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Interventions to reduce anticholinergic burden in adults aged 65 and over: A systematic review

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Brief summary:

- Pharmacists, either individually or as part of a team, provided the intervention in the majority of studies.
- Most involved individual patient medication review followed by feedback to the prescriber.
- Three of the four RCTs and all four non-RCTs reported a decrease in ACB following the intervention.

Keywords: intervention, anticholinergic burden, inappropriate prescribing, older adult

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Conflicts of interest:

There are no conflicts of interest.

Author contribution

AN: concept, design, protocol, screening, data extraction, critical appraisal using bias tools, interpretation of data, drafting the manuscript, approving final manuscript.

PKM: concept, supervision, design, protocol, screening, adjudication, interpretation of data, drafting the manuscript, approving final manuscript.

CMB: concept, supervision, design, protocol, screening, adjudication, interpretation of data, drafting the manuscript, approving final manuscript.

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Interventions to reduce anticholinergic burden in adults aged 65 and over: A systematic review

ABSTRACT

Introduction: Older age is associated with multi-morbidity and polypharmacy with high anticholinergic burden (ACB). High ACB is linked to adverse events such as poor physical functioning, dementia, cardiovascular disease and falls. Interventions are needed to reduce this burden.

Aims/Objectives: The aim was to systematically review the literature to identify and describe studies of clinical and cost effectiveness of interventions designed to reduce ACB in adults(≥65years), on polypharmacy regimes, compared with usual care. The objective was to answer the questions: What are the contents of the interventions? Were these interventions clinically effective? Were these interventions cost effective?

Design, Setting and Participants: Systematic review of interventions to reduce anticholinergic burden in adults aged 65 and over in any clinical setting

Methods: Eligible papers reported primary or secondary research describing any type of intervention including systematic reviews, Randomised Controlled Trials (RCTs), Controlled Clinical trials or pre/post non-randomised intervention studies (PPIs) published in English from January 2010 to February 2019. Databases searched included CINAHL, Ovid MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL).

Results: The search yielded 5862 records. Eight studies (4 RCTs, 4PPIs) conducted in hospital (4), community (2), nursing homes (1), and retirement villages (1) met the inclusion criteria. Pharmacists, either individually or as part of a team, provided the intervention in the majority of studies (6/8). Most (7/8) involved individual patient medication review followed by

feedback to the prescriber. Two of the four RCTs and all non-RCTs reported a decrease in ACB following the intervention. No study reported cost outcome.

Conclusions and Implications: Pharmacists may be well placed to implement an ACB reduction intervention. This is the first systematic review of interventions to reduce ACB in older adults and highlights the need for development and testing of high quality pragmatic clinical and cost-effectiveness trials in community and specific patient populations at high risk of harm from ACB.

[PROSPERO registration: CRD42018089764]

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Introduction

Anticholinergic drugs act by blocking parasympathetic nerve impulses [1] and, hence, control involuntary muscle movement [2]. They are, therefore, commonly prescribed to treat gastrointestinal disorders (e.g. diarrhoea, ulcers, spasms), overactive bladder (e.g. incontinence) and to relieve symptoms of Parkinsonism. In addition, antidepressants and antipsychotics which are often used among older people also have anticholinergic properties. The prevalence of their use is steadily increasing (estimates vary from 37-63%) [3-5], particularly in the ageing population. However, anticholinergics are associated with a wide range of adverse effects, and there have been numerous calls for interventions to reduce the use of such drugs. The challenge is to minimise the adverse effects of anticholinergic drugs whist still retaining the benefits.

The term "anticholinergic burden" refers to the cumulative anticholinergic action resulting from concomitant use of multiple medications with anticholinergic properties [1]. It is recognised that high anticholinergic burden is linked to adverse events such as poor physical functioning, dementia, and falls [6, 7]. However, to date there are few studies which examine the clinical and cost effectiveness of using these tools in practice to change prescribing.

Therefore, the aim of this study was to systematically review the literature to identify and describe studies of the clinical and cost effectiveness of interventions designed to reduce the anticholinergic burden in adults aged 65 and over compared with usual care, and assessed with any outcome measure. The specific research questions were: What are the contents, or ingredients, of the interventions? Were the interventions clinically effective? Were the interventions cost effective?

Methods

The systematic review protocol was registered in PROSPERO (CRD42018089764). The literature search was systematically conducted in accordance with the general principles of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in healthcare [8] and the Cochrane Handbook for Systematic Reviews of Interventions [9], and is reported in accordance with the PRISMA statement [10]. The studies and interventions are described according to the TIDieR, CONSORT or STROBE checklists [11-13], as appropriate.

Search strategy, inclusion and exclusion criteria

This review included primary or secondary research studies that reported a relevant intervention or interventions, including systematic reviews, randomised controlled trials (RCTs), controlled clinical trials (CCTs), pre-post intervention non randomised studies (PPIs), either delivered by a single health care professional or by multidisciplinary team, published from January 2010 to February 2019 in English language. We restricted the time period of studies to 2010 onwards to provide a realistic picture of contemporary practice and populations as well as based on our knowledge that most studies which have demonstrated adverse effects of ACB have been published from early 2000s with some intervention studies from 2010. Epidemiological studies, case reports, reports published in non-English language for which a translation could not be organised and animal studies were excluded. The participants eligible for inclusion were adults aged 65 and over on long term medication, which was defined as using medications for more than 12 weeks, for the purposes of this study. Eligible interventions were any interventions/strategies that aimed to reduce anticholinergic burden. The comparator was usual care in the respective setting. The

outcome measures were 1) medication use, including number of drugs and anticholinergic burden or other score, 2) patient outcomes such as falls etc., and 3) costs outcomes.

