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SYSTEMATIC REVIEW

Interventions for reducing anticholinergic medication burden in older adults—a systematic review and meta-analysis

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Abstract

Introduction: Anticholinergic medications block the neurotransmitter acetylcholine in the brain and peripheral nervous system. Many medications have anticholinergic properties, and the cumulative effect of these medications is termed anticholinergic burden. Increased anticholinergic burden can have short-term side effects such as dry mouth, blurred vision and urinary retention as well as long-term effects including dementia, worsening physical function and falls.
Methods: We carried out a systematic review (SR) with meta-analysis (MA) looking at randomised controlled trials addressing interventions to reduce anticholinergic burden in older adults.
Results: We identified seven papers suitable for inclusion in our SR and MA. Interventions included multi-disciplinary involvement in medication reviews and deprescribing of AC medications. Pooled data revealed no significant difference in outcomes between control and intervention group for falls (OR = 0.76, 95% CI: 0.52–1.11, $n = 647$), cognition (mean difference = 1.54, 95% CI: −0.04 to 3.13, $n = 405$), anticholinergic burden (mean difference = 0.04, 95% CI: −0.11 to 0.18, $n = 710$) or quality of life (mean difference = 0.04, 95% CI: −0.04 to 0.12, $n = 461$).
Discussion: Overall, there was no significant difference with interventions to reduce anticholinergic burden. As we did not see a significant change in anticholinergic burden scores following interventions, it is likely other outcomes would not change. Short follow-up time and lack of training and support surrounding successful deprescribing may have contributed.

Keywords: older adult, falls, cognition, meta-analysis, anticholinergic medication, systematic review, older people

Key Points

- This systematic review and meta-analysis synthesised interventions targeting anticholinergic burden in older people.
- Results indicate no clear impact on key outcomes of anticholinergic burden score, cognition, falls or quality of life.
- Short follow-up time and lack of training and support surrounding successful deprescribing may have contributed.
- Future interventions should focus on key intervention components required to reduce anticholinergic burden.

- Future interventions should only proceed to definitive evaluation once impact on anticholinergic burden can be demonstrated.

Introduction

Anticholinergic (AC) medications block the neurotransmitter acetylcholine in the brain and peripheral nervous system, reducing involuntary muscle contractions in areas of the body including the gastrointestinal tract, bladder and lungs. As such, they are commonly used to manage wide-ranging symptoms including irritable bowel, overactive bladder, pain and respiratory problems. However, their effects can lead to constipation, dry mouth, blurred vision, urinary retention, and impact memory and thinking. In addition, many medications used for other clinical indications such as pain, allergy and mental health conditions have AC properties that may go unrecognised by prescribers. These adverse effects are particularly troublesome for older people, especially those with existing conditions such as frailty or dementia.

Available prevalence estimates indicate that around 20% of older people are prescribed AC medications [1]. Growing evidence indicates that AC medications are associated with cognitive and physical decline in older age [2, 3]. The cumulative adverse effect of multiple AC drugs and medications with AC properties is referred to as 'anticholinergic burden' and is associated with potential harm. Anticholinergic burden is associated with increased risk of delirium (acute confusion) and falls, both of which are common reasons for hospital admission. Longer-term adverse effects include dementia, loss of physical function and loss of independence [3]. These outcomes are especially problematic for older people, their families and carers, and are associated with considerable cost to the health and social care systems worldwide.

There are multiple AC burden scores available such as Anticholinergic Cognitive Burden, Anticholinergic Drug Scale (ADS), Drug Burden Index (DBI) or the Anticholinergic Risk Scale. These scores identify people at risk of adverse effects from AC burden and those who may benefit from a targeted medication review, but there is no clear guidance on which one to use in routine clinical practice. Several interventions have been developed that aim to reduce anticholinergic burden for patients with the intention of preventing adverse outcomes. Interventions are typically based around initial calculation of AC burden then using this to trigger health care professionals to review medications with the aim of supervised withdrawal of any inappropriate medications (deprescribing) [4].

A 2018 systematic review of interventions to reduce anticholinergic burden in older adults reported evidence for a reduction in AC burden through targeted interventions [5]. However, the review included studies only undertaken since 2010, risking exclusion of earlier trials. Reported evidence for reduced AC burden was mainly from non-randomised studies, with attendant risk of bias, and limited evidence was reported on clinically relevant outcomes. Furthermore, no meta-analysis was performed in the review, impacting on the ability to make robust evidence statements.

