 2005).

Why it is important to do this review

In the current review, we will update and combine two previous Cochrane Reviews. Both were published when concern about the use of antipsychotics began to emerge. The first concerned haloperidol for agitation in dementia (Lonergan 2002). This review did not cover psychosis in dementia. The second concerned atypical antipsychotics for neuropsychiatric symptoms (Ballard 2006). The present review will focus on agitation (with or without aggression) and psychosis.

In addition, we wish to present the evidence for atypical and typical antipsychotics in one review so that the reader can make an informed choice between the two groups. This review will sup-

port decision making for clinicians, carers, and patients. Finally, the widespread use of antipsychotics as well as the harmful adverse effects that might outweigh efficacy call for an up-to-date review.

OBJECTIVES

To assess the effectiveness and safety of antipsychotics for the treatment of agitation and psychosis in people with Alzheimer's disease and vascular dementia.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised, placebo-controlled trials comparing the effects of antipsychotics and placebo for the treatment of agitation or psychosis in people with dementia due to Alzheimer's disease or vascular dementia. We will include full journal publications, online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts. We will also include studies which report insufficient data for analysis and will describe the results narratively. We will exclude studies that were non-randomised, case reports, and clinical observations. We will also exclude studies using antipsychotics that are no longer available on the US or EU market, studies of antipsychotics that are used for acute short-term sedation in emergency situations, studies comparing different antipsychotics head to head, and antipsychotic withdrawal trials. There will be no language restrictions.

Types of participants

We will include trials in people with a diagnosis of dementia due to Alzheimer's disease, vascular dementia, or both irrespective of age, severity of cognitive impairment, and setting. Diagnoses of dementia must have been made with established diagnostic criteria for Alzheimer's or vascular dementia. We will include studies with mixed dementia populations if at least 80% of the participants have Alzheimer's or vascular dementia. We will exclude trials in people with other types of dementia, or delirium.

Participants must have clinically significant agitation (including aggression) or psychosis or both at baseline. We will accept definitions of clinically significant agitation or psychosis from the included trials based either on scores on validated measurement instruments or on reports of clinical relevance from informal carers or healthcare professionals. Validated measurement instruments often used to assess agitation are the CMAI, the agitation subscale of the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), or the Neuropsychiatric Inventory (NPI). The psychosis subscale of BEHAVE-AD or NPI are frequently used to assess psychosis.

Types of interventions

We will include all studies using typical and atypical antipsychotics that are presently available for use on the US or EU market.

As typical antipsychotics, we will consider substances coded in the Anatomical Therapeutic Chemical Classification System (ATC) as N05AA, N05AB, N05AD, N05AF, and N05AG (e.g. chlorpromazine, chlorprothixene, flupentixol, fluphenazine, haloperidol, levomepromazine, perphenazine, pimozide, thiothixene, trifluoperazine, zuclopenthixol). Atypical antipsychotics are ATC coded as N05AE, N05AH, N05AL, and N05AX (e.g. amisulpride, aripiprazole, clozapine, lurasidone, olanzapine, quetiapine, risperidone, sertindole, sulpiride, zotepine, ziprasidone) (WHO 2017).

Types of outcome measures

Primary outcomes

- Efficacy:
  - agitation or psychosis in participants with agitation or psychosis respectively at baseline.
- Adverse effects:
  - number of participants with somnolence;
  - number of participants with EPS;
  - number of participants with any adverse event;
  - number of participants with any serious adverse event (SAE), which is defined by the FDA/European Medicines Agency (EMA) as resulting in death, being life-threatening, requiring hospitalisation, or causing prolongation of existing hospitalisation, resulting in persistent or significant disability/incapacity or requiring interventions to prevent permanent impairment or damage. This includes stroke, thromboembolism, and pneumonia;
  - number of deaths.

Secondary outcomes

- Number of responders for agitation or psychosis (response according to definition of primary study authors, or improvement on Clinical Global Impression scale) in trials that include participants with agitation or psychosis respectively at baseline.
- Number of participants who discontinued treatment (any reason).
- Number of participants who discontinued treatment due to adverse events.