Methods for identification of studies

Databases including CINAHL, Ovid MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials [CENTRAL]) were searched for original articles and conference abstracts, and the grey literature was identified in Google Scholar from 2010 to March 2018. This was updated in February 2019. The search terms used were: anticholinergic$.tw. OR cholinergic antagonist$.tw. OR antimuscarinic$.tw. OR muscarinic antagonist$.tw. AND Anticholinergic Syndrome OR Drug-Related Side Effects OR adverse effect$.tw. OR adverse adj2 effect$.tw. OR adverse reaction$.tw. OR adverse adj2 reaction$.tw. OR side effect$.tw. OR burden.tw AND limit to (human and year= "2010-Current" and "all aged (65 and over)"). The search strategy was developed for Ovid MEDLINE and was adapted for use in the other databases (CINAHL, EMBASE and CENTRAL).

Data collection and analysis

Two reviewers (AN, together with one of PKM, CMB or MC) independently screened titles and abstracts of records to determine whether they potentially met the inclusion criteria. Next, full-texts of potentially eligible studies were further examined by two reviewers (AN, together with one of PKM, CMB or MC) against the inclusion criteria to determine eligibility. Discrepancies were resolved by discussion between reviewers.

A data extraction form was developed for the purposes of this review; one reviewer (AN) extracted data from all eligible studies and one reviewer (MC) cross-checked the data. Items from standard reporting checklists were included in the form; they were the TIDieR checklist

[11] to describe the interventions, the CONSORT 2010 checklist [12] to describe the RCTs and the STROBE checklist [13] for observational (non-randomised) studies, respectively. Disagreements were resolved by discussion between a minimum of two reviewers.

Quality assessment

Two reviewers (AN and MC) independently assessed risk of bias of included studies. The RCTs were assessed by the Cochrane Collaboration tool for assessing risk of bias [9]. Non randomised studies were assessed using the Critical Appraisal notes and checklists from the Scottish Intercollegiate Guidelines Network (SIGN), UK [14].

Strategy for data synthesis

Information extracted was tabulated and described narratively. The original intention was to quantify the evidence by meta-analysis, but this was not possible due to heterogeneity of the included studies.

Results

Description of included studies

The search strategy yielded 5862 records. After removing 325 duplicates, 5543 titles and abstracts were screened; of these, full text articles were retrieved for 33 potentially eligible papers from which eight (seven full text papers[15-17, 19-22] and one conference abstract [18] met the eligibility criteria and were included in the review. Details of the study selection process are shown in Figure 1.

Study characteristics

The eight included studies (4 Randomised Controlled Trials (RCTs) [15-18] and 4 (Non-randomised Pre-Post Intervention studies) (PPIs) [19-22]) were from Australia [15, 19], Norway [16], Spain [21], the Netherlands [18], United States [17, 20] and United Kingdom [22]. One RCT was a pilot study using an unblinded cluster randomized design [15]. No systematic reviews were identified. Pharmacists, either individually or as part of a team, provided the intervention in the majority of studies (six of eight studies) [16-21]. A summary of the characteristics of the eight included studies is presented in Table 1. Participants were predominantly Caucasian and female. The intervention duration of the studies varied from median 6.5 days [21] to 3 months [15, 18]. The audit and feedback study [22] was conducted in two phases; first, in April/May 2011 and, second, in June 2011. There was one multi-centre RCT [15], and the remainder were single centre studies [16-22].

Studies were conducted in various settings including hospital [17, 20-22], the community [18, 19], nursing homes [16] and self-care retirement village [15]. The majority of studies had small sample sizes (n=50-115 participants) with the exception of one community-based PPI that included 372 participants[19]. The mean age of participants in all eight studies was over 75 years. Study design and participant characteristics for each included study are presented in Appendix 1. None of the studies mentioned the involvement of patients and/or other stakeholders (e.g. health professionals, policy makers) with regards to study/intervention design.

Risk of bias assessment

None of the four RCTs complied fully with the Cochrane Collaboration tool for risk of bias assessment, and one study met only one criterion [15]. Blinding of participants and outcomes had the lowest compliance. Sequence generation was judged to be adequate in only one

147 study [17], whilst the remaining three studies did not report sufficient detail to enable an
148 assessment. The conference abstract [18] included little methodological detail resulting in a
149 high proportion of 'unclear' judgements. The risk of bias assessments of the RCTs are
150 displayed in Figure 2.

151 Assessment of the risk of bias for the four PPI studies demonstrated that they addressed
152 appropriate and clearly focused research questions, had reliable methods of assessment of
153 exposure, and valid and reliable outcome measures. However, the criterion of selection bias
154 was not applicable given that there was no control arm in the four PPI studies [19-22]. The
155 summary of the critical appraisal notes and SIGN checklists for individual PPIs is provided in
156 Appendix 2.

157 *Contents of the interventions*

158 The summary of interventions in the included studies is presented in Appendix 3 and
159 reported according to the TIDieR checklist. The intervention provider(s) in six of the eight
160 included studies was a pharmacist, either individually or as part of a team undertaking
161 patient medication review followed by feedback to the prescriber [16-21]; in another study a
162 clinical pharmacologist and geriatrician made recommendations for prescribing to a GP [15];
163 and the final study used an audit and feedback intervention delivered by consultants in
164 geriatric medicine [22].

165 The interventions that included recommendations to the prescriber adopted a range of
166 different approaches, for example, in one hospital study conducted in Spain, pharmacists
167 conducted clinical interviews, followed by medicine reconciliation and checking of medicine
168 appropriateness against the STOPP/START criteria before providing recommendations to the

prescriber [21]. In other studies, a clinical pharmacist performed a note based medication review and then provided verbal recommendations to respective physicians in nursing homes (Norway) [16], community settings (the Netherlands) [18], or in an Alzheimer's Disease Centre (United States) [17]. In another US study, a pharmacist undertook a patient medication review using the hospital Electronic Health Record (EHR) to review patients' medication and then provided electronic recommendations to the prescribers [20]. In self-care retirement villages (Australia), recommendations were made by a geriatrician and clinical pharmacologist [15]. The pre-post intervention clinical audit study in the UK [22] involved feedback to the clinicians by posting a list of drugs with respective anticholinergic burden in the second phase of audit on the ward drug trolley to inform the geriatrician who looked after the patient.

