Anticholinergic burden for prediction of cognitive decline or neuropsychiatric symptoms in older adults with mild cognitive impairment or dementia (Protocol)

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[Prognosis Protocol]

Anticholinergic burden for prediction of cognitive decline or neuropsychiatric symptoms in older adults with mild cognitive impairment or dementia

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A B S T R A C T

Objectives

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

Primary objective

- To assess whether anticholinergic burden, as defined at the level of each individual scale, is a prognostic factor for further cognitive decline or neuropsychiatric disturbances in people with mild cognitive impairment (MCI) or dementia.

Secondary objective

- To compare the prognostic validity of different anticholinergic burden scales.
- To examine the effect of type of dementia and severity of dementia on the association between anticholinergic burden and rate of cognitive decline or neuropsychiatric disturbances.
- To examine the effect of setting (care home versus non-care home) on the association between anticholinergic burden and rate of cognitive decline or neuropsychiatric disturbances.
- To examine whether anticholinergic burden is a prognostic factor for other clinical outcomes in people with MCI or dementia

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BACKGROUND

Description of the condition

Cognition (or cognitive function) is the mental process of acquiring 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 of which are included in the World Health Organization International Classification of Diseases (ICD) and the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM). The most recent iteration of the DSM (DSM-5) refers to 'major neurocognitive disorder' instead of dementia.

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 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 care-giver burden, healthcare support requirements, and institutionalisation. In addition, neuropsychiatric disturbances are a common consequence of declining cognition. Up to 90% of people with Alzheimer's disease experience neuropsychiatric symptoms such as mood disturbance, depression, agitation, anxiety, sleep disorder, psychosis, hallucinations, and delusions (Steinberg 2008).

Occurrence of neuropsychiatric disturbances are the most frequent complication of dementia that require hospitalisation, accounting for 49.4% of admissions (Soto 2012).

Some prognostic factors, such as type of dementia and number of comorbidities, can predict more rapid cognitive decline or increased neuropsychiatric disturbances in people with dementia (Haaksma 2019). Identification of prognostic factors can assist healthcare professionals in predicting outcomes for people with MCI or dementia and help policymakers in planning for future population healthcare needs. If these prognostic factors are modifiable, they serve as potential targets for reducing the rate of decline and frequency of neuropsychiatric disturbances in people with these cognitive syndromes.

Description of the prognostic factor

A prognostic factor is any measure that is associated with a future clinical outcome. The prognostic factor of interest for this review is anticholinergic burden from medication use.

People with dementia are commonly prescribed anticholinergic medications. Prevalence varies internationally and by setting; however, example estimates suggest around 23.3% of community-based dementia patients in the USA, 11.7% of memory clinic attendees in Australia, and 37.9% of 'Psychiatry of Later Life' service attendees in Ireland are reported to be taking 'clinically significant' anticholinergic medications (Sura 2013; Cross 2016; Vaughan 2019). Some medications, such as oxybutynin (for overactive bladder), exert their intended action through their anticholinergic activity. For other medications, such as amitriptyline for depression, anticholinergic activity is probably incidental to their intended mechanism of action. The accumulation of medications with anticholinergic properties is referred to as the anticholinergic burden. Anticholinergics block the binding of acetylcholine to cholinergic receptors in the brain. Acetylcholine is a neurotransmitter that plays a major role in numerous functions of the central nervous system, including cognition, behaviour, and emotion. As such, anticholinergics are hypothesised to cause disruption to cognitive functioning and increase neuropsychiatric disturbance, with greater anticholinergic burden causing greater disruption.

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 prognostic information. Generally, anticholinergic burden measures use a person's medication list and assign a score to certain medications. A cumulative total based on all prescribed medications is then calculated.

Although these measures should be similar, overlap is limited; they include differing medications and assign differing scores to these medications. Methodologies for developing respective scales vary significantly. Where some incorporate expert clinical opinion in their development and 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. Therefore, any prognostic review should be completed at the level of the individual scale in addition

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to creating summary estimates for all anticholinergic burden measures coalesced.

