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Cochrane Database of Systematic Reviews 2022, Issue 12. Art. No.: CD015405.
DOI: [10.1002/14651858.CD015405](https://doi.org/10.1002/14651858.CD015405).

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[Intervention Protocol]

Anticholinergic deprescribing interventions for reducing risk of cognitive decline or dementia in older adults with and without prior cognitive impairment

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Editorial group: Cochrane Dementia and Cognitive Improvement Group.

Publication status and date: New, published in Issue 12, 2022.

Citation: Taylor-Rowan M, Alharthi AA, Noel-Storr AH, Myint PK, Stewart C, McCleery J, Quinn TJ. Anticholinergic deprescribing interventions for reducing risk of cognitive decline or dementia in older adults with and without prior cognitive impairment (Protocol). *Cochrane Database of Systematic Reviews* 2022, Issue 12. Art. No.: CD015405. DOI: [10.1002/14651858.CD015405](https://doi.org/10.1002/14651858.CD015405).

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ABSTRACT

Objectives

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

Primary objective

- To assess the efficacy and safety of anticholinergic medication reduction interventions to improve cognitive outcomes in both cognitively healthy older adults and older adults with pre-existing cognitive issues.

Secondary objectives

- To compare the effectiveness of different types of reduction interventions (e.g. pharmacist-led versus GP-led; educational versus audit and feedback) in reducing overall anticholinergic burden.
- To establish optimal duration of anticholinergic reduction interventions; sustainability, and lessons learned for upscaling
- To compare results according to differing anticholinergic scales used in medication reduction intervention trials.
- To assess the efficacy of anticholinergic medication reduction interventions to improve other clinical outcomes, including mortality, quality of life, clinical global impression, physical function, institutionalisation, falls, cardiovascular diseases, and neurobehavioral outcomes in people with pre-existing cognitive impairment.

BACKGROUND

Description of the condition

Cognition (or cognitive function) is the mental process of acquiring and manipulating knowledge and understanding through experience, senses, and thought. It includes the domains of memory, language, attention, executive functioning, and visuospatial processing. Cognitive impairment is the disruption of functioning of any one of these domains. Cognitive function may be assessed in detail using a battery of neuropsychological tests covering multiple domains; although in clinical practice, brief assessment tools such as the Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) are often used (Folstein 1975; Nasreddine 2005).

Dementia is a syndrome of decline in cognitive function beyond that expected from normal ageing and to an extent that interferes with usual functioning. It may affect memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. There are a variety of internationally accepted diagnostic criteria for dementia. The most widely used are included in the World Health Organization (WHO) International Classification of Diseases (ICD) (WHO 1993), and the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM). The most recent iteration of the DSM refers to "major neurocognitive disorder" instead of dementia (DSM 5).

The labels of 'dementia' or 'major neurocognitive disorder' encompass a variety of pathologies, with specific diagnostic criteria also available for pathologically defined dementia subtypes, such as the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for dementia due to Alzheimer's disease (McKhann 1984; McKhann 2011); McKeith criteria for Lewy body dementia (McKeith 2005); Lund criteria for frontotemporal dementias (McKhann 2001); and the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia (Román 1993).

An individual may experience a decline in cognition that is not enough to merit a label of dementia, but that is more than would be expected as part of ageing. An objective cognitive impairment that is not severe enough to have a significant impact on daily activities is referred to as a mild cognitive impairment (MCI). This is a risk factor for future dementia as one in five people with MCI may go on to develop dementia within five years (Petersen 2001).

Dementia is a major public health issue. There are currently more than 40 million people worldwide with dementia due to Alzheimer's disease – the most common subtype – and this number is projected to increase to more than 100 million by 2050 (Prince 2016). As cognitive functioning declines, people's ability to live independently also decreases. This in turn increases caregiver burden, healthcare support requirements, and institutionalisation.