Objective

The aim of this review is to synthesise the international evidence on randomised trials of interventions for reducing anticholinergic burden and related adverse outcomes in older people aged $\geq$ 65 years.

Methods

The review methodology followed Cochrane guidance and is reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations [6] (Appendix 1). The protocol was prospectively registered with Prospero (http://www.crd.york.ac.uk/PROSPERO/; reference CRD42021279187).

Eligibility criteria

Randomised controlled trials (RCTs) and cluster RCTs of deprescribing interventions including a focus on AC burden reduction involving older adults (mean age $\geq$ 65), with participant use of AC medications, in all healthcare settings, were eligible for inclusion. Non-randomised intervention trials and observational studies were excluded.

Search strategy and information sources

An inclusive MEDLINE search strategy was developed with an experienced research librarian at the University of Leeds, and adapted for CINAHL, EMBASE, EMBASE Classic, Cochrane Database of Systematic Reviews, Cochrane CENTRAL (Trials) and PsycINFO. All databases were searched for English-language publications between 1946 and 22 April 2022. The search strategy for MEDLINE (Ovid) is available (Appendix2).

Data collection process

Two independent reviewers (EB, and AA or RH) assessed titles and abstracts for potentially eligible studies and reviewed full-text papers against the eligibility criteria, with any disagreements settled by consensus discussion.

Two authors independently extracted the data from included trials using a piloted data extraction form and any disagreements were settled by consensus. Extracted data included trial setting, description of intervention, patient baseline characteristics (age, sex, comorbidities including dementia, AC burden scores and care home residence), outcomes of interest and study drop-out rates.

Data items

The primary outcomes included new diagnosis of dementia, delirium episodes and falls. Planned secondary outcomes included worsening of existing dementia; cognition; activities of daily living—basic or instrumental; quality of life; mortality; AC burden score; side effects including dry mouth, constipation and urinary retention; hospital admission; and cost-effectiveness. All outcomes were collected at each reported timepoint.

Study risk-of-bias assessment

Two independent reviewers (EB, and AA or RH) assessed risk of bias for each study using Cochrane criteria as described in the Cochrane Handbook for Systematic Reviews of Interventions [7]. We assessed included trials for adequacy of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias. For each domain, a judgement of low risk, high risk or unclear risk of bias was reached. Disagreements were resolved by consensus and risk of bias summary figures generated using Review Manager (RevMan) software [8].

Synthesis methods

Where required, we converted outcome data to an appropriate format for meta-analysis using established methods [7] and contacted study authors for additional information if this was not possible.

We synthesised data for meta-analysis, calculating pooled odds ratios with 95% confidence intervals for dichotomous outcomes to create summary forest plots using Mantel–Haenszel random-effects methods [8]. We calculated pooled mean differences with 95% confidence intervals for continuous outcomes using generic inverse variance random-effects modelling. Where we identified unit of analysis issues, we calculated standardised mean differences with 95% confidence intervals. In cases where the standard deviation for a study's point estimate was missing, where this represented a small proportion of the pooled estimates, these were imputed [9]. If available data or clear trial heterogeneity precluded meta-analysis, a narrative evidence synthesis was provided. We assessed for the proportion of total variability due to between-study heterogeneity using the I^2 statistic with values approaching 25%, 50% and 75% representing low, moderate and high levels, respectively. Since fewer than 10 studies were identified to provide data for each outcome, assessment for publication bias with funnel plots was not appropriate.

Results

Study selection

Details of the study selection are presented in Figure 1. Following detailed assessment, seven studies were eligible for inclusion in the review [10–16].

Study characteristics

Of the seven studies, four were RCTs [11–14] and three were cluster RCTs [10, 15, 16], with a total of 1,774 participants (study population range 49–781 participants) and mean follow-up period of 38 weeks (range 8 weeks to 4 years). Two studies were conducted in the Netherlands [14, 15], two in Australia [10, 16], one in Finland [12], one in Norway [11] and one in the United Kingdom [13]. The mean age was 80.8 years (mean age range 76.2–85.5 years) and 70% (range 61–79%) were female. Where reported (in four studies) [11–13, 15], diagnosed dementia rates ranged from 10 to 70%. Trial drop-out rates ranged from 2 to 22%.