In order to determine if anticholinergic burden measures can be used as a prognostic factor for increased cognitive decline or neuropsychiatric disturbance in people with MCI or dementia, there needs to be a comprehensive assessment of the available literature. The relationship may vary based on a multitude of factors, including the clinical and demographic make-up of the population being investigated (e.g. care-home populations versus non care-home populations), or the duration of the drug exposure period. The severity and subtype of dementia may also be important; 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 anticholinergic medications may affect rate of cognitive deterioration more substantially in people with Alzheimer's dementia than in other dementia subtypes. If anticholinergic burden is a prognostic factor, the strength of the association and the quality of the supporting evidence should also be described. Looking at the prognostic properties of each anticholinergic burden measure may assist in choosing a preferred scale for anticholinergic burden assessment in clinical practice.

Why is it important to do this review?

This review is intended to serve as a companion to the recently published Cochrane Review on anticholinergic burden as a prognostic factor for development of cognitive decline or dementia in cognitively healthy older adults (Taylor-Rowan 2021). As associations between anticholinergic burden and cognitive decline in cognitively healthy older adults have been consistently reported (Taylor-Rowan 2021), drugs with anticholinergic properties are hypothesised to cause further disruption to cognition and increased occurrence of neuropsychiatric disturbance in those with MCI and dementia. However, to date, the evidence to support this hypothesis has been mixed (Wang 2021). Consequently, there is uncertainty regarding the clinical value of measuring anticholinergic burden within an already cognitively-impaired population. In this systematic review, we aim to estimate the prognostic utility (adjusted and unadjusted) of different anticholinergic burden measures for predicting cognitive decline or neuropsychiatric disturbances in people with MCI or dementia, and to assess the certainty of the supporting evidence.

OBJECTIVES

Primary objective

- To assess whether anticholinergic burden, as defined at the level of each individual scale, is a prognostic factor for further cognitive decline or neuropsychiatric disturbances in people with mild cognitive impairment (MCI) or dementia.

Secondary objective

- To compare the prognostic validity of different anticholinergic burden scales.
- To examine the effect of type of dementia and severity of dementia on the association between anticholinergic burden and rate of cognitive decline or neuropsychiatric disturbances.

- To examine the effect of setting (care home versus non-care home) on the association between anticholinergic burden and rate of cognitive decline or neuropsychiatric disturbances.
- To examine whether anticholinergic burden is a prognostic factor for other clinical outcomes in people with MCI or dementia

METHODS

We will follow best practice in design, conduct, and reporting of our prognosis review as detailed in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2019). The review will be supported by the Cochrane Prognostic Methods Group, partners within the Cochrane Mental Health and Neuroscience Network, and the UK National Institute for Health Research Complex Reviews Support Unit (NIHR CRSU).

We used the PICOT (Patient/Problem; Intervention; Comparison; Outcome; Timing) system to design our review question (Schardt 2007) (Table 1). As recommended by the Cochrane Prognosis Methods Group, we will follow guidelines suggested by Riley 2019, to ensure that our review is designed, conducted, and reported in keeping with best practice recommendations.

Criteria for considering studies for this review

Types of studies

We will include prospective and retrospective longitudinal cohort and case-control observational studies. We will not include cross-sectional studies, as it is not possible to determine prognosis from this design. We will not include prospective case studies, defined here as having fewer than 20 participants. We will exclude studies that are published only as abstracts or posters at conferences, as these have not undergone peer review.

Types of participants

We will include any studies that recruited older adults (defined as mean age 50 years or above) that, at time of recruitment and at time of application of the anticholinergic burden measure, have either a known diagnosis of MCI or dementia established by a medical practitioner, cognitive impairment established via a cut-off on a formal cognitive assessment, or are taking cholinesterase inhibitor drugs. Where a mixed population was recruited, we will only include the study if the prevalence of dementia or MCI was more than 70%.

We will make no restrictions based on comorbidity or polypharmacy, but will record these factors in our data extraction. We will assess whether Acetylcholinesterase (AChE) inhibitor use was measured and consider any potential impact of this in our risk of bias assessment. We will include studies conducted in specific patient subgroups, such as Parkinson's disease, Schizophrenia, or stroke, provided they meet our other inclusion criteria.