Description of the intervention

Anticholinergics are medications which block the action of acetylcholine in the central and or peripheral nervous system. Sometimes this is the main mechanism of action of the medication (e.g. treatments for overactive bladder) and sometimes it is an

incidental effect which is not thought to be essential for the therapeutic action of the drug (e.g. some antidepressants). Many medications which are commonly prescribed to older adults are anticholinergic to a greater or lesser extent. Observational evidence has shown a consistent association between use of anticholinergic medications and development of cognitive decline or dementia in cognitively healthy older adults (Taylor-Rowan 2021). Moreover, there is evidence that anticholinergics may increase risk of poor outcomes, such as mortality, in older adults with pre-existing cognitive problems (Taylor-Rowan 2022). Recent dementia guidelines now recommend reviewing anticholinergic burden in older adults (NICE 2021). There is therefore increasing interest in interventions that seek to reduce prescriptions of anticholinergic medications to improve cognitive and clinical outcomes in older adults. Anticholinergic reduction interventions seek to reduce a person's anticholinergic burden by deprescribing commonly used anticholinergic medications. Deprescribing can include partial or complete removal of anticholinergic burden depending upon the types of anticholinergic medications a person is taking.

How the intervention might work

Previous studies have demonstrated that anticholinergic burden can be effectively reduced (Nakham 2020). There are a number of different methods to reduce anticholinergic medications ranging from audit, audit and feedback, education, and expert prescriber approaches (i.e. people with the skills and knowledge to make decisions on prescriptions - this is not just people from a medical background and would include pharmacists and other prescribers). Sources by which potentially inappropriate medications are identified also differ between studies: some employ clinical interviews and check medication appropriateness against STOPP (Screening Tool of Older Persons' Prescriptions)/START (Screening Tool to Alert to Right Treatment) criteria, whereas others rely on note-based medication reviews. Moreover, the type of professional employed to lead the drug reduction intervention typically varies: pharmacists are the most commonly appointed professionals, but some studies have used GPs or secondary care physicians. (Nakham 2020).

There are various mechanisms by which anticholinergics could interfere with cognitive outcomes. Anticholinergics block the binding of acetylcholine to cholinergic receptors in the brain and the peripheral nervous system. Acetylcholine is a neurotransmitter that plays a major role in numerous functions of the nervous system. In the brain, these include learning and memory. Via disruption to the cholinergic system, along with potential inflammatory (Sanghavi 2022), or vascular pathways (Singh 2013), anticholinergic drugs are hypothesised to cause disruption to short and long-term cognitive functioning, with greater anticholinergic burden causing greater disruption.

There are also reasons to believe that anticholinergics may increase risk of specific types of cognitive impairment or dementia. For instance, the cholinergic hypothesis proposes that the pathology and cognitive deterioration seen in Alzheimer's disease may be significantly influenced by a disruption of cholinergic neurotransmission (Francis 1999); hence, prolonged use of anticholinergics may be more likely to induce Alzheimer's disease. On the other hand, anticholinergics have also been associated with cerebral vascular dysregulation (Marzoughi 2021);

thus, the risk of vascular dementia may be particularly heightened by the use of anticholinergics.

Anticholinergics may also exacerbate issues in established disease. The current strategy to treat Alzheimer's disease, for instance, is based on restoration of cholinergic function (Hampel 2018). This is primarily done via cholinesterase inhibitors; however, anticholinergics are often taken concurrently by people on cholinesterase inhibitors (Carnahan 2004), which is antagonistic to cholinergic restoration treatments. Moreover, heightened risk of cardiovascular issues, including stroke (Tan 2018), after taking anticholinergics may indirectly increase rates of cognitive deterioration in people with pre-existing dementia.

Evidence from interventions that promote cholinergic function suggests disease modifying effects may be possible, including reductions in degree of long-term cortical thinning as well as hippocampal atrophy (Hampel 2018). Reducing the prescription of anticholinergics could therefore reduce the risk of developing long-term cognitive problems in older adults, or reduce rate of cognitive decline in older adults with pre-existing neurodegenerative diseases.