- Health-related quality of life.
- Functioning in activities of daily living (ADL).
- Cognitive function.
- Carer burden or carer quality of life.

Search methods for identification of studies

We will search ALOIS (www.medicine.ox.ac.uk/alois), which is the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) specialized register.
ALOIS is maintained by the Information Specialists for the CDCIG, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. The studies are identified through searching:

- the Cochrane Library's Central Register of Controlled Trials (CENTRAL);
- major healthcare databases: MEDLINE (OvidSP), Embase (OvidSP), CINAHL (EBSCOhost), and PsycINFO (OvidSP);
- trial registers: ClinicalTrials.gov and the World Health Organization's (WHO) International Clinical Trials Register Platform (ICTRP) which covers ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials; and the Netherlands National Trials Register, plus others;
- grey literature sources: ISI Web of Science Core Collection.

To view a list of all sources searched, see the ALOIS website (www.medicine.ox.ac.uk/alois).
Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement, and cognitive enhancement trials, can be viewed on the CDCIG's website (dementia.cochrane.org/searches).
We will run additional searches in MEDLINE (OvidSP), Embase (OvidSP), PsycINFO (OvidSP), CINAHL (EBSCOhost), LILACs (Bireme), ClinicalTrials.gov, and the WHO Portal/ICTRP to ensure that the searches for this review are as comprehensive and up-to-date as possible. The search strategy that will be used for the retrieval of reports of trials from MEDLINE (via the OvidSP platform) can be seen in Appendix 1.
Furthermore, we will contact pharmaceutical companies that market antipsychotics and the investigators of included trials to request information on unpublished and additional trials. We will search relevant trial registers of pharmaceutical companies such as those listed in Section 6.2.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In addition, we will search regulatory agency sources (specifically FDA and EMA) for relevant clinical study reports following the recommendation made by Isojarvi 2018 and Schroll 2015.

Data collection and analysis

Selection of studies

After removing duplicates, two review authors will independently assess eligibility of studies identified by the search with the defined inclusion criteria. Both review authors will independently review full texts of each study deemed possibly relevant. We will use Covidence to facilitate the process. There will be no language restrictions. We will resolve disagreements in consensus discussions or consultation of a third review author. We will report reasons for exclusion in a 'Characteristics of excluded studies' table. We will report details of included studies in a 'Characteristics of included studies' table.
We will collate multiple reports of the same study including retraction statements and errata, and other unpublished key information. We will include a PRISMA flow chart in the full review showing the status of identified studies (Moher 2009), as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will include studies irrespective of whether measured outcome data are reported in a 'usable' way.

Data extraction and management

Two review authors will independently extract data using a prespecified data collection form that will be piloted before use. We will collect the following data from the main article and other data sources.

- General study characteristics: drug (and daily dose) tested, setting, type of dementia, number randomised, indication (agitation/psychosis).
- Outcomes: we will extract mean changes per treatment group for continuous outcomes and number of participants for binary outcome data, preferably for all randomised participants or otherwise for all participants available at endpoint assessment (we will report the number of participants at endpoint). If standard deviations (SDs) are not available, we will calculate them from reported data if possible.

Clinical response will be treated as a binary variable (present or not) and we will use the definition of the study authors. If response was not defined but measured with the Clinical Global Impression scale or a comparable instrument, we will use the categories 'improved' and 'no change (not worsened)'.
We will resolve any disagreements by discussion and consensus using Covidence. After reaching consensus, we will transfer data into Review Manager 5 (Review Manager 2014).

Assessment of risk of bias in included studies

We will assess risk of bias using the Cochrane 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors will independently assess and rate the methodological quality of the studies to identify any potential source of bias. We will assess risk of bias in

the following domains: randomisation, blinding of outcome assessors (detection bias), attrition/incomplete outcome data, protocol deviations (performance bias), and other sources (use of run-in period). We will categorise studies as having low, high, or unclear risk of bias. We will support our judgements with information from the available data sources. The judgements will be compared automatically so that discrepancies can be discussed and resolved using Covidence.