We will include studies conducted in all settings. People recruited in various settings (e.g. care-home vs community care) may differ in important demographics (e.g. mean age, dementia severity, clinical or lifestyle factors) that could alter the strength of the association between anticholinergic burden and cognitive decline or neuropsychiatric disturbance. If a study was conducted in a care-home setting but does not report numbers with previous MCI or dementia, we will include the study in the review but remove it via a sensitivity analysis, if required.

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Index prognostic factor

The prognostic factor of interest is anticholinergic burden from medications. We will include any study describing use of a scale that purports to measure cumulative exposure to medications with anticholinergic properties. Scales do not need to be described as validated for prediction of cognitive outcomes. Previously identified scales are listed in Appendix 1.

We will not choose a particular measure of primary interest as there is no consensus on the preferred measure, and there is substantial heterogeneity in clinical practice. However, if the Drug Burden Index (DBI) scale is utilised, we will only include data if anticholinergic burden data were reported separately.

Due to our expectation of a relatively sparse literature, we will not exclude studies that simply use a dichotomised present/absent method to investigate the association between anticholinergic medication use and risk of cognitive decline or neuropsychiatric disturbance. However, as severity of anticholinergic burden may play an important role in identifying any association, we will consider the potential impact of this approach in our risk of bias assessment.

We will not include studies that only measure use of anticholinergic burden via serum radioreceptor assay (SAA) measurement as this has limited clinical applicability.

Comparator prognostic factors

We are interested in the value of anticholinergic burden as a prognostic factor over and above other prognostic factors that may be common in this population. Hence, while we will include studies that only assess the unadjusted anticholinergic burden prognosis, we will also evaluate the prognostic effect of anticholinergic burden adjustment for core variables identified as fundamental to the putative link between anticholinergic burden and further cognitive decline or neuropsychiatric disturbance in people with MCI or dementia. We selected these variables on the basis of a Delphi discussion between the review authors and a wider multicentre collaborative, working in the field of anticholinergic burden research (Appendix 2). The chosen core variables were age, sex, comorbidities, and use of AChE inhibitors.

We will assess use of additional adjustments in our risk of bias assessment.

Outcome measures

Primary outcomes: we will include any study that assesses cognitive decline (i.e. change on a measure of cognitive function) or neuropsychiatric disturbance (defined as stressed and distressed behaviours, such as those measured via the Neuropsychiatric Inventory) as an outcome. In the case of people with MCI, we will also include studies that assess incident dementia as an outcome. For the outcome of cognitive decline, we will accept any multidomain cognitive assessment tool that is validated for the direct assessment of cognition. We will not include papers that only measure a single cognitive domain. Only primary outcomes will be included in our summary of findings table.

Secondary outcomes: we will also include studies that assess for risk of mortality, decline in physical functioning, and

institutionalisation--defined as admission to a care home -- in people with pre-existing cognitive impairment.

Timing: on the basis that anticholinergic effects on cognition or neuropsychiatric disturbance may be more rapid in a dementia population than in a cognitively-unimpaired population, we will accept assessment for cognitive decline or neuropsychiatric disturbance at one month or longer following baseline anticholinergic burden assessment. We will evaluate the risk of reverse causality based on duration of follow-up in our risk of bias assessment.

Search methods for identification of studies

Electronic searches

As reporting of prognostic factor studies is variable, it can be challenging to identify all relevant studies. We will adopt the procedure proposed by Geersing 2012 to maximise our ability to identify relevant prognostic studies. Specifically, as we will search for one prognostic factor, we will not adopt any specific search filter, but instead adopt a search that combines our prognostic factor (anticholinergic burden) with the population of interest (people with MCI or dementia).

We will search the following databases: 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), and ISI Web of Science Core Collection (1928 to present; ISI Web of Science) (Appendix 3). We will apply no language restrictions.

Searching other resources

We will supplement this with hand-searches of references of all included studies and identified systematic reviews.