Outcomes of interventions

A summary of results of clinical effectiveness of individual studies is presented in Table 2. A meta-analysis was not possible due to heterogeneity of the studies with regard to study designs (e.g. use of different measures of anticholinergic burden) and outcome measures. Almost all the studies chose to focus on measures of anticholinergic use as their main outcome [15, 17, 20-22].

RCTs

Two of the four RCTs reported that anticholinergic burden decreased significantly following the intervention [16-17]. The trial carried out in the nursing home setting resulted in a statistically significant reduction in the median Anticholinergic Drug Scale (ADS) from baseline for the intervention group and remained unchanged in the control group ($p<0.0001$) [16]. The trial in the Alzheimer's Disease Centre showed a statistically significant improvement in the Medication Appropriateness Index (MAI) ($p=0.04$) and reduced ADS score ($p=0.03$) in the

intervention group compared with the control group [17]. However, the changes in DBI following the intervention in the cluster RCT conducted in the Australian retirement villages were not significantly different between the intervention and control group [15]. Furthermore, the RCT that involved a medication review by a pharmacist in the community (n= 157, with 4.3% attrition rate over 3 months duration) showed no difference between the groups in the proportion of patients having a decrease in DBI ≥0.5 (14.7% vs. 15.9%; OR=0.91, 95%CI=0.38-2.18), although there was a reduction in sedative side effect [18].

Non-randomised PPI studies

All four pre-post intervention studies (PPIs) showed significant reductions in anticholinergic burden following the intervention [19-22]. In the study in Australia conducted in the community, the total DBI was significantly reduced (p<0.001) and pharmacists' recommendations were associated with a decrease in the use of Potential Inappropriate Medications (PIMs) [19]. In the Electronic Health Record (EHR) medication review study, the acceptance rate of pharmacists' recommendations by primary care physicians was 50% (95%CI:37-63%) and the Anticholinergic Risk Scale (ARS) score was reduced significantly (p=0.0003) after intervention [20]. In the STOPP/START study, both the ADS and ARS scores decreased significantly (p=0.001 and p=0.047 respectively) between admission and discharge [21]. Finally, in the feedback audit and feedback study, the ARS scores were significantly decreased and there was a higher proportion of patients on anticholinergics who had their medications either stopped or reduced (OR=5.0, 95%CI:1.4-17.8) compared to pre-intervention [22].

Clinical and Cost effectiveness of interventions

One RCT reported no significant differences in the results of cognitive function tests between groups, despite a significant decrease in anticholinergic use following the intervention [16].

None of the included studies reported information on the cost-effectiveness of the interventions.

Discussion

This is believed to be the first systematic review assessing information about interventions that reduce anticholinergic burden in adults aged 65 and over. This work identified eight studies reporting interventions to reduce anticholinergic burden in patients aged 65 and over. The interventions were primarily provided by pharmacists using patient-centred approaches, but there was no consistency in the specific approach used. Systematic reviews of general deprescribing in older people have also reported the delivery of deprescribing interventions by pharmacists, albeit in a smaller number of included studies (4/9 and 2/18 studies included in the respective reviews) [23, 24].

Two of the four identified RCTs [16-17] and all four PPIs [19-22] demonstrated that the intervention reduced anticholinergic burden effectively. These findings are in line with two systematic reviews (including randomised and non-randomised studies) of general deprescribing in people aged 65 and over, which reported that deprescribing reduced medication use [24, 25]. The two RCTs that reduced anticholinergic burden were both small trials of short duration [16, 17]. The RCT conducted in the Alzheimer's Disease Centre was the only study to report a clinical outcome (i.e. cognitive function; the Consortium to Establish a Registry for Alzheimer's Disease 10-wordlist test for immediate recall) but showed no statistical differences between the intervention and control group [16]. Loss to follow-up rate in three of the four RCTs was low [15, 17, 18] ,suggesting that the interventions were acceptable and feasible, in line with the findings of a systematic review of general deprescribing in older adults [24].

However, no studies in the review reported costs or cost-effectiveness and the majority of the studies did not include an objective clinical outcome such as physical function, cardiovascular diseases, falls and mortality. Recent systematic reviews have found the evidence on the impact of general deprescribing on clinical outcomes to be ambiguous [23-25]. Therefore, it appears that the current evidence base on the impact of deprescribing in older adults is inconclusive.

Strengths of the review included a comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria in the selection of articles included. The search was limited to 2010 onwards, providing contemporary practice relevant to the current ageing population with multi-morbidity and polypharmacy as well as the growing number of ACB medications in the literature. The search strategy was conducted on more than one database and a minimum of two researchers screened abstracts and full texts independently to select eligible publications. Furthermore, the review was conducted rigorously according to published guidelines [9]. Whilst emphasizing the need for RCT evidence - the 'gold standard' for health research- this review has also summarised evidence from other types of studies.

However, overall the studies included had many limitations. Sample sizes were small, and two self-identified as pilot studies. Most had considerable methodological limitations introducing bias, and there were only four randomised controlled trials. In the RCTs, it was not possible to blind participants or personnel due to the nature of the interventions. The inclusion of non-randomised PPIs in the review increased the available body of evidence but the limitations of this study design should be borne in mind and their findings interpreted with caution. In addition, interpretation of PPI studies is not straight forward. Changes in the outcome of interest may be due to the intervention; however, it may also reflect disease natural history

(as the condition improves over time or clinical therapy improves with experience), patient selection (patients before and after the intervention may have differed in clinically important attributes), or placebo effects (because neither patient nor provider is blinded). In addition, there is a natural tendency for processes to regress to the mean, which may occur without intervention.