Measures of anticholinergic burden

Anticholinergic burden can be measured using a variety of approaches. There is no consensus on which anticholinergic burden measure provides the most accurate and clinically useful information to guide anticholinergic burden reduction. Generally, anticholinergic burden measures assign a score to certain individual medications before a cumulative total based on all prescribed medications is calculated. Although these measures should be similar, overlap is limited; they include differing medications and assign differing scores to these medications. Methodologies for developing scales vary significantly. Where some are designed to measure both central and peripheral anticholinergic effects, others focus on serum radioreceptor anticholinergic activity assay or muscarinic receptor affinity measurements and may only capture peripheral anticholinergic effects. Consequently, variation in the anticholinergic measurement scale used to help reduce anticholinergic medications may lead to differing impacts on clinical outcomes (Hanlon 2020). Therefore, any intervention review should be completed at the level of the individual scale in addition to creating summary estimates for all anticholinergic burden measures coalesced. Evaluation at the individual scale level will provide clinically applicable information on the ability of respective anticholinergic burden scales to successfully guide reduction of prescribed anticholinergic medications and improve clinical outcomes, while a coalesced estimate will provide greater statistical power and precision.

Why it is important to do this review

This review is intended to serve as a companion to two recently published Cochrane Prognostic Factor Reviews on anticholinergic burden and the risk of cognitive decline or dementia (Taylor-Rowan 2021; Taylor-Rowan 2022). As associations between anticholinergic burden and cognitive decline have been regularly reported (Taylor-Rowan 2021), interventions that aim to reduce anticholinergic burden are hypothesised to reduce future risk of cognitive decline or dementia. However, it is currently unclear if the anticholinergic properties of these medications are truly the mechanism behind

the apparent association. Our previous reviews highlighted the considerable risk of confounding and prodromal bias that exists within the observational literature. Consequently, we do not know if reducing prescriptions of these medications will truly have any clinical benefit on cognitive and other clinical outcomes. In this review, we aim to evaluate the interventional evidence of reducing anticholinergic burden and the subsequent impact of these interventions on cognition and other related clinical outcomes.

OBJECTIVES

Primary objective

- To assess the efficacy and safety of anticholinergic medication reduction interventions to improve cognitive outcomes in both cognitively healthy older adults and older adults with pre-existing cognitive issues.

Secondary objectives

- To compare the effectiveness of different types of reduction interventions (e.g. pharmacist-led versus GP-led; educational versus audit and feedback) in reducing overall anticholinergic burden.
- To establish optimal duration of anticholinergic reduction interventions; sustainability, and lessons learned for upscaling
- To compare results according to differing anticholinergic scales used in medication reduction intervention trials.
- To assess the efficacy of anticholinergic medication reduction interventions to improve other clinical outcomes, including mortality, quality of life, clinical global impression, physical function, institutionalisation, falls, cardiovascular diseases, and neurobehavioral outcomes in people with pre-existing cognitive impairment.

METHODS

Criteria for considering studies for this review

Types of studies

Initial scoping of the literature suggests a mix of randomised and non-randomised evidence describing anticholinergic reduction. As it is feasible to perform randomised controlled trials (RCTs) to address our study question, and they provide the highest-quality evidence, we will include RCTs only. As we are interested in the decline of overall anticholinergic burden, we will not include studies that seek to reduce only a single, specific anticholinergic drug. We will not include non-randomised or case-control intervention studies.

Types of participants

We will include studies that recruited older adults (defined as sample population mean age ≥ 50 years). We will include studies whose participants were either cognitively healthy before the intervention or had pre-existing cognitive problems, but we will evaluate these two populations separately. We will include studies conducted in specific patient subgroups, such as those with Parkinson's disease, schizophrenia, or stroke, provided they meet our other inclusion criteria.

We will include studies conducted in all healthcare settings. Studies conducted in differing settings (e.g. care-home versus primary care) may differ in important population demographics (e.g. mean age, dementia severity, clinical or lifestyle factors) that could alter the strength of the association between anticholinergic burden reduction and cognitive outcomes.

Types of interventions

We will include interventions to reduce prescription of anticholinergic medications (reduce anticholinergic burden). This could involve complete cessation of a certain drug or drugs, or a reduction of dose frequency or number of a drug. Where possible, we will compare reduction interventions versus complete cessation of anticholinergic interventions separately. We will not impose any restrictions on the duration of the intervention. We will accept any recognised anticholinergic burden measurement scale that is used to measure degree of anticholinergic medication reduction within the trial. Some interventions may be unsuccessful at reducing anticholinergic burden. We will consider the success of the intervention when exploring reasons for heterogeneity of results.

The control arm of the studies will be no intervention intended to reduce anticholinergic medication (treatment as usual).