Data collection and analysis

Selection of studies

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

Two review authors (OK and CK) 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 (MT) will act as arbiter and make the final decision on study inclusion/exclusion.

Data extraction and management

Two review authors (OK and CK) will independently extract the data to a piloted proforma based on the CHARMS-PF (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies, adapted for prognostic factors) template (Riley 2019). We will contact authors for missing data where required. We will select two studies to trial our data extraction proforma (Fox 2011; Bishara 2020). We will extract all data onto a standard form (Appendix 4).

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Assessment of methodological quality

Two review authors (OK and CK) will independently use the QUIPS (Quality in Prognosis Studies) checklist (Hayden 2012), assessing the included studies across the domains of: study participation; study attrition; prognostic factor measurement; outcome measurement; adjustment for covariates; reverse causation; statistical analyses; and reporting. We will use the QUIPS anchoring statements, but modify the content to suit our review topic based on consensus within the review author team.

We will judge each domain as low risk of bias, moderate/unclear risk of bias, or high risk of bias (Appendix 5). In cases of uncertainty we will contact original study authors for clarification, where possible.

Discussing reporting deficiencies: prognosis research is frequently confounded by poor reporting and possible publication bias. We will supplement our risk of bias assessment with a narrative discussion of reporting issues, highlighting when missing information may have affected results. Prognostic factor studies often do not register protocols, increasing the risk that not all studies (published and unpublished) will be identified, and there is a risk of small-study effects (in which smaller studies with higher odds ratios (ORs) are more likely to be published than smaller studies with non-significant ORs), which can bias meta-analyses (Peat 2014; Riley 2019). We will use sensitive search filters for the population (people with MCI or dementia) and the prognostic factor (anticholinergic burden) without any specific filter for prognostic research to increase retrieval, and attempt to examine the likelihood of small-study effects in our review by generating a funnel plot.

Data synthesis

We will evaluate risk of future cognitive decline or neuropsychiatric disturbance for anticholinergic drug users against non-users. Where possible, we will pool summary estimates for each anticholinergic burden tool individually; then, as an exploratory analysis, pool summary estimates across all scales. We will conduct each meta-analysis in two ways. First, as an all-encompassing 'any anticholinergic drug use' variable; second, as an ordinal, hierarchical variable in which low, moderate, and high users are pooled separately, to investigate possible differential relationships based on anticholinergic burden severity. Low users are defined as those with a cumulative score of 1 on an anticholinergic scale; moderate users are defined as those with a cumulative score of 2 on an anticholinergic scale; high users are defined as those with a cumulative anticholinergic scale score of 3 or above.

We will pool data in two separate ways. In the first instance, we will pool data obtained from unadjusted analyses. In the second instance, we will pool data from fully adjusted analyses, provided age, sex, and comorbidities are controlled for as a minimum. We will pool ORs and hazard ratios (HRs) separately. We will calculate standardised mean difference (SMD) for linear data and pool this separately from dichotomous outcome data. Where data are not available, we will attempt to estimate data based on methods suggested by Tierney 2007. Where data are sufficiently similar to permit pooling, we will use a random-effects approach given our expectation of high heterogeneity between studies. We will use Comprehensive Meta-Analysis software to conduct all meta-analyses (Comprehensive Meta-Analysis Version 3).

We will conduct a sensitivity analysis, restricting to studies that have no high risk of bias domains.

For secondary (subgroup) analysis, we will assess risk by type of dementia, severity of dementia, APOe4 status, and by setting. We will also conduct analysis based on duration of follow-up. We will create categories of <1 year and > 1 year, considering pooled rates for each timeframe individually.

These additional outcomes were decided upon through discussion among the review authors. We also plan to assess exposure, including exposure before enrolment into the study and exposure during the study.

Finally, if sufficient data are available, we plan to conduct a comparative analysis of the prognostic performance of the differing anticholinergic burden measures using a network meta-analysis.