Across studies, the outcomes that were measured were not similar enough to be statistically combined, for example, Anticholinergic Drug Scale (ADS), Anticholinergic Risk Scale (ARS), Anticholinergic Cognitive Burden (ACB) scale, Drug Burden Index (DBI) changes, Medication Appropriate Index (MAI) changes, recommendation acceptance rate, perceived health status and also Consortium to Establish a Registry for Alzheimer's disease 10-wordlist test. None of the included studies tested long-term effectiveness of the intervention, with the longest study duration being 3 months. All studies were conducted in different countries and therefore generalisability across countries is uncertain due to differences in infrastructure and also background (e.g. lifestyle and ethnicity) of participants.

Only one study examined a clinical outcome. In that study, participants' cognitive function did not change despite the median ADS score decreasing by 2 units in the intervention group [16]. However, a previous study suggested that performance of individuals with higher anticholinergic burden in cognitive tasks was poorer than that of those with lower ACB [26]. This may be due to the fact that detection of the impact of reducing ACB on cognition could require a longer follow-up. A study with 8 week of follow up was not of sufficient length to assess the long-term impact of the intervention [17]. One study did not include short-term medications when calculating anticholinergic burden, and that might have influenced the

283 outcome measurement in ACB scores or scales [21]. Current knowledge gaps identified in this
284 review and recommendations for future research are presented in Table 3.

285

286 ## Conclusions and Implications

287 This systematic review suggests that pharmacists may be well placed to provide an
288 anticholinergic reduction intervention. Further rigorous research is needed to confirm this
289 finding, identify the best approach, its cost effectiveness and longer term patient outcomes
290 in community settings as well as for specific patient populations.

291 *Conflict of Interest*

292 There are no conflicts of interest.

293

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Figure 1: PRISMA Flow Diagram

Figure 2: Risk of bias in individual RCT studies

Table 1 Summary of study characteristics of the eight included studies

Study ID	Inclusion and exclusion criteria (participants)	Length of follow-up	Baseline anticholinergic drug scores	Baseline information	Outcomes reported
RCTs					
Gnjidic 2010 [15]	Inclusion criteria: Residents were included if they were aged ≥ 70 years and if they consulted their GPs regularly. Exclusion criteria: NR	3 months	NR	Exposed to anticholinergic drugs Intervention group = 8 (14.0%), Control group =19 (32.8%); mean DBI score Intervention group = = 0.22 +/- 0.42 , Control group = 0.26 +/- 0.34	Primary: change in DBI at 3 months after intervention as compared to baseline.
Kersten 2013 [16]	Inclusion criteria: Patients who have anticholinergic drug scale (ADS) of greater than or equal 3 (by Channahan et. al., 2006) Exclusion criteria: Patients with blindness, deafness, aphasia, delirium, or severe dementia (score 3 on the Clinical Dementia Rating scale)	8 weeks	ADS median Intervention group = 4 (IQR=3-5), Control group 4(IQR=3-5) Overall median ADS score 4	Baseline Mini-Mental State Examination score Intervention group = 20.5 (16-25), Control group = 20 (16-22); Whole mouth resting salivary flow (g/min) Intervention group = 0.21 (0.07-0.54), Control group = 0.22 (0.16-0.37); SAA (pmol/mL atropine equivalents) Intervention group = 4.27 (2.43-7.96), Control group = 4.79 (2.68-8.71)	Primary: Consortium to Establish a Registry for Alzheimer's Disease 10-wordlist test for immediate recall. Secondary: Mini-Mental Sate Examination for delayed recall and recognition of words, Dry mouth (saliva flow at 4 week follow-up), and serum anticholinergic activity (SAA) at 4 and 8 weeks following intervention. Consortium to Establish a Registry for AD 10-wordlist for delayed recall and recognition

Study ID	Inclusion and exclusion criteria (participants)	Length of follow-up	Baseline anticholinergic drug scores	Baseline information	Outcomes reported
Moga 2017 [17]	Inclusion criteria: Patients who were actively enrolled in the ADC cohort; 65 years of age and older; reporting at least one drug with anticholinergic properties at their annual ADC visit; and willing to participate in our intervention study. Exclusion criteria: Patient who were moderate or severe dementia as measured by a Clinical Dementia Rating (CDR) global score ≥ 2, or lived in a long-term care facility at the time of enrolment	8 weeks	ADS median Intervention group = 2.8 +/- 1.9, Control group 2.9 +/- 1.3	Medication appropriateness index Intervention group mean ;12.2 +/- 7.9 , Control group 13.0 +/- 4.4 ; Intervention group; number of anticholinergic drugs 1, ≥2 = 14 (56.0%), 11(44.0%), respectively, number of anticholinergic drugs 1, ≥2 = 11 (44.0%), 14(56.0%), respectively	Co-primary: the impact of the targeted MTM intervention on potentially inappropriate anticholinergic use by evaluating change from baseline to end of study in: appropriateness of anticholinergic medication prescribing, as measured by the medication appropriateness index (MAI); and anticholinergic burden as measured by the number of anticholinergic drugs used and the anticholinergic drug scale (ADS) Secondary: the change in perceived health status from baseline to the end-of-study visit as measured using the SF-36, a validated instrument that evaluates eight health domains categorized into three major health attributes.
van der Meer 2016 [18]	Inclusion criteria: Community-dwelling patients aged ≥ 65 years, using ≥ 5 medications for ≥ 3 months including at least one medication with an ATC code from the groups N05 or N06 and having a DBI ≥ 1 were included in the study Exclusion criteria: NR	3 months	NR	Mean DBI 2.6	Primary outcome: the difference in proportion of patients having a decrease of DBI ≥ 0.5 between the intervention and control arm at 3 month follow-up Secondary: anticholinergic and sedative effects, falls, cognitive function, activities of daily living, quality of life, hospital admission and mortality