The included studies were all community based, with two of the studies conducted in nursing homes [11, 15]. A detailed description of the interventions is provided (Table 1).

For the primary outcomes of this review, falls were reported in three studies [14–16], but data were not available for new diagnosis of dementia or delirium episodes. For secondary outcomes, anticholinergic burden was measured in all studies, cognition in five studies [11, 12, 14–16], quality of life in three studies [13–15], hospital admissions in one study [14], side effects relating to dry mouth in one study [11] and cost-effectiveness in one study [15]; data were not available for other pre-specified secondary outcomes.

Primary outcomes

Falls

Pooled data from three trials [14–16] indicated no clear difference in odds of falling between intervention and control groups (OR 0.76, 95% CI 0.52 to 1.11, $n = 647$) (Figure 2a).

Secondary outcomes

Cognition

Pooled data from two trials [11, 15] indicated uncertainty in the effect of interventions on cognition, based on Mini-Mental State Examination (MMSE) score (mean difference 1.54, 95% CI −0.04 to 3.13, $n = 405$) (Figure 2b).

One further study [12] also reported cognitive impairment using MMSE; however, the follow-up period was 4 years and therefore was not sufficiently similar to pool in the meta-analysis. There was no significant difference in MMSE at follow-up between the intervention and control groups (MMSE 23.7 and 23.7, respectively) at this timepoint.

One study [16] reported change in cognition using Mini Cog score at follow-up. There was no significant difference at follow-up between the intervention and control groups (OR −0.01, 95% CI −0.32 to 0.30).

One study [14] reported that the intervention was associated with no significant difference in individual cognitive domains (measured using the 7-minute screen (7MS)) of category fluency (unstandardised beta −0.18, 95% CI −1.55 to 1.20, $n = 145$), enhanced cued recall (OR 0.54, 95% CI 0.15 to 1.9), temporal orientation (OR 1.38, 95% CI 0.28

Table 1. Characteristics of intervention

Study	Intervention	Description and method	Provider	Setting	Frequency
Gnjidic [10]	DBI + prompt to GPs	Step 1: Interview by researcher with medication review Step 2: DBI calculated Step 3: Letter and phone call to GP to prompt medication changes. Phone call by pharmacologist or geriatrician	Researcher and phone calls to GP from pharmacologist or geriatrician	Self-care retirement villages in Australia	Once
Kersten [11]	Pharmacist drug review based on ADS	Step 1: MDT drug review guided by the ADS score model Step 2: Advice to nursing home physician to reduce/stop or change drug	Pharmacists	Nursing homes Norway	Once
Lampela [12]	CGA including medication review	CGA including medication review by physicians (trainees with 10+ years' experience of GP and older adults). No formal use of an anticholinergic score. Discussed weekly with senior geriatrician	Physician (medication review), dentist, physiotherapist, nutritionist	Finland—population based	Annually 2004–2007
Moga [13]	Targeted medication therapy management intervention	Medication therapy management programme Step 1: Label anticholinergics as potentially inappropriate Step 2: Evaluation of each drug risk/benefit Step 3: Recommendations to reduce, stop/change drugs Step 4: Discussion with participant at week 1 visit	Pharmacists and physicians	UK. Alzheimer's coordinating centre cohort	Once
Kouladjian O'Donnell [16]	Goal-directed medication review electronic decision support system	Clinical decision support system that produces patient-specific deprescribing reports to the GP, including: 1. Identify patient's goals of care with medications 2. Calculate the DBI 3. Explore patient's attitudes towards deprescribing 2-hour self-directed training programme for accredited clinical pharmacists (ACP) but not GP	ACP undertake reports that are sent to GPs	Patients referred to pharmacist home medication reviews	Once
van der Meer [14]	MDT medication review	Step 1: Patient and pharmacist to discuss medication use Step 2: Pharmacist review and recommendations Step 3: MDT with GP and pharmacist to make action plan Step 4: Discussion with patient Step 5: Follow-up	Pharmacist and GPs	Community pharmacists with GP—Netherlands	Once
Wouters [15]	3MR Multidisciplinary Multistep Medication Review	Step 1: Assessing patient perspective and medical information Step 2: Review drugs using STOPP/START criteria Step 3: MDT meeting and pharmacotherapeutic actions Step 4: Execution and evaluation of actions Total process approximately 45 min. Brief training given	Geriatricians and pharmacists	Nursing homes Netherlands	Once

Characteristics include intervention description and method, provider, setting and frequency. ADS = Anticholinergic Drug Scale; CGA = comprehensive geriatric assessment; DBI = Drug Burden Index; GP = general practitioner; MDT = multi-disciplinary team; MR = medication review; STOPP = Screening Tool of Older Person's Prescriptions; START = Screening Tool to Alert doctors to Right i.e. appropriate, indicated Treatments.