Investigation/description of heterogeneity

We will describe heterogeneity narratively based on consistency of association and effect size between anticholinergic burden and cognitive decline or neuropsychiatric disturbance, measurement of prognostic factor, outcome measurement and definition, and study design. We will not employ the I^2 statistic in our evaluation of heterogeneity. In prognosis research, individual studies often have large sample sizes resulting in narrow confidence intervals (CIs); this can cause high I^2 values even if inconsistency between studies is moderate (Iorio 2015).

It is possible that observed associations between anticholinergic drugs and cognitive decline or neuropsychiatric disturbance in people with MCI or dementia are driven by uncontrolled variables. Number of medical conditions or overall polypharmacy are possible moderators of observed effects and could differ by setting. To investigate this, if data allow, we will conduct a meta-regression based on study recruitment setting (nursing home versus non-nursing home), severity of dementia (mild/moderate/severe), comorbidity ('number of comorbidities' controlled for as a covariate, yes/no), and polypharmacy (controlled for as a covariate, yes/no).

We will also investigate potential differences in effect size based on control for concomitant use of AChE medications (control for AChE medication (yes/no).

Grading the evidence

We will use the GRADE approach to evaluate our overall confidence in the results. We will adapt the GRADE approach to suit prognosis research using methods consistent with Huguet 2013. Specifically, we will evaluate reported evidence in the following eight areas.

• Phase of investigation: phase 3 explanatory studies derived from bespoke cohort study designs that seek to explain the mechanisms behind an underlying association between anticholinergic burden and cognitive decline/ neuropsychiatric disturbances in people with MCI or dementia are considered to be a high level of evidence. Phase 2 explanatory studies that seek to confirm an independent association between anticholinergic burden and cognitive decline/ neuropsychiatric disturbances are treated as moderate evidence, and hypothesis-generating phase 1 explanatory studies are treated as weak evidence for any association between anticholinergic burden and cognitive decline/ neuropsychiatric disturbances.

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• Study limitations: we will use the previously described QUIPS tool to evaluate the overall risk of bias of included studies. Our GRADE judgement will be based upon the overall certainty of the evidence. That is, if most (more than 50%) included studies are considered at high risk of bias in their reported association between anticholinergic burden and cognitive decline or neuropsychiatric disturbance, we will downgrade the evidence accordingly.

• Inconsistency: we will downgrade the evidence if associations between anticholinergic burden and cognitive decline/ neuropsychiatric disturbances are heterogeneous (i.e. estimates of effect are variable across studies with regards to showing beneficial or detrimental effects and their confidence intervals show minimal or no overlap; the measure of the prognostic factor is highly variable; outcome measurement is highly variable; and there is methodological heterogeneity due to study design); and 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.

• Indirectness: we will downgrade studies where their investigation does not fully match with our broader review question. Specifically, if the population in the included studies only represent a subset of the population of interest (e.g. a specific subtype of dementia only) then the evidence for the association between anticholinergic burden and cognitive decline/ neuropsychiatric disturbances will be downgraded for indirectness.

• Imprecision: we will downgrade if the evidence is generated by a few studies involving a small number of participants and most of the studies provide imprecise results; if there are insufficient numbers to meet the optimal information size in the meta-analysis (i.e. if the total number of patients included is less than the number of patients 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: due to inherent issues regarding publication bias in prognostic research, we will adopt the default position that publication bias is likely and downgrade the evidence unless our assessment of publication bias provided significant evidence to the contrary (i.e. a symmetrically distributed funnel plot, and evidence that the prognostic factor has been investigated in numerous cohort studies).

• Effect size: we will upgrade our confidence in the effect estimate when the effect size was moderate to large (e.g. a hazard ratio of 2.5 or above).

• Exposure-response gradient: we will upgrade the evidence if there is an incremental increase in effect size with increasing anticholinergic burden.

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Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16.

Vaughan 2019

Vaughan RM, Flynn R, Greene N. Anticholinergic burden of patients with dementia attending a Psychiatry of Later Life service. *Irish Journal of Psychological Medicine* 2019;**Epub ahead of print**:1-6.