Study ID	Inclusion and exclusion criteria (participants)	Length of follow-up	Baseline anticholinergic drug scores	Baseline information	Outcomes reported
Non-randomised PPI studies					
Castelino 2010 [19]	Inclusion criteria: Patients (aged ≥65 years). Patients were referred to the HMR service on the basis of standard criteria, e.g. taking ≥ 5 regular medications; taking ≥ 12 doses of medication/day; significant changes made to the medication regimen in the last 3 months; taking a medication with a narrow therapeutic index; and recent (within the last 4 weeks) discharge from a facility/hospital. Exclusion criteria: NR	NR	NR	Drug Burden Index medications prescribed (no.[mean(SD)] = 390 [1.05(1.1)], Anticholinergic medication prescribed (no.[mean(SD)] = 110 [0.29(0.5)]; Potentially Inappropriate Medications (PIMs) prescribed (no.) = 196, PIMs independent of diagnosis [no.(SD)] = 170 (86.7), PIMs dependent of diagnosis [no.(SD)] = 26 (13.3)	Primary: the total DBI score at baseline and post-HMR. The data were also examined to determine the extent of PIM use (2003 Beers' criteria), and the number and nature of pharmacists' recommendations
Hanus 2016 [20]	Inclusion criteria: The medical records of patients who met the following criteria were evaluated bimonthly: 1) Primary Care Physician (PCP) visit within 2 weeks; (2) three or more inpatient hospitalizations or emergency department visits in the past year; and (3) ten or more active medications. Exclusion criteria: NR	NR	average ARS = 5.2 +/- 2.5	NR	Primary: ARS score was calculated for all eligible patients. Patients with an ARS score of 3 or more underwent comprehensive medical record review to establish clinically relevant medication therapy recommendations. These recommendations were made to patients' PCPs via the shared EHR before the patient's upcoming visit, with enough time for the PCP to evaluate and implement them. Finally, post-visit recommendation outcomes were determined by the pharmacist and

Study ID	Inclusion and exclusion criteria (participants)	Length of follow-up	Baseline anticholinergic drug scores	Baseline information	Outcomes reported
					categorized as “accepted” if implemented or “rejected” if ignored.
Rojo-Sanchıs 2017 [21]	Inclusion criteria: Patients more than 80 years old who were admitted to the acute geriatric unit of tertiary hospital Exclusion criteria: Patients who were readmission in less than 3 months, receiving palliative care before or during admission, and death within the hospitalization period	Median length of stay was 6.5 days	ACB = 1.9 (95%CI=1.6-2.2), ADS = 1.4 (95%CI=1.2-1.8), ARS =0.9 (95%CI=0.7-1.2)	At admission, 71.6%, 50.7%, and 79.1% of the study patients were treated with an anticholinergic drug listed on the ADS, ARS, and ACB scales, respectively. The most commonly used anticholinergic drugs at admission were furosemide (61.2% of patients; when considering ADS and ACB scales) and trazodone (28.4% of patients; when considering ARS scale).	Primary: anticholinergic burden was calculated according to the score assigned to each drug on the ADS, ARS, and ACB scales. Thus, the anticholinergic burden of each patient on admission and at discharge was determined using each of the three scales

Study ID	Inclusion and exclusion criteria (participants)	Length of follow-up	Baseline anticholinergic drug scores	Baseline information	Outcomes reported
Tay 2014 [22]	Inclusion criteria: Patients age at least 65 years who admitted to the word Exclusion criteria: NR	First phase: 25th April 2011 to 9th May; second phase: 5th June 2011 to 20th June 2011	Median ARS (IQR); First phase preadmission = 0(0-1) First phase Post review = 0(0-1) p=0.01, Second phase preadmission = 0(0-1) First phase Post review = 0(0-0) p=0.002	On anticholinergics First phase = 33%, Second phase = 31%	Primary: Anticholinergic drug exposure [number of anticholinergic drugs and Anticholinergic Risk Scale (ARS) score]

Note ACB = Anticholinergic Cognitive Burden Scale, ADS = Anticholinergic Drug Scale, ARS = Anticholinergic Risk Scale, CI= Confidence Interval, DBI = Drug Burden Index, HMR = Home Medication Review, IQR = Interquartile range, NR = Not reported, PIMs = Potential Inappropriate Medication

Table 2 Summary of results of cost-effectiveness of the eight included studies

Study ID	Summary of results reported by the eight included studies
RCTs	
Gnjidic 2010 [15]	In this cluster randomized trial, there was a significant imbalance at baseline where 19 of 57 (33.3%) participants in the intervention group and 31 of 58 (53.4%) participants in the control group had a DBI >0. Following the intervention, DBI decreased in 6 of 19 (32%) in the intervention group, and 6 of 31 (19%) in the control group (p=0.13). DBI increased in 4 participants in the intervention group (two in each group, DBI=0 and DBI >0, respectively) and none in the control group. GPs identified the following barriers to reducing anticholinergic and sedative drugs: uncomfortable altering prescriptions initiated by specialists; unable to influence patients' altitudes; unaware of patients' medications and strong clinical indication.
Kersten 2013 [16]	After 8 weeks, the median ADS score was significantly reduced from 4 to 2 in the intervention group, whereas it remained unchanged in the control group (p <0.0001). The significant reduction in ADS score was achieved by replacement or withdrawal of anticholinergic drugs. No statistically significant difference between the means was detected in any of the cognitive tests after 8 weeks (p > 0.19). The saliva flow or SAA did not differ significantly between the subgroups at the follow-ups, that is, at 4 weeks (p = 0.34) and 8 weeks (p = 0.83), respectively.
Moga 2017 [17]	The number of anticholinergic drugs was reduced significantly in the intervention group. The intervention group was over 5 times as likely as the control group to discontinue an inappropriate anticholinergic medication. The targeted MTM intervention resulted in statistically significant CDR adjusted differences between groups with regard to improved MAI (change score of 3.6 (±1.1) for the MTM group as compared with 1.0 (±0.9) for the control group, p = 0.04) and ADS (change score of 1.0 (±0.3) for the MTM group as compared with 0.2 (±0.3) for the control group, p = 0.03).
van der Meer 2016 [18]	Multilevel analysis showed no significant difference in the proportion of participants having a decrease in DBI ≥ 0.5 between intervention- and control arm (14.7% versus 15.9%, OR=0.91, 95% CI 0.38-2.18], p=0.836). Patients in the intervention group reported fewer sedative effects (p=0.002). The intervention was not effective in reducing the DBI in this frail group of older people.
Non-randomised PPI studies	
Castelino 2010 [19]	Overall, medications contributing to the DBI (i.e. medications with sedative or anticholinergic properties) and PIMs were identified in 60.5% (n = 225) and 39.8% (n = 148) of the patients, respectively. Following pharmacist recommendations during the HMR service, medications contributing to the DBI were identified in 51.6% (n = 192) of the patients. A statistically significant reduction in the sum total of DBI scores for all patients was observed following pharmacists' recommendations during the HMR service (206.9 VS 157.3, p < 0.001). Pharmacists' recommendations also led to a decrease in the use of PIMs, which were identified in 28.2% (n = 105) of the patients following the HMR service.
Hanus 2016 [20]	The aggregate post-intervention mean ARS score was 3.8±3.3, resulting in a mean change of 1.3±2.6 (p=0.0003). 89 medication therapy recommendations made to 21 PCPs. An overall recommendation acceptance rate of 50% (95%CI= 37%-63%) was observed.