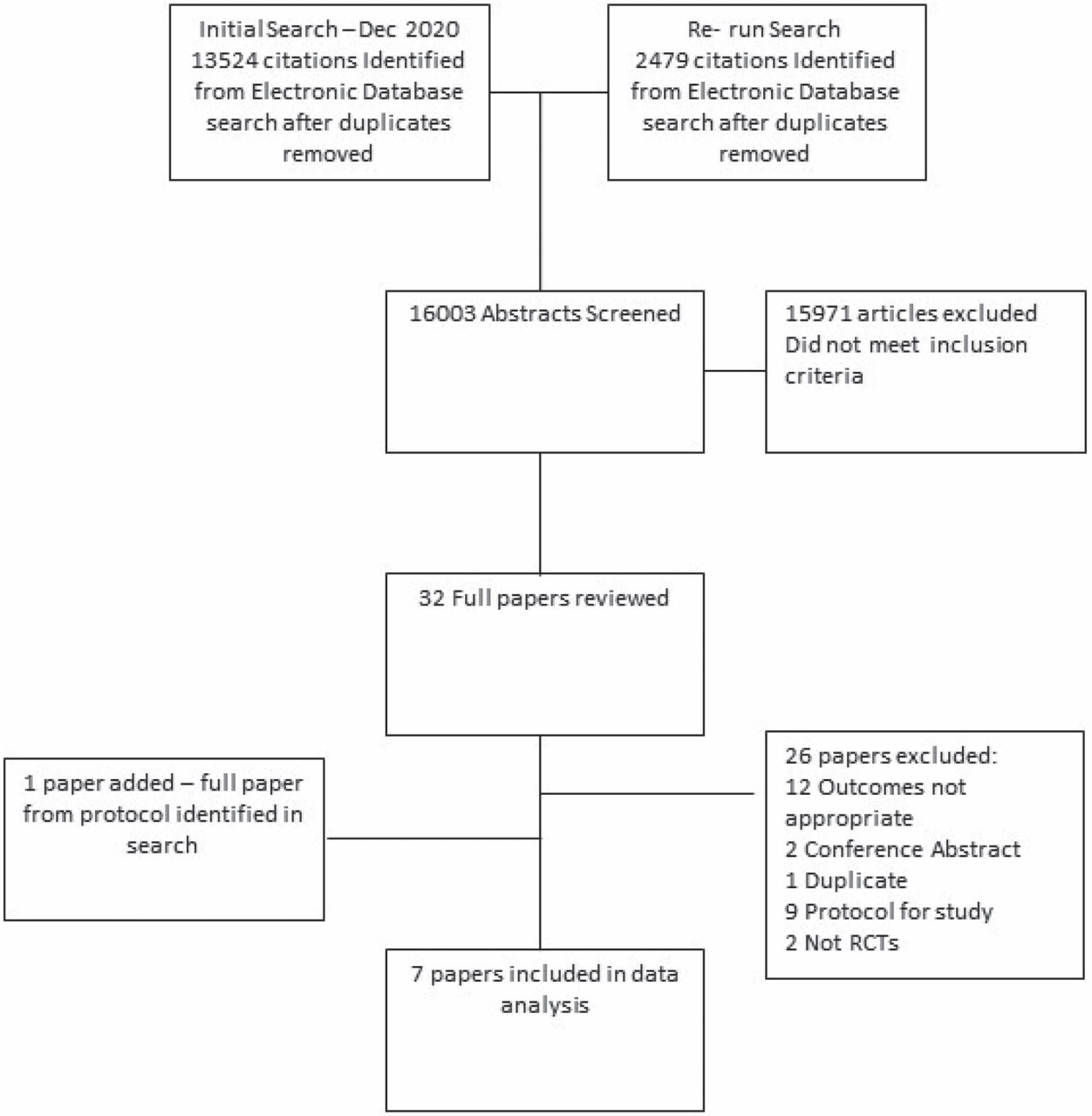


Figure 1. Flowchart of included studies.

to 6.88) or clock drawing (OR 0.67, 95% CI 0.28 to 1.62) compared to the control group.