Wang 2021

Wang K, Alan J, Page AT, Dimopolous E, Etherton-Beer C. Anticholinergics and clinical outcomes amongst people with pre-existing dementia: a systematic review. *Maturitas* 2021;**151**:1-14.

ADDITIONAL TABLES

Table 1. PICOTS

Population	Older adults (mean age ≥ 50 years) with prior cognitive impairment, MCI, dementia, or AChE use at baseline
Index prognostic factor	Anticholinergic burden as measured by any validated ordinal anticholinergic burden scale
Comparator prognostic factors (covariates of interest)	Age, sex, comorbidity, and AChE use
Outcomes	Cognitive decline (multidomain) or neuropsychiatric disturbances
Timing	Prognostic factors should be measured at baseline. Outcomes should be obtained at a minimum of 1-month follow-up via longitudinal, observational cohort/case-control study design
Setting	Recruitment from primary, secondary, or community, or care-home settings.

AChE; Anticholinesterese inhibitor
MCI; Mild Cognitive impairment

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APPENDICES

Appendix 1. Anticholinergic burden scales

AAS: Anticholinergic Activity Scale

AAS-r: Revised Anticholinergic Activity Scale

ABC: Anticholinergic Burden Classification

ABS: Anticholinergic Burden Scale

ACB: Anticholinergic Cognitive Burden

ADS: Anticholinergic Drug Scale

AEC: Anticholinergic EFect on Cognition

AIS: Anticholinergic Impregnation Scale

ALS: Anticholinergic Loading Scale

ARS: Anticholinergic Risk Scale

BAAS: Brazilian Anticholinergic Activity Scale

Chew's list

CrAS: Clinician-rated Anticholinergic Scale

Ellett's list

KABS: Korean Anticholinergic Burden Scale

MARANTE: Muscarinic Acetylcholinergic Receptor Antagonist Exposure Scale

mARS: Modified Anticholinergic Risk Scale

Appendix 2. Contributors to Delphi

Contributors to Delphi for selection of adjustment variables were researchers and clinicians from a range of specialities (medicine and psychology). Specific contributors were Dr Carrie Stewart, Dr Martin Taylor-Rowan, Professor Phyo Myint, Dr Terry Quinn, and Dr Amanda Cross.

Appendix 3. Sources searched and search strategies

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.

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(Continued)

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/

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.

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(Continued)

	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.
	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.

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	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.
	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.

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(Continued)

	21. FTLD.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
	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

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(Continued)

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

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"

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(Continued)

	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.

Appendix 4. Contents of proforma

Extracted information	Includeddetails
General information	Author, title, source, publication date, language, related or duplicate publications
Source of data	Cohort (retrospective or prospective data collection), case-control, or secondary analysis of registry data.
Participant information	Participant eligibility and recruitment method (e.g. consecutive or other recruitment, number of centres, inclusion and exclusion criteria); participant demographics (e.g. age, sex, severity/type of dementia); details of ongoing treatments/medications; study dates; country of recruitment; setting (using our definitions of primary, secondary, community and care-home settings).
Prognostic factor	Definition and method of measurement of prognostic factor. Duration of exposure (pre- or post-study commencement) may not be regularly recorded; however, where possible, we will record timing of prognostic factor measurement (number of weeks participants have been on the anticholinergic drugs prior to baseline assessment); where data were available, we also collected duration of exposure during the study.
Outcomes to be predicted	Definition and method of measurement of outcome; time of outcome ascertainment, or summary of duration of follow-up.
Adjustment for other prognostic factors (covariates)	List of all the covariates that were adjusted for in any regression model.
Sample size	Number of participants and number of outcomes/events; how missing data were handled (e.g. complete-case analysis, imputation, or other methods).
Reported results	We will record incidence of cognitive decline or neuropsychiatric disturbance. Where possible, we will extract estimates and corresponding confidence intervals from each included paper. We will also record additional clinical outcome variables assessed.