Rojo-Sanchıs 2017 [21]	There was a significant reduction in anticholinergic burden between admission and discharge according to the ARS (P = 0.001) and ACB (P = 0.047) scales, and a non-significant reduction in anticholinergic burden according to the ADS scale (P = 0.087). The anticholinergic burden was reduced in 32.8%, 34.3%, and 37.3% of the patients according to the ARS, ACB and ADS scales, respectively.
Tay 2014 [22]	Fifty-three anticholinergic drugs were prescribed at baseline (preadmission) to 45/140 (32%) patients included throughout both phases of the audit. ARS scores fell significantly in both arms of the audit, more so in the second arm. The proportion of patients on anticholinergics who had their medications either stopped or reduced rose significantly from 8 out of 23 (35%) in the first arm to 16 out of 22 (72%) in the second arm (OR 5.0, 95% CI 1.4–17.8). The total number of anticholinergic drugs prescribed fell from 29 to 20 in the first phase, and from 24 to 11 in the second.

Note CDR= Clinical Dementia Rating, DBI = Drug Burden Index, HMR = Home Medication Review, NR = Not reported, PIMs = Potential Inappropriate Medications

Table 3 Current knowledge gaps identified in this review and recommendations for future studies

Current knowledge gaps	Recommendations for future studies
No RCTs reported the involvement of stakeholders during intervention design and/or process evaluation of the interventions.	Patients and other stakeholders should be involved from the design stage to evaluation and implementation of any future interventions.
No studies in the review reported costs or cost-effectiveness.	We recommend the assessment of costs or cost-effectiveness in future studies.
No long-term follow-up of clinical outcome(s) which are associated with ACB reduction intervention are available.	Longer-term follow up of clinical outcomes, such as cognitive function, is recommended.

Table

Appendix 1 Study design and participant characteristics for eight included studies

Study ID, country, publication type	Setting	Sample size (n)	Age	Sex	Disease characteristics	Mean no of medications
RCTs						
Gnjidic 2010, Australia, full-text [15]	Self-care retirement villages	115 (intervention group n = 57, control group n=58)	Intervention group mean ; 80.4 +/- 5.7 years, Control group 84.1 +/- 5.7 years	Intervention group; Women = 41 (71.9%), Men =16 (28.1%), Control group; Women = 15 (25.9%), Men =43 (74.1%)	NR	Mean Intervention group = 6.7 +/- 3.8 , Control group 6.2 +/- 3.3
Kersten 2013, Norway, full-text [16]	Nursing home	101 (intervention group n=51, control group n=50) 87 were assesses at baseline and more were lost to follow-up	Intervention group median (IQR); 86 years (73-99), Control group 85 years (74-97) Overall mean age 85 years	Intervention group; Women = 39/47 (83%), Control group; Women = 30/40 (75%)	Intervention group; Clinical dementia rate 0,1,2 = 19(40.4%), 17(36.2%), 11 (23.4%), respectively, Control group; Clinical dementia rate 0,1,2 = 8(20%), 19(47.5%), 13 (32.5%), respectively	Median of scheduled drugs Intervention group = 10 (IQR=7-13), Control group 9(IQR=6-11) Overall median drugs 9
Moga 2017, the United States, full-text [17]	Hospital	50 (intervention group n = 25, control group n=25)	Intervention group mean ; 76.3 +/- 6.2 years, Control group 79.1 +/- 6.9 years	Intervention group; Women = 18 (72.0%), Control group; Women = 17 (68.0%)	Intervention group; Clinical dementia rating 0,0.5,1 = 20(80.0%), 4(16.0%), 1 (4.0%), respectively, Control group; Clinical dementia rate 0,0.5,1 = 13(52.0%), 8(32.0%), 4(16.0%), respectively	NR

Study ID, country, publication type	Setting	Sample size (n)	Age	Sex	Disease characteristics	Mean no of medications
van der Meer 2016, the Netherlands, conference abstract [18]	Community	157, 4.3% drop out	mean 75.5 year	Women = 70.9%	NR	8.9
Non-randomised PPI studies						
Castelino 2010, Australia, full-text [19]	Community	372	mean (SD)= 76.1 (7.8)	Women = 55.0%	mean (SD) chronic medication per patient = 6.0 (3.0),	mean (SD) regular prescription 8.7 (3.0)
Hanus 2016, the United States, full-text [20]	Hospital	59	mean 77 +/- 9.3 years	Women = 30 (50.9%), Men =29 (49.1%)	ER visit = 2.6 +/- 1.8, Hospitalisations + ER visit = 1.6 +/- 1.4, Hospitalisations = 0.7 +/-1.0	19.6 +/- 6.7
Rojo-Sanchıs 2017, Spain, full-text [21]	Hospital	67	mean 91.3 years (95%CI=90.9-93.6)	Women = 67.2 % (54.6-78.2)	Dementia 35.8% (95%CI=24.0-47.6) Previous fall 11.9%(95%CI=5.3-22.2) Auditory impairment 56.7%(95%CI=44.0-68.8), Constipation 25.4%(95%CI=15.5-37.5), Stroke 14.9%(95%CI=7.4-25.7), DM 16.2%(95%CI=8.3-27.1), CKD 36.85(95%CI=25.4-49.3), Institutionalised 32.8%(95%CI=21.8-45.4)	7.6 (95%CI=4.9-10.9)