Measures of treatment effect

Where possible, we will express the treatment effect for each continuous outcome (change from baseline in psychosis or agitation) as pooled standardised mean differences (SMD) with 95% confidence intervals (CI). We will include validated measurement instruments for agitation and psychosis in these analyses and ensure that higher scores have the same meaning across instruments.
We will express the treatment effect of dichotomous outcomes as risk ratio (RR) with 95% CI. Where informative, we will perform meta-analyses to calculate the number needed to treat for an additional beneficial outcome (NNTB) or harmful outcome (NNTH) where appropriate based on pooled risk differences (RD).
We will report the SMDs, relative and absolute risks in a 'Summary of findings' table and perform statistical analysis using Review Manager 5 (Review Manager 2014). We will report the results of trials that did not report usable data for the meta-analysis qualitatively.

Unit of analysis issues

We will combine data from multiple active drug groups within a trial if they test the same drug (multiple dosages). If studies tested more than one drug, we will split the sample size for the control group as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will include cross-over studies using first-phase data only to rule out carry-over effects. In multi-arm studies, we will include antipsychotic and placebo groups only and will exclude groups treated with more than one drug in the same group or groups treated with other psychotropic drugs. We will include studies that have a run-in period before randomisation, even though some eligible participants, who met inclusion criteria for the study at the start of the run-in period, might have been excluded from participation at the end of the run-in period.

Dealing with missing data

Where possible, we will contact authors of the included studies to obtain any missing data. We will use data from intention-to-treat analyses if available. Otherwise, we will also include data from per-protocol analyses but perform sensitivity analyses to assess for their effect.

Assessment of heterogeneity

We will assess heterogeneity of the treatment effect between the trials with a Chi² statistic and conduct meta-analyses. We will use a fixed-effect model, unless the I^2 statistic is greater than 40%, in which case we will use a random-effects model. We will use Review Manager 5 to calculate statistical heterogeneity (Review Manager 2014).

Assessment of reporting biases

We will assess reporting bias with a funnel plot if at least 10 studies are available for meta-analysis.

Data synthesis

We will assess the effects of typical and atypical antipsychotics separately. When assessing adverse effects, we will pool data from studies which target agitation or psychosis. We will use Review Manager 5 to analyse the results of clinically and statistically homogeneous outcomes using a fixed-effect model except in cases of heterogeneity (see above; Review Manager 2014). If meta-analysis is not suitable because of heterogeneity or insufficient data, we will present a narrative synthesis. We will assess the quality of the evidence following the GRADE approach and rating the quality of evidence behind each result as high, moderate, low, or very low (Balshem 2011).

Subgroup analysis and investigation of heterogeneity

We will rerun all analyses including only haloperidol and risperidone studies, as these are the antipsychotics of first choice in many countries to date (2019). We will not perform subgroup analyses related to participant characteristics.

Sensitivity analysis

We will perform a sensitivity analysis and rerun the above analyses without trials that had at least one rating of high risk of bias with the Cochrane 'Risk of bias' tool. We will also perform a sensitivity analysis without trials that only report per-protocol analysis.

'Summary of findings' tables

We will assess the overall quality of the body of evidence for each outcome using the GRADE approach (Guyatt 2013a; Guyatt 2013b). We will present the results of the following outcomes in 'Summary of findings' tables.

- Agitation or psychosis in participants with agitation or psychosis.
- Adverse effects:
    - number of participants with somnolence;
    - number of participants with EPS;

- number of participants with any adverse event;
- number of participants with any SAE;
- number of deaths.

ACKNOWLEDGEMENTS

We are grateful for the support of the Cochrane Dementia and Cognitive Improvement Group. Also, we acknowledge the contribution to former versions of this protocol by T Hulshof, K Riemann-Lorenz, and E Wolschon, and the help of PhD students S Galama, MKA Almaghlouth, and C Smeets.