Appendix 5. QUIPS(Quality in PrognosisStudies) anchoring statements

Specific considerations

• Study participation: we will consider whether the method of recruitment was at risk of selection bias (e.g. consecutive recruitment versus convenience sample) and if there was adequate reporting of comorbidities and demographics (age, sex, severity/type of dementia). If either a convenience sample was used or there was inadequate reporting of comorbidities/demographics, we will assign a moderate/unclear risk of bias.

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• Attrition: we will assess extent of loss to follow-up. Specifically, if attrition is greater than 20%, we will assig a high risk of bias rating. In addition, we will assess reporting of, and methods for dealing with, missing data. We will assign a moderate/unclear risk of bias if no analysis was carried out to evaluate if participants with missing data differed in baseline anticholinergic burden score compared to those with full data.

• Prognostic factor measurement: we will consider how medication data were obtained. If medication was not established via at least two methods and capable of establishing non-prescription medications taken, along with duration of exposure and adherence, we assigned a moderate/unclear risk of bias. If repeated anticholinergic burden measurements were not made overtime for studies with a follow-up duration of more than one year, we will assign a high risk of bias. We anticipate that some studies will utilise validated anticholinergic burden scales but adjust these scales, for instance to incorporate dosage into the anticholinergic calculation. We will not consider utilisation of anticholinergic burden scales as part of the 'Risk of Bias' assessment, as it is a purpose of the review to establish which anticholinergic burden scales have the greatest prognostic accuracy.

• Outcome measurement: we will consider the method utilised for dealing with missing data in relation to the outcome. If 'last diagnosis carried forward' was used when final outcome data were not available,we will assign a high risk of bias. We will assess whether the outcome was established via a comprehensive neuropsychological assessment or via a brief cognitive assessment tool only (such as the MMSE). If outcome was reliant upon brief screening tools alone, we will assign a moderate/unclear risk of bias rating as these may be subject to practice effects or floor effects (particularly for more severe forms of dementia). We will also assess if the outcome was determined without knowledge of the prognostic factor. If there was no blinding to outcome and the cognitive diagnosis was conducted after the anticholinergic burden measurement was taken, we will assign a high risk of bias.

• Covariates: we will assess whether studies adjusted for age, sex, comorbidities, and AChE inhibitor use as a minimum. If these covariates were not adjusted for, we will assign a high risk of bias. Assessment for comorbidities requires control for at least three comorbidities that cover both physical and psychiatric domains; failure to do so will result in a rating of moderate/unclear risk of bias.

• Reverse causation: we will evaluate studies on perceived risk that anticholinergic drugs were prescribed for treatment of symptoms of worsening of dementia. If studies did not explicitly report restricting anticholinergic burden measurement to at least 12 months before outcome measurement, a rating of high risk of bias will be applied. Studies that restrict anticholinergic burden measurement to 1-2 years before outcome assessment will be rated as at moderate/unclear risk of bias.

• Statistical analysis: we will evaluate how the analysis was conducted. Specific issues of consideration in each area were decided upon via discussion among the review authors. We will assign a high risk of bias if: a multivariate analysis was not conducted; if the analysis was not appropriately powered based on a sample size calculation or the '10 events per covariate' rule for logistic regression; if the method for selecting covariates for inclusion in a multivariate model was based on P values in a univariate analysis without incorporation of prior knowledge of relevant associations into selection; if the method of analysis was inconsistent with the stated protocol (where protocols are not available, we will assign a moderate/unclear risk of bias); and if the reported results were inconsistent with the stated method of analysis. We will assign a moderate/unclear risk of bias if relevant assumptions were not checked.

CONTRIBUTIONS OF AUTHORS

Martin Taylor-Rowan drafted the initial manuscript. Christina Kolliopoulou and Olga Kraria will be primary reviewers of all studies. Dr Terry Quinn is the supervising author. Jenny Mcleery, Amanda Cross, Carrie Stewart, Phyo Myint and Terry Quinn revised the manuscript and contributed to intellectual content. All authors contributed to writing.

DECLARATIONS OF INTEREST

MT: None

TQ: None

JM: None

CS: None

PM:None

AJC: None

OK: None

CK: None

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SOURCES OF SUPPORT

Internal sources

External sources

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