Anticholinergic burden

Synthesis of data from two trials [14, 15] identified no clear difference in post-intervention anticholinergic burden, measured using the DBI to measure exposure to anticholinergic and sedative medications (mean difference 0.04, 95% CI −0.11 to 0.18, $n = 710$) (Figure 2c).

One trial [10] reported that the intervention was associated with an overall increase in anticholinergic burden compared to the control group.

One trial [11] reported that the intervention was associated with a reduction in anticholinergic burden of 2 units, measured using the ADS, compared to the control group. One further trial demonstrated the intervention was associated with reduction in anticholinergic burden (intervention: mean change score 1 (standard error of mean (SEM) 0.3); control: mean change score 0.2 (SEM 0.3)).

One trial [12] demonstrated that the intervention was associated with no difference in anticholinergic burden compared to the control group using multiple different anticholinergic burden scales (Anticholinergic Drug Scale, Chew Score, Anticholinergic Cognitive Burden Scale and Rudolph's Anticholinergic Risk Scale).

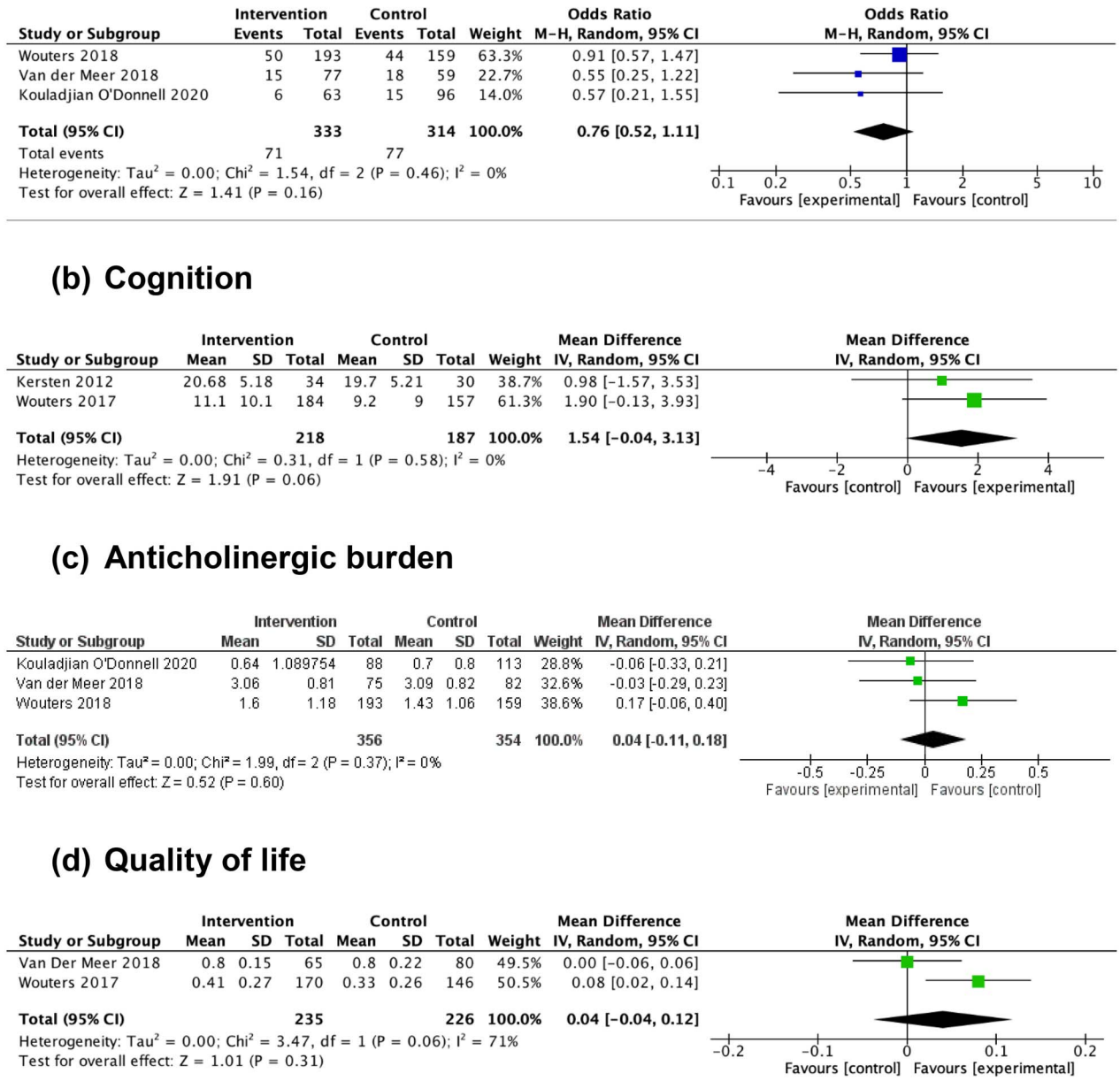


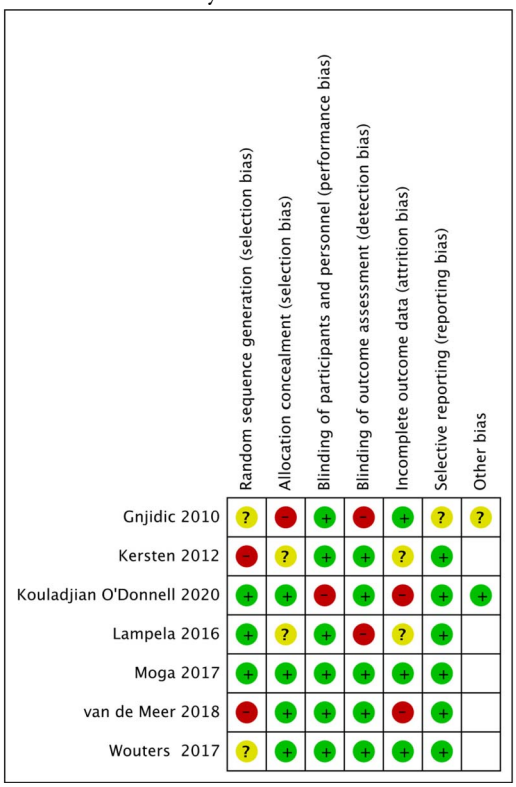
Figure 2. Forest plots demonstrating at follow-up, in the intervention and the control groups: (**a**) pooled risk estimates of fall frequency; (**b**) pooled mean differences in Mini-Mental State Examination (MMSE) scores; (**c**) pooled mean differences in Drug Burden Index (DBI) scores; (**d**) pooled mean differences in EuroQol five-dimension health questionnaire (EQ-5D) scores. In (a), odds ratios less than 1 favour the intervention group; odds