Types of outcome measures

Primary outcomes

- Cognitive decline (i.e. change on a measure of cognitive function measured with a validated multi-domain instrument or neuropsychological test battery or composite derived from scores in two or more cognitive domains). We will not include outcomes of change on a single cognitive domain (e.g. memory only)
- Incidence of clinical dementia diagnosed according to DSM or ICD criteria
- Adverse effects of anticholinergic de-prescribing interventions

Secondary outcomes

We will also investigate the following outcomes.

- Change in anticholinergic burden
- Clinical global impression (CGI)
- Neuropsychiatric disturbances
- Mortality
- Functional impairment
- Falls
- Cardiovascular diseases
- Quality of life
- Institutionalisation
- Proportion of people that remain on reduced anticholinergic medications

However, we will not run a specific search to look for these additional outcomes.

Timing of outcomes

We will not impose any restrictions on the timing of outcome assessments. We anticipate that studies will vary by timescale

evaluated. We will pool last outcome measured for the following timescales.

- 0 to 3 months
- Greater than 3 months to 12 months
- Greater than 12 months to 2 years
- Greater than 2 years

Search methods for identification of studies

We will adopt a search that combines our topic of interest (anticholinergic burden) with the outcome of interest (cognitive decline or dementia).

Electronic searches

We will search the following databases ([Appendix 1](#)):

- MEDLINE (1946 to present; OvidSP)
- Embase (1974 to present; OvidSP)
- PsycINFO (1806 to present; OvidSP)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature; 1950 to present; EBSCOhost)
- ISI Web of Science Core Collection (1928 to present; ISI Web of Science)

We will apply no language restrictions.

Searching other resources

We will supplement our search by checking references of relevant reviews and related studies.

Data collection and analysis

Selection of studies

We will use [Covidence](#) systematic review software to identify relevant studies. The review group Information Specialist will perform a 'first pass' screen to remove clearly irrelevant titles.

Two review authors (MT, AA) will independently screen studies identified via our search method. Titles and abstracts will be screened in the first instance, with the full text of potentially relevant studies then accessed to determine if the study meets our inclusion criteria. In cases of disagreement, a third review author (TQ) will act as arbiter and make the final decision on study inclusion and exclusion.

Data extraction and management

Two review authors (MT, AA) will independently extract the data to a piloted proforma based on the CDPL (Cochrane Developmental, Psychosocial and Learning Problems) RCT-only template. We will contact study authors for missing data where required. We will select two studies to trial our data extraction proforma ([Kersten 2012](#); [Van der Meer 2018](#)). We will extract all data onto a standard form ([Appendix 2](#)).

For each outcome of interest, we will extract odds ratios (OR), hazard ratios (HR) and standardised mean differences (SMD) data, where available.

We will also evaluate quality of reporting of interventions in respective studies using the TIDieR checklist ([Hoffmann 2014](#)).

Planned comparisons

Where possible, we plan the following comparisons.

- Reduction in total anticholinergic burden versus no intervention (treatment as usual)
- Cessation of anticholinergic medications versus no intervention (treatment as usual)

Assessment of risk of bias in included studies

Two review authors (MT, AA) will independently use the Risk of bias (RoB) 2 tool (Sterne 2019), assessing the included studies across the domains of: selection bias; performance bias; detection bias; attrition bias; reporting bias; and 'other' bias. For cluster-RCTs, we will use the variant of the RoB 2 tool designed specifically for such studies. We will use anchoring statements for each category to suit our review topic based on consensus within the review author team.

We will judge each domain as low risk of bias, some concerns, or high risk of bias (Appendix 3). In cases of uncertainty, we will contact original study authors for clarification, where possible.

Measures of treatment effect

Dichotomous data

We will evaluate dichotomous outcomes, such as incident dementia, by calculating risk ratios (RR) and 95% confidence intervals (CIs).