REFERENCES

Additional references

Almutairi 2018
Almutairi S, Masters K, Donyai P. The health professional experience of using antipsychotic medication for dementia in care homes: a study using grounded theory and focussing on inappropriate prescribing. *Journal of Psychiatric and Mental Health Nursing* 2018;**25**(5-6):307–18. [PUBMED: 29719932]

Arai 2016
Arai H, Nakamura Y, Taguchi M, Kobayashi H, Yamauchi K, Schneider LS. Mortality risk in current and new antipsychotic Alzheimer's disease users: large scale Japanese study. *Alzheimer's & Dementia* 2016;**12**(7):823–30. [PUBMED: 27106669]

Ballard 2005
Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. *BMJ (Clinical Research Ed.)* 2005;**330**(7496):874. [PUBMED: 15722369]

Ballard 2006
Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2006, Issue 1. DOI: 10.1002/14651858.CD003476.pub2; PUBMED: 16437455

Balshem 2011
Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(4):401–6. [PUBMED: 21208779]

Banerjee 2010
Banerjee S. The use of antipsychotic medication for people with dementia: time for action. A report, 2010. webarchive.nationalarchives.gov.uk/20130104175837/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_108302.pdf (accessed prior to 1 April 2019).

Borsje 2018
Borsje P, Lucassen PL, Wetzels RB, Pot AM, Koopmans RT. Neuropsychiatric symptoms and psychotropic drug use in patients with dementia in general practices. *Family Practice* 2018;**35**(1):22–8. [PUBMED: 28985387]

Cohen-Mansfield 1996
Cohen-Mansfield J. Conceptualization of agitation: results based on the Cohen-Mansfield Agitation Inventory and the Agitation Behavior Mapping Instrument. *International Psychogeriatrics / IPA* 1996;**8 Suppl 3**:309-15; discussion 351-4. [PUBMED: 9154580]

Covidence [Computer program]
Veritas Health Innovation. Covidence systematic review software. Melbourne (Australia): Veritas Health Innovation, 2013.

Cummings 2015
Cummings J, Mintzer J, Brodaty H, Sano M, Banerjee S, Devanand DP, et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. *International Psychogeriatrics / IPA* 2015;**27**(1):7–17. [PUBMED: 25311499]

EMA 2008
European Medicines Agency. Questions and answers on the review of the use of conventional antipsychotic medicines in elderly patients with dementia, 2008. www.ema.europa.eu/en/documents/other/questions-answers-review-use-conventional-antipsychotic-medicines-elderly-patients-dementia_en.pdf (accessed prior to 1 April 2019).

Furniss 1998
Furniss L, Craig SK, Burns A. Medication use in nursing homes for elderly people. *International Journal of Geriatric Psychiatry* 1998;**13**(7):433–9. [PUBMED: 9695030]

Gilley 1991
Gilley DW, Whalen ME, Wilson RS, Bennett DA. Hallucinations and associated factors in Alzheimer's disease.

Journal of Neuropsychiatry and Clinical Neurosciences 1991;**3** (4):371–6. [PUBMED: 1821255]

Guyatt 2013a

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables - binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158–72. [PUBMED: 22609141]

Guyatt 2013b

Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles - continuous outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):173–83. [PUBMED: 23116689]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. Chichester (UK): John Wiley & Sons.