ratios more than 1 favour the control group. In (b, c, d), mean difference less than 0 favours the control group, mean difference more than 0 favours the intervention group. CI = confidence interval; I^2 = I^2 statistic; IV = inverse variance; M-H = Mantel–Haenszel method; P = *P* value; Random = random effects; Z = *Z* value.

Quality of life

Synthesis of data from two trials [14, 15] indicates no clear difference in quality of life for intervention participants, measured using the EuroQol five-dimension health questionnaire (EQ-5D), compared to the control group (mean difference 0.04, 95% CI −0.04 to 0.12, $n = 461$) (Figure 2d).

One trial [13] reported that the intervention was associated with no difference in quality of life, measured using the Rand Short-Form 36-Item Health Survey (RAND

Table 2. Summary of risk of bias assessment



Risk of bias assessment using the Cochrane tool [7].

SF36), compared to the control group: physical component summary scores: for intervention, mean change score −1.2 (±13.2); for control, mean change score 1.5 (±16.5); mental component summary scores: for intervention, mean change score 2.1 (±12.9); for control, mean change score −4.7 (±14), $n = 49$.

Risk of bias

We carried out a comprehensive review of risk of bias for each of the studies included using the Cochrane tool for assessing risk of bias, as summarised in Table 2. Most included studies scored low to moderate risk of bias in most domains. One study [13] scored as low risk in all domains. In the other studies, the most common domains in which they scored at high risk of bias were selection bias and detection bias. No study was assessed as at overall high risk of bias.