Study ID, country, publication type	Setting	Sample size (n)	Age	Sex	Disease characteristics	Mean no of medications
Tay 2014, the United Kingdom, full-text [22]	Hospital	70 each phase	First phase, mean (SD); 84.2 (7.3), Second phase 83.0 (6.3),p=0.30	Women; First phase 76%, Second phase 61%, p=0.10	Dementia First phase = 20%, Second phase = 19%, p=1; Delirium First phase = 37%, Second phase = 41%,p=0.73	First phase = 6, Second phase = 7, p=0.14

Note ACB = Anticholinergic Cognitive Burden Scale, ADS= Anticholinergic Drug Scale, ARS = Anticholinergic Risk Scale, CI= Confidential Interval, IQR = Interquartile range, no. = Number, NR = Not Reported, SD = Standards Deviation

Table

Appendix 2 Summary of risk of bias assessment of non-randomised PPI studies included in the review, based on SIGN checklist

	Questions	Castelino 2010 [19]	Hanus 2016 [20]	Rojo-Sanchis 2017 [21]	Tay 2014 [22]
SECTION 1	Internal validity				
1.1	The study addresses an appropriate and clearly focused question.	Yes	Yes	No	Yes
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	NA	NA	NA	NA
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	NA	NA	NA	NA
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	NA	NA	NA	NA
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?	NA	NA	NA	NA
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	NA	NA	NA	NA
1.7	The outcomes are clearly defined.	Yes	No	No	No
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	NA	NA	Yes	NA
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	NA	NA	NA	NA
1.10	The method of assessment of exposure is reliable.	Yes	Yes	Yes	Yes
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes	Yes	Yes	Yes
	Questions	Castelino	Hanus	Rojo-	Tay

		2010 [19]	2016 [20]	Sanchis 2017 [21]	2014 [22]
1.12	Exposure level or prognostic factor is assessed more than once.	Yes	Yes	Yes	Yes
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Can't say	Can't say	Can't say	Can't say
1.14	Have confidence intervals been provided?	No	Yes	Yes	Yes
SECTION 2	Overall assessment of the study				
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality	High quality	High quality	High quality
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes	Yes	Yes	Yes
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes	Yes	Yes	Yes

Note NA = Not Applicable

Table

Appendix 3 Summary of content of interventions (based on TIDieR checklist) reported in the eight included studies

Study ID	Brief name of intervention	Goal of the elements essential to the intervention	Material or procedure that is used in the intervention	Intervention provider(s)	Mode of interventional delivery
RCTs					
Gnjidic 2010 [15]	Information provision to GPs on prescribing for older people	The aim of this cluster randomized clinical trial was to establish whether the DBI can be used as a clinical tool to guide prescribing to reduce exposure to anticholinergic and sedative medications in community dwelling older people.	The study intervention included a letter and phone call to GPs, using DBI to prompt them to consider dose reduction or cessation of anticholinergic and sedative medications. For the intervention group, a feedback letter was designed for GPs. The letter included information on the evidence base for minimizing DBI, a list of their patient's medications, information on their patient's DBI, and it' s likely impact on the patient's function. GPs were asked to consider whether the doses of medications contributing to the DBI could be reduced or withdrawn.	Geriatrician and clinical pharmacologist	The intervention involved using the DBI to prompt general practitioners (GPs) to consider reducing their patients' exposure to medications that have been shown to impair function.
Kersten 2013 [16]	Pharmacist-initiated reduction of ADS score after multi-disciplinary drug reviews	This study investigated if reduced anticholinergic drug burden (facilitated by pharmacist intervention) could improve cognitive function in nursing home residents	The intervention was based on a multidisciplinary drug review within 3 days after the baseline assessment. For patients randomised to the intervention group, the clinical pharmacist performed drug reviews guided by the ADS score model to advise the respective nursing home physician	Individual clinical pharmacist	The clinical pharmacist performed drug reviews guided by the ADS score model to advice the respective nursing home physician whether to discontinue or replace an anticholinergic drug with a drug alternative with less or no AA.

Study ID	Brief name of intervention	Goal of the elements essential to the intervention	Material or procedure that is used in the intervention	Intervention provider(s)	Mode of interventional delivery
			whether to discontinue or replace an anticholinergic drug with a drug alternative with less or no AA. When drug alternatives were unavailable, reduction in dosage was attempted to reduce the anticholinergic burden, but dose reductions did not affect the patients' overall ADS score		
Moga 2017 [17]	Targeted patient-centred pharmacist–physician team MTM intervention	This study investigated whether a targeted multidisciplinary team intervention would be successful at reducing inappropriate anticholinergic medication use in older patients enrolled in a cohort at the Alzheimer's Disease Centre (ADC) at University of Kentucky (USA)	All anticholinergic medications taken by each participant were labelled "potentially inappropriate" and were subject to review by the study team .The second step was conducted during the targeted MTM intervention when each of the previously flagged medications was evaluated using a risk–benefit approach with final recommendations based on the participant's input and preference.	Pharmacist and clinician	The targeted MTM intervention was based on the pharmacist–clinician team drug review between enrolment and visit 1. Typical MTM interventions evaluate all medications used by a patient and determine treatment necessity and potential changes; our intervention only targeted medications known to have anticholinergic properties. For patients randomised to the intervention group, the study pharmacist provided a revised medication plan based on the drug review, which was discussed with the participant and/or their Legally Authorized Representative. Specifically, the proposed plan attempted to recommend discontinuation or replacement of anypotentially inappropriate drug with anticholinergic properties, with safer drug alternatives (i.e., with less or noanticholinergic