Continuous data

We anticipate that most continuous outcomes will be measured on a number of different cognitive scales. We will therefore use the standardised mean difference (SMD) for the estimated effect, wherever possible. We will use mean difference (MD) to estimate effect for outcomes measured on a single scale. When interpreting size of SMD effects, we will follow guidance set out by the *Cochrane Handbook for Systematic Reviews of Interventions*; an effect size of less than or equal to 0.2 will be viewed as a small effect, 0.5 to 0.79 a moderate effect, and 0.8 or greater than, a large effect (Higgins 2022a). Where available, we will look at the mean difference in anticholinergic burden at different time points throughout the study follow-up. We will also look at the proportion of people who restart anticholinergic medications or, if provided, the mean difference of the proportion of people who restart anticholinergic medications in the intervention and control groups.

Unit of analysis issues

Cluster-RCTs

We anticipate that some eligible studies may use cluster randomisation. We will seek to extract from the primary studies measures of treatment effect from analyses which have properly accounted for the cluster design. If these are not available, but a study reports an intra-cluster correlation coefficient (ICC), or we can obtain a reasonable estimate of ICC from a similar study, then we will use these to adjust the effective sample size as described in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b). If this is not possible, then we will consider that the precision of the effect estimate is likely to be exaggerated and will exclude such studies in sensitivity analyses in order to investigate any impact on conclusions.

Dealing with missing data

We will contact study authors to obtain missing data where necessary. We will report any imputation methods used by study authors and consider these as possible subjects for sensitivity analyses.

Assessment of heterogeneity

We will assess the proportion of statistical heterogeneity caused by between-study heterogeneity using the I^2 statistic (Deeks 2022), guided by conventional 'rules of thumb' for high (75%), moderate (50%), and low (25%) levels of heterogeneity.

Assessment of reporting biases

We will assess study reporting bias as a part of our risk of bias assessment. We will view all study protocols and compare planned analyses with reported analyses to identify inconsistencies. If our search identifies protocols of unpublished studies, we will contact study authors to determine status. If we have sufficient relevant studies (more than 10) we will plot the studies on a funnel plot and visually inspect for asymmetry.

Data synthesis

Where sufficient data are available, we will evaluate comparative risk of cognitive decline or dementia between the intervention and control arms. We will also evaluate intervention success in reducing overall anticholinergic burden. Where possible, we will pool summary estimates for intervention effectiveness at the level of individual scales and, as an exploratory analysis, pool summary estimates across all scales.

We will calculate MDs for single-scale analyses and SMDs for across-scales-analyses involving linear data. We will pool MD and SMD data separately from dichotomous outcome data (dichotomous outcome data will be pooled via RR). We will use a fixed-effect or random-effects approach depending on the level of heterogeneity between studies. We will use Comprehensive Meta-Analysis software to conduct all meta-analyses (Comprehensive Meta-Analysis Version 3).

Subgroup analysis and investigation of heterogeneity

In studies involving older adults with pre-existing cognitive issues, we will evaluate the influence of:

- Severity of impairment
- Type of dementia

In studies involving cognitively healthy older adults at baseline, we will investigate the effect of:

- Duration of anticholinergic use prior to intervention

For both populations, we will additionally investigate effects of:

- Age (< 75 years versus \geq 75 years)
- Sex
- Nature of intervention (e.g. audit versus education; GP-led versus pharmacist-led)
- Duration of follow-up
- Magnitude and persistence of change in the anticholinergic burden score after intervention

- Setting (e.g. community versus secondary care)
- Condition-specific subgroups (e.g. stroke; schizophrenia)

Each variable will be evaluated via meta-regression. However, we will only investigate respective outcomes if at least 10 studies are available with relevant data.

Sensitivity analysis

We will conduct a sensitivity analysis including only studies which were at low risk of bias in all domains.

We will conduct a sensitivity analysis excluding any cluster-RCTs for which it was not possible to extract or derive a treatment effect estimate correctly adjusted for clustering.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach to evaluate our overall confidence in the results. Two review authors (MT, AA) will independently rate the GRADE evidence and disagreements will be arbitrated by a third review author (TQ).

We will evaluate reported evidence in the following areas.

• **Risk of bias:** we will use the previously described RoB 2 tool to evaluate the overall risk of bias of included studies. Our GRADE judgement of certainty will be based upon the overall certainty of the evidence. That is, if most (> 50%) included studies are considered at high risk of bias we will consider this to be a 'very serious' limitation, and downgrade by two levels.