Hughes 2008

Hughes R. Chemical restraint in nursing older people. *Nursing Older People* 2008;**20**(3):33-8; quiz 39. [PUBMED: 18500132]

Isojarvi 2018

Isojarvi J, Wood H, Lefebvre C, Glanville J. Challenges of identifying unpublished data from clinical trials: getting the best out of clinical trials registers and other novel sources.. *Research Synthesis Methods* 2018;**9**(4):561–78. [PUBMED: 29411948]

Janus 2016

Janus SI, van Manen JG, IJzerman MJ, Zuidema SU. Psychotropic drug prescriptions in Western European nursing homes. *International Psychogeriatrics / IPA* 2016;**28** (11):1775–90. [PUBMED: 27469071]

Janus 2017

Janus SI, van Manen JG, IJzerman MJ, Bisseling M, Drossaert CH, Zuidema SU. Determinants of the nurses' and nursing assistants' request for antipsychotics for people with dementia. *International Psychogeriatrics / IPA* 2017;**29** (3):475–84. [PUBMED: 27866485]

Kales 2007

Kales HC, Valenstein M, Kim HM, McCarthy JF, Ganoczy D, Cunningham F, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. *American Journal of Psychiatry* 2007;**164**(10): 1568-76; quiz 1623. [PUBMED: 17898349]

Kales 2012

Kales HC, Kim HM, Zivin K, Valenstein M, Seyfried LS, Chiang C, et al. Risk of mortality among individual antipsychotics in patients with dementia. *American Journal of Psychiatry* 2012;**169**(1):71–9. [PUBMED: 22193526]

Kirchner 2001

Kirchner V, Kelly CA, Harvey RJ. Thioridazine for dementia. *Cochrane Database of Systematic Reviews* 2001, Issue 3. DOI: 10.1002/14651858.CD000464; PUBMED: 11686961

Knol 2008

Knol W, van Marum RJ, Jansen PA, Souverein PC, Schobben AF, Egberts AC. Antipsychotic drug use and risk of pneumonia in elderly people. *Journal of the American Geriatrics Society* 2008;**56**(4):661–6. [PUBMED: 18266664]

Kuehn 2005

Kuehn BM. FDA warns antipsychotic drugs may be risky for elderly. JAMA 2005; Vol. 293, issue 20:2462. [PUBMED: 15914734]

Livingston 2014

Livingston G, Kelly L, Lewis-Holmes E, Baio G, Morris S, Patel N, et al. A systematic review of the clinical effectiveness and cost-effectiveness of sensory, psychological and behavioural interventions for managing agitation in older adults with dementia. *Health Technology Assessment (Winchester, England)* 2014;**18**(39):1-226, v-vi. [PUBMED: 24947468]

Livingston 2017

Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *Lancet* 2017;**390**(10113):2673–734. [PUBMED: 28735855]

Lonergan 2002

Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. *Cochrane Database of Systematic Reviews* 2002, Issue 2. DOI: 10.1002/ 14651858.CD002852; PUBMED: 12076456

Luijendijk 2016

Luijendijk HJ, de Bruin NC, Hulshof TA, Koolman X. Terminal illness and the increased mortality risk of conventional antipsychotics in observational studies: a systematic review. *Pharmacoepidemiology and Drug Safety* 2016;**25**(2):113–22. [PUBMED: 26601922]

MHRA 2009

Medicines and Healthcare products Regulatory Agency. Antipsychotics: use in elderly people with dementia. *Drug Safety Update* 2009;**2**(8):5–6.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006–12. [PUBMED: 19631508]

Morris 2015

Morris S, Patel N, Baio G, Kelly L, Lewis-Holmes E, Omar RZ, et al. Monetary costs of agitation in older adults with Alzheimer's disease in the UK: prospective cohort study. *BMJ Open* 2015;**5**(3):e007382. [PUBMED: 25770235]

Murray 2014

Murray PS, Kumar S, Demichele-Sweet MA, Sweet RA. Psychosis in Alzheimer's disease. *Biological Psychiatry* 2014; **75**(7):542–52. [PUBMED: 24103379]

Pierre 2005

Pierre JM. Extrapyramidal symptoms with atypical antipsychotics: incidence, prevention and management. *Drug Safety* 2005;**28**(3):191–208. [PUBMED: 15733025]

Renom-Guiteras 2018
Renom-Guiteras A, Thurmann PA, Miralles R, Klaassen-Mielke R, Thiem U, Stephan A, et al. Potentially inappropriate medication among people with dementia in eight European countries. *Age and Ageing* 2018;**47**(1): 68–74. [PUBMED: 28985257]