Discussion

Our review has identified no clear evidence that interventions targeting AC burden in older people reduce overall AC burden score, improve cognition, impact on quality of life-related outcomes or falls. Generated evidence was from a relatively small number of trials, but included trials were generally assessed as being of low to moderate risk of methodological bias.

Key amongst these findings is that there did not appear to be a clear intervention effect on anticholinergic burden scores measured post-intervention. This is of importance as it is unlikely that downstream effects on measures of cognition or other outcomes can be generated, or attributed to the intervention, in the absence of a reduction in anticholinergic burden scores.

The challenges associated with deprescribing medicines in older people are well recognised. These include a lack of continuity in health care, time constraints during consultations, fear of the consequences of deprescribing [17, 18] and specifically in relation to anticholinergic burden, the complexity of deprescribing interventions across multiple drug classes. Alongside this, hesitancy amongst health care practitioners to deprescribe if medications were prescribed by another practitioner has been recognised and patients and relatives may also be reluctant to stop medications prescribed following a set guideline [19]. A study reporting successful deprescribing of antihypertensive medications in older adults used a clear deprescribing algorithm alongside a safety monitoring algorithm to support clinicians in the process [20]. This suggests that clearer guidance for prescribers may support deprescribing such as use of the STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right i.e. appropriate, indicated Treatments) criteria [21]. In addition, shared decision-making, person-centred care and increased communication may facilitate successful deprescribing [17].

In addition, there is evidence that certain medications with AC effects are more straightforward to deprescribe than others, with the highest success in deprescribing antihistamines and lower success deprescribing antipsychotic and antidepressant medications [22]. All studies used only single time point interventions at the beginning of the trial, which is also likely to have affected successful deprescribing, as previously demonstrated [23, 24]. Continued clinician–patient engagement would also improve effective deprescribing and subsequent reduction in AC burden scores [25]. Future work to develop and evaluate interventions to reduce anticholinergic burden in older people should aim to address these factors as key steps in intervention development.

Only one study [15] reported that intervention training was provided to staff delivering the intervention. Lack of training of those performing interventions in the remaining studies may have influenced the final outcomes. Future intervention development and evaluation should pay close attention to development of training packages that support delivery, incorporating the necessary behaviour change approaches to achieve successful deprescribing. Initial intervention feasibility testing should include a focus on fidelity of training, intervention delivery, receipt and enactment and ideally only proceed to definitive evaluation once an overall reduction in AC score can be demonstrated as it is unlikely that effects attributable to the intervention could otherwise be generated.

Limitations of the review

Although we were able to synthesise evidence for meta-analysis of outcomes, this was only possible using data from a small number of trials, resulting in considerable uncertainty in overall estimates. Consensus agreement on common data elements and reporting methods for deprescribing trials in older people and establishment of international repositories for trial data to support individual participant data meta-analysis would support generation of robust findings from future trial-based work. Use of published Core Outcome Sets may support future research [26, 27].

Five of the trials [10, 11, 13–15] had a relatively short follow-up time, so changes in outcomes such as cognition may not necessarily be expected. The selection of outcome measures for trials of AC medications and appropriate time horizon to record impact on key outcomes should be considered in future work, acknowledging the constraints of trial-based evaluations in terms of resource required for longer-term follow-up. More widespread use of routinely available data to support evaluations may help, allowing a focus on related outcomes such as hospitalisation with falls, delirium, dementia, and other health and care-related outcomes. Other limitations of the general deprescribing trial literature are also applicable to the RCTs included in the review, such as the need to consider barriers and enablers at the level of individual, practitioner and system; the need to integrate implementation into clinical decision support systems and the need to measure patient centred outcomes [28].

Conclusion

Evidence from a small number of RCTs of interventions targeting AC burden has identified no clear impact on key outcomes of AC burden score, cognition, falls or quality of life. Future interventions should focus on key intervention components required to reduce AC burden, addressing known barriers to achieving successful deprescribing. Interventions should ideally only proceed to definitive evaluation once impact on AC burden score can be demonstrated as otherwise it is implausible that intervention effect on clinical outcomes such as cognition can be generated or attributed to the intervention. Particular attention should be given to implementation and assessment of overall intervention fidelity as part of intervention optimisation. Future trials should clearly justify outcome selection and ensure that sufficient time is allocated to generate impact on outcomes such as cognition that may require a relatively long-time horizon to achieve.

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Data Availability The data used for the current study are available from the corresponding author on request.

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