• **Inconsistency of results:** we will downgrade the evidence if the effect of anticholinergic reduction interventions on long-term cognition are heterogeneous (i.e. estimates of effect are variable across studies with regard to showing beneficial or detrimental effects and their CIs show minimal or no overlap); if the P value is

low for the test of the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect; or there is substantial ($I^2 > 50\%$) heterogeneity based upon the I^2 statistic (Higgins 2003).

• **Indirectness of evidence:** we will downgrade studies where their investigation does not fully match with our broader review question. Specifically, if the intervention reduces more than just the anticholinergic burden (such as also reducing sedatives via the Drug Burden Index (DBI) scale) we will downgrade for indirectness.

• **Imprecision of results:** we will downgrade if there are insufficient numbers to meet the optimal information size in the meta-analysis (i.e. if the total number of participants included is less than the number of participants generated by a conventional sample size calculation for a single adequately powered study), or if the CIs fail to exclude important benefit or important harm.

• **Publication bias:** we will downgrade evidence if there is evidence of publication bias from a funnel plot or if there are registered protocols of unpublished studies that are not still ongoing.

• **Dose effect:** we will upgrade evidence if there is evidence that larger reductions in anticholinergic burden are linearly associated with better cognitive scores.

We will use GRADEpro software to conduct the GRADE evaluation process (GRADEpro GDT). The summary of findings table will compare anticholinergic reduction intervention versus no anticholinergic reduction intervention for our primary outcome (cognitive decline or dementia) only.

ACKNOWLEDGEMENTS

We would like to thank peer reviewers Roy Soiza and Edwin Tan and consumer reviewer Cathie Hofstetter for their comments and feedback

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APPENDICES

Appendix 1. Sources and search strategy

Source	Search strategy
MEDLINE In-process and other non-indexed citations and MEDLINE (OvidSP) from 1946	1. cholinergic antag*.ti,ab. 2. anticholinergic*.ti,ab. 3. anti-cholinergic*.ti,ab. 4. cholinergic Antagonists/tu 5. Cholinergic Antagonists/ae 6. AAS.ti,ab. 7. ACB.ti,ab. 8. ADS.ti,ab. 9. DAPs.ti,ab. 10. ARS.ti,ab. 11. DBI-ACh.ti,ab. 12. SAMS.ti,ab. 13. ("chew* score" or "chew* list").ti,ab. 14. ("han's score" or "han score").ti,ab. 15. or/1-14 16. Cognition/ 17. Cognition Disorders/ 18. Dementia/ 19. cognit*.ti,ab. 20. dement*.ti,ab. 21. alzheimer*.ti,ab. 22. "lewy bod*".ti,ab. 23. FTLD.ti,ab. 24. PDD.ti,ab. 25. "executive function*".ti,ab. 26. Attention/ 27. (speed adj2 processing).ti,ab. 28. memory.ti,ab. 29. Memory Disorders/ 30. "episodic memory".ti,ab. 31. Memory, Episodic/ 32. MCI.ti,ab. 33. Mild Cognitive Impairment/

(Continued)

34. (nMCI or aMCI or mMCI or MCIa).ti,ab.
35. AAMI.ti,ab.
36. ACMI.ti,ab.
37. ARCD.ti,ab.
38. CIND.ti,ab.
39. VCI.ti,ab.
40. VAD.ti,ab.
41. major neurocognitive disorder*.ti,ab.
42. minor neurocognitive disorder*.ti,ab.
43. neurocognitive dysfunction.ti,ab.
44. Neurocognitive Disorders/
45. or/16-44
46. 15 and 45

Embase (OvidSP) from 1974

1. cholinergic antag*.ti,ab.
2. anticholinergic*.ti,ab.
3. anti-cholinergic*.ti,ab.
4. *cholinergic receptor blocking agent/
5. AAS.ti,ab.
6. ACB.ti,ab.
7. ADS.ti,ab.
8. DAPs.ti,ab.
9. ARS.ti,ab.
10. DBI-ACh.ti,ab.
11. SAMS.ti,ab.
12. ("chew* score" or "chew* list").ti,ab.
13. ("han's score" or "han score").ti,ab.
14. or/1-13
15. Cognition/
16. Cognition Disorders/
17. Dementia/
18. cognit*.ti,ab.
19. dement*.ti,ab.
20. alzheimer*.ti,ab.
21. "lewy bod*".ti,ab.