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Scarmeas 2005
Scarmeas N, Brandt J, Albert M, Hadjigeorgiou G, Papadimitriou A, Dubois B, et al. Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Archives of Neurology* 2005;**62**(10): 1601–8. [PUBMED: 16216946]

Schmidt 2012
Schmidt SG, Dichter MN, Palm R, Hasselhorn HM. Distress experienced by nurses in response to the challenging behaviour of residents - evidence from German nursing homes. *Journal of Clinical Nursing* 2012;**21**(21-22): 3134–42. [PUBMED: 23083388]

Schneider 2005
Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA* 2005;**294**(15):1934–43. [PUBMED: 16234500]

Schneider 2006
Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *New England Journal of Medicine* 2006;**355**(15):1525–38. [PUBMED: 17035647]

Schroll 2015
Schroll J, Bero L. Regulatory agencies hold the key to improving Cochrane Reviews of drugs. *Cochrane Database of Systematic Reviews (Online)* 2015;**4**:Art. No.: ED000098. DOI: 10.1002/14651858.ED000098

Tampi 2016
Tampi RR, Tampi DJ, Balachandran S, Srinivasan S. Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses. *Therapeutic Advances in Chronic Disease* 2016;**7**(5):229–45. [PUBMED: 27583123]

Testad 2010
Testad I, Ballard C, Bronnick K, Aarsland D. The effect of staff training on agitation and use of restraint in nursing home residents with dementia: a single-blind, randomized controlled trial. *Journal of Clinical Psychiatry* 2010;**71**(1): 80–6. [PUBMED: 20129008]

Toot 2017
Toot S, Swinson T, Devine M, Challis D, Orrell M. Causes of nursing home placement for older people with dementia: a systematic review and meta-analysis. *International Psychogeriatrics / IPA* 2017;**29**(2):195–208. [PUBMED: 27806743]

Van Leeuwen 2018
Van Leeuwen E, Petrovic M, van Driel ML, De Sutter AI, Vander Stichele R, Declercq T, et al. Withdrawal versus continuation of long-term antipsychotic drug use for behavioural and psychological symptoms in older people with dementia. *Cochrane Database of Systematic Reviews* 2018, Issue 3. DOI: 10.1002/14651858.CD007726.pub3; PUBMED: 29605970

Wetzels 2010
Wetzels RB, Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Determinants of quality of life in nursing home residents with dementia. *Dementia and Geriatric Cognitive Disorders* 2010;**29**(3):189–97. [PUBMED: 20215750]

WHO 2017
WHO Collaborating Centre for Drug Statistics Methodology. *ATC Classification Index with DDDs, 2018*. Oslo (Norway): World Health Organization, 2017.