(Continued)

22. FTLD.ti,ab.
23. PDD.ti,ab.
24. "executive function*".ti,ab.
25. Attention/
26. (speed adj2 processing).ti,ab.
27. memory.ti,ab.
28. Memory Disorders/
29. "episodic memory".ti,ab.
30. Memory, Episodic/ 31. MCI.ti,ab.
31. MCI.ti,ab.
32. Mild Cognitive Impairment/
33. (nMCI or aMCI or mMCI or MCIa).ti,ab.
34. AAMI.ti,ab.
35. ACMI.ti,ab.
36. ARCD.ti,ab.
37. CIND.ti,ab.
38. VCI.ti,ab.
39. VAD.ti,ab.
40. major neurocognitive disorder*.ti,ab.
41. minor neurocognitive disorder*.ti,ab.
42. neurocognitive dysfunction.ti,ab.
43. Neurocognitive Disorders/
44. or/15-43
45. 14 and 44

PsycINFO (OvidSP) from 1806

1. cholinergic antag*.ti,ab.
2. anticholinergic*.ti,ab.
3. anti-cholinergic*.ti,ab.
4. exp Cholinergic Receptors/
5. AAS.ti,ab.
6. ACB.ti,ab.
7. ADS.ti,ab.
8. DAPs.ti,ab.
9. ARS.ti,ab.
10. DBI-ACh.ti,ab.

(Continued)

11. SAMS.ti,ab.
12. ("chew* score" or "chew* list").ti,ab.
13. ("han's score" or "han score").ti,ab.
14. or/1-13
15. exp Cognition/
16. exp Dementia/
17. cognit*.ti,ab.
18. dement*.ti,ab.
19. alzheimer*.ti,ab.
20. "lewy bod*".ti,ab.
21. FTLT.ti,ab.
22. PDD.ti,ab.
23. "executive function*".ti,ab.
24. exp Attention/
25. (speed adj2 processing).ti,ab.
26. memory.ti,ab.
27. exp Memory Disorders/
28. "episodic memory".ti,ab.
29. exp Episodic Memory/
30. exp Cognitive Impairment/
31. MCI.ti,ab.
32. exp Cognitive Assessment/
33. (nMCI or aMCI or mMCI or MCIa).ti,ab.
34. AAMI.ti,ab.
35. ACMI.ti,ab.
36. ARCD.ti,ab.
37. CIND.ti,ab.
38. VCI.ti,ab.
39. VAD.ti,ab.
40. major neurocognitive disorder*.ti,ab.
41. minor neurocognitive disorder*.ti,ab.
42. neurocognitive dysfunction.ti,ab.
43. exp Neurocognitive Disorders/
44. or/15-43

(Continued)

45. 14 and 44

CINAHL (EBSCOhost)	S1 TX cholinergic antag* S2 TX anticholinergic* S3 TX anti-cholinergic* S4 (MH "Cholinergic Antagonists+") S5 TX AAS S6 TX ACB S7 TX ADS S8 TX DAPs S9 TX ARS S10 TX DBI-ACh S11 TX SAMS S12 TX "chew* score" or "chew* list" S13 TX "han's score" or "han score" S14 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 S15 (MH "Cognition+") S16 (MH "Cognition Disorders+") S17 (MH "Dementia+") S18 TX cognit* S19 TX dement* S20 TX alzheimer* S21 TX "lewy bod**" S22 TX FTLD S23 TX PDD S24 TX "executive function**" S25 (MH "Attention") S26 TX speed AND processing S27 TX memory S28 (MH "Memory Disorders") S29 TX "episodic memory" S30 (MH "Memory Disorders") OR (MH "Memory") S31 TX MCI S32 "Mild Cognitive Impairment" S33 TX nMCI or aMCI or mMCI or MCIa
--------------------	--

(Continued)

S34 TX AAMI

S35 TX ACMI

S36 TX ARCD

S37 TX CIND

S38 TX VCI

S39 TX VAD

S40 TX major neurocognitive disorder*

S41 TX minor neurocognitive disorder*

S42 TX neurocognitive dysfunction

S43 "Neurocognitive Disorders"

S44 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 S45 S14 AND S44

Web of Science core collection TOPIC: ("cholinergic antag*" OR anticholinergic* OR "anti-cholinergic*" OR AAS OR ACB OR ADS OR DAPs OR ARS OR "DBI-ACh" OR SAMS OR "chew* score" OR "chew* list" OR "hands score" OR "hans score" OR "han score") AND TOPIC: (cognit* OR dement* OR alzheimer* OR "lewy bod*" OR FTLD OR PDD OR "executive function*" OR attention OR memory OR MCI OR "major neurocognitive disorder*" OR "minor neurocognitive disorder*") Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.

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Appendix 2. Contents of Proforma

	Description	Location in text
Population description	(from which study participants are drawn; Age restricted?)	
Setting (care home, community etc)		
Inclusion criteria		
Exclusion criteria		
Sample size		
Method of recruitment of participants	(e.g. phone, mail, clinic patients)	
Type of intervention (education versus audit and feedback etc;		

(Continued)

who led? i.e. GP versus pharmacist etc)

Details of intervention (e.g. scale used to identify drugs;

degree of decline in anticholinergic burden;

duration of intervention;

specific drugs reduced; mode of delivery)

Duration of anticholinergic drug use before intervention (if reported)

Informed consent obtained

Total no. randomised (or total pop. at start of study for non-RCTs)

Clusters (if applicable, no., type, no. people per cluster)

Degree of cross-over

(i.e. change from control to intervention group despite allocation)

Baseline imbalances

Duration of follow-up

Withdrawals and exclusions (if not provided below by outcome)

Age

Sex

Race/ethnicity

Severity of illness

Co-morbidities

Other relevant sociodemographics

Subgroups measured

Subgroups reported

Outcome measure(s)

Outcome data (N event/N total for intervention and control; OR/HR etc)

Notes:

Appendix 3. ROB-2 anchoring statements

Random sequence generation: we will assess the allocation sequence used. If it is possible for the next allocation to be predicted we will assign a high risk of bias. Similarly, we will evaluate the balance of prognostic factors in each group. If groups are unbalanced beyond what would be expected by chance we will assign a high or uncertain risk of bias, depending upon degree of imbalance.

Allocation concealment: allocation concealment is likely to be challenging for most trials due the requirement for medical practitioners to know who is in the intervention group such that anticholinergic medication can be reduced. We will therefore rate trials as being at 'uncertain' risk of bias if it is necessary to the trial's design that paractioners be made aware of the allocation of the participant.

Blinding of participants and personnel: blinding of participants to intervention or control is also likely to be challenging in most trials. We will evaluate the impact of lack of blinding based upon the extent of deviations from allocation. If deviation is large, we will assign a high risk of bias.

Blinding of outcome assessment: the impact of blinding will likely vary by outcome assessment. We will assign a high risk of bias if no blinding to outcome assessment was performed for any subjective outcome assessments, such as self report questionnaires, or if aspects of cognitive assessments require assessor interpretation (e.g. clock draw).

Incomplete outcome data: we will assess the extent of missing data and the impact this is likely to have on the outcome. We will apply the following rule of thumb to evaluate extent of missing data: 5% missing data will be considered small; > 20% will be considered large. Judgement of overall risk of bias will consider both the proportion of missing data in respective groups and the methods used to deal with missing data (i.e. imputation versus complete data analysis only). If missing data is considerable and/or deemed to be a product of important study features that could systematically influence the outcome assessed, we will assign a high risk of bias.

Selective outcome reporting: we will evaluate study protocols to establish risk of bias in outcome reporting. If any study outcomes are omitted, we will assign a high risk of bias. If no study protocol is provided, we will assign an uncertain risk of bias.

CONTRIBUTIONS OF AUTHORS

MT drafted the protocol manuscript. AN-S will conduct the search. MT and AA will perform the study screening, data extraction, risk of bias assessment and GRADE evaluation. All authors contributed to intellectual output and writing.

DECLARATIONS OF INTEREST

MT: none

AA: none

TQ: none

JM: none

CS: none

PM: none

AA:none

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- NIHR, UK

This protocol was supported by the National Institute for Health and Care 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.