Yohanna 2017
Yohanna D, Cifu AS. Antipsychotics to treat agitation or psychosis in patients with dementia. *JAMA* 2017;**318**(11): 1057–8. [PUBMED: 28975291]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Dementia/
2 Delirium/
3 Wernicke Encephalopathy/
4 Neurocognitive Disorders/
5 dement*.mp.
6 alzheimer*.mp.
7 (lewy* adj2 bod*).mp.
8 (chronic adj2 cerebrovascular).mp.
9 ("organic brain disease" or "organic brain syndrome").mp.
10 "benign senescent forgetfulness".mp.
11 (cerebr* adj2 deteriorat*).mp.
12 (cerebral* adj2 insufficient*).mp.
13 "major neurocognitive disorder".mp.
14 or/1-13
15 Antipsychotic Agents/
16 (antipsychotic* or neuroleptic*).ti,ab.
17 (neurolept* or antipsychotic* or Amisulpride* or Chormethiazole* or Clomethiazole* or Distraneurin* or Chlorpromazin* or Aminazine* or Chlorazine* or Chlordelazine* or Contomin* or Fenactil* or Largactil* or Propaphenin* or Thorazine* or Flupenthixol decanoate* or Emergil* or Fluanxol* or Flupentixol* or alphaFlupenthixol* or cisFlupenthixol* or Fluphenazin* or Fluphenazine decanoate* or Flufenazin* or Fluphenazine Hydrochloride* or Lyogen* or Prolixin* or Haloperidol* or Haldol* or Levomepromazin* or Levomeprazin* or Levopromazine* or Tisercin* or Tizercine* or Tizertsin* or Methotrimeprazine* or Loxapine* or Loxapinsuccinate* or Oxilapine* or Cloxazepine* or Loxapine Monohydrochloride* or Loxipine Maleate* or Loxipine Succinate* or Loxitane* or Asendin* or Desmethylloxapine* or Amoxapine* or Olanzapine* or Perphenazine* or Chlorpiprazine* or Perfenazine* or Trilafonor* or Pimozide* or Prothipendyl* or Quetiapine* or Fumarate* or Risperidone* or Risperidal* or Sulpiride* or Dogmatil* or Eglonyl* or Sulperide* or Thioridazine* or Meleril* or Mellaril* or Melleril* or Melleryl* or Sonapax* or Thioridazine Hydrochloride* or Tiaprid* or Tiapridal* or Trifluoperazine Hydrochloride* or Trifluoroperazine* or Triftazin* or Stelazine* or "Trifluperazine*or Tripfluoperazine Hydrochloride* or Cisordinol*" or Zuclopenthixol* or Clopenthixol* or Clozapine*or Melperone hydrochloride* or Ziprasidone* or Zotemine*).ti,ab.
18 PIMOZIDE/
19 PERPHENAZINE/
20 LOXAPINE/
21 METHOTRIMEPRAZINE/
22 HALOPERIDOL/
23 FLUPHENAZINE/
24 FLUPENTHIXOL/
25 CHLORPROMAZINE/
26 CHLORMETHIAZOLE/
27 CLOPENTHIXOL/
28 TRIFLUOPERAZINE/
29 THIORIDAZINE/
30 SULPIRIDE/
31 RISPERIDONE/
32 FUMARATES/
33 or/15-32
34 14 and 33
35 exp Psychotic Disorders/
36 Psychoses.ti,ab.
37 Psychosis.ti,ab.
38 exp VIOLENCE/

39 exp HOSTILITY/
40 exp Irritable Mood/
41 exp Impulsive Behavior/
42 exp Paranoid Behavior/
43 Agitat*.ti,ab.
44 aggress*.ti,ab.
45 violen*.ti,ab.
46 impuls*.ti,ab.
47 irritabl*.ti,ab.
48 hostil*.ti,ab.
49 anger.ti,ab.
50 angry.ti,ab.
51 anti-social.ti,ab.
52 impuls*.ti,ab.
53 Restless*.ti,ab.
54 or/35-53
55 34 and 54
56 randomized controlled trial.pt.
57 controlled clinical trial.pt.
58 randomized.ab.
59 placebo.ab.
60 drug therapy.fs.
61 randomly.ab.
62 trial.ab.
63 groups.ab.
64 or/56-63
65 exp animals/ not humans.sh.
66 64 not 65
67 55 and 66

CONTRIBUTIONS OF AUTHORS

VM: developing the main concept, reviewing relevant literature, and drafting the protocol.

HL: developing the main concept, reviewing relevant literature, and drafting the protocol.

MND: reviewing relevant literature and drafting the protocol.

RM: reviewing relevant literature and drafting the protocol.

SUZ: reviewing relevant literature and drafting the protocol.

SK: developing the main concept, reviewing relevant literature, and drafting the protocol.

DECLARATIONS OF INTEREST

VM: none known

HL: none known

MND: none known

RM: none known

SUZ: none nknown

SK: none known

SOURCES OF SUPPORT

Internal sources

- University of Lübeck, Germany.

External sources

- NIHR, UK.

This protocol was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Dementia and Cognitive Improvement group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health