Study ID	Brief name of intervention	Goal of the elements essential to the intervention	Material or procedure that is used in the intervention	Intervention provider(s)	Mode of interventional delivery
					activity). When drug alternatives were unavailable, reduction in dosage was recommended whenever possible to reduce the anticholinergic burden. Similar to routine clinical practice, the study clinician ultimately made the recommendations about prescription changes to the participant, while the study pharmacist was responsible for recommendations and provision of information to educate the participant about medication safety and the importance of patient involvement in medication awareness and oversight. Appropriate changes were determined by the licensed prescriber, but the participant had the freedom to acceptor reject the recommendations
van der Meer 2016 [18]	Medication review by a pharmacist	This study evaluated whether medication reviews provide an effective intervention to reduce a patients' Drug Burden Index (DBI)	A medication review by the pharmacist in cooperation with the patient's general practitioner.	Pharmacist	NR
Non-randomised PPI studies					
Castelino 2010 [19]	Home Medicines Review (HMR) services by pharmacists	The main aim of the study was to investigate whether Home Medicines	This retrospective study involved the collection of a purposive sample of de-identified HMR cases and reports pertaining to 372	Pharmacist	The retrospective analysis of medication reviews was performed for who received and HMR service from the pharmacists

Study ID	Brief name of intervention	Goal of the elements essential to the intervention	Material or procedure that is used in the intervention	Intervention provider(s)	Mode of interventional delivery
		Review (HMR) services by pharmacists for community-dwelling older people would lead to an improvement in the use of medications, as measured by a decrease in the DBI score. The study also aimed to investigate the (i) distribution of DBI scores and PIMs among older people living in the community, and (ii) impact of pharmacists' recommendations on DBI scores and PIMs.	community dwelling older people (aged ≥65 years). Patients were referred to the HMR service on the basis of standard criteria, e.g. taking ≥ 5 regular medications; taking >12 doses of medication/day ; significant changes made to the medication regimen in the last 3 months; taking a medication with a narrow therapeutic index; and recent (within the last 4 weeks) discharge from a facility/hospital.		
Hanus 2016 [20]	Electronic Medication therapy recommendation	This study was to determine the physician acceptance rates of medication therapy recommendations delivered electronically by means of the ARS service. Secondary aims included	A pharmacist-led Electronic Health Record-based medication therapy recommendation service to notify Primary Care Physicians (PCP). Patients with an ARS score of 3 or more underwent comprehensive medical record review to establish clinically relevant medication therapy recommendations. The business intelligence and decision support departments at DHS	Pharmacist-led team	These recommendations were made to patients' PCPs via the shared EHR before the patient's upcoming visit, with enough time for the PCP to evaluate and implement them. Finally, post-visit recommendation outcomes were determined by the pharmacist and categorized as "accepted" if implemented or "rejected" if ignored.

Study ID	Brief name of intervention	Goal of the elements essential to the intervention	Material or procedure that is used in the intervention	Intervention provider(s)	Mode of interventional delivery
		exploring potential associations between recommendation acceptance rates and patient and provider characteristics.	generated a bimonthly report to identify eligible patients for the pharmacist-led ARS service. The report identified patients at least 60 years old who had (1) an established PCP in the internal medicine or family medicine department, (2) a PCP visit in the following 2-week window, (3) at least 3 inpatient hospitalizations or emergency department (ED) visits in the past year, and (4) at least 10 active medications on their medication list. ARS score was calculated for all eligible patients. Patients with an ARS score of 3 or more underwent comprehensive medical record review to establish clinically relevant medication therapy recommendations.		
Rojo-Sanchis 2017 [21]	Standard Geriatric Pharmaceutical practice	This study was to determine, variations in anticholinergic burden of long-term medication in acute geriatric patients undergoing standard geriatric-pharmaceutical	During hospitalization, the geriatric and pharmaceutical care of patients was performed according to standard clinical practice. Pharmacists collaborated in the clinical interview, performed medication reconciliation, reviewed data from the clinical history, validated the	Individual Pharmacist	Anticholinergic burden was calculated according to the score assigned to each drug on the ADS, ARS, and ACB scales. Thus, the anticholinergic burden of each patient on admission and at discharge was determined using each of the three scales

Study ID	Brief name of intervention	Goal of the elements essential to the intervention	Material or procedure that is used in the intervention	Intervention provider(s)	Mode of interventional delivery
		practice between admission and discharge	daily treatments based on the STOPP/START validation criteria and recommended changes on patients' chronic treatments, which included deprescription, to geriatricians.		
Tay 2014 [22]	Consultant-led medication review targeting anticholinergics	The aim of study to identify whether a consultant-led medication review targeting anticholinergics would reduce anticholinergic drug exposure [number of anticholinergic drugs and ARS score	The first phase of audit assessed standard practice. Re-audit is a list of drugs with ARS scores was then pasted on the ward round trolley and the doctors' room wall, as a reminder of the anticholinergic drugs.	Multidisciplinary team including a ward pharmacist (1st audit only)	Standard practice involved a review of all new admissions to the ward by one of the four consultant geriatricians, as well as a multidisciplinary team of therapists, including a ward pharmacist. They would undertake comprehensive geriatric assessment, which included a review of the appropriateness of prescribed medications. Re-audit was undertaken. The same four consultants were told about the result of the first audit at an informal unit presentation. A list of drugs with ARS scores was then pasted on the ward round trolley and the doctors' room wall, as a reminder of the anticholinergic drugs

Note AA = Anticholinergic Activity, ACB = Anticholinergic Cognitive Burden Scale, ADS= Anticholinergic Drug Scale, ARS = Anticholinergic Risk Scale, DBI = Drug Burden Index, HMR = Home Medication Review, MTM = Medication Therapy Management, PIMs = Potential Inappropriate Medications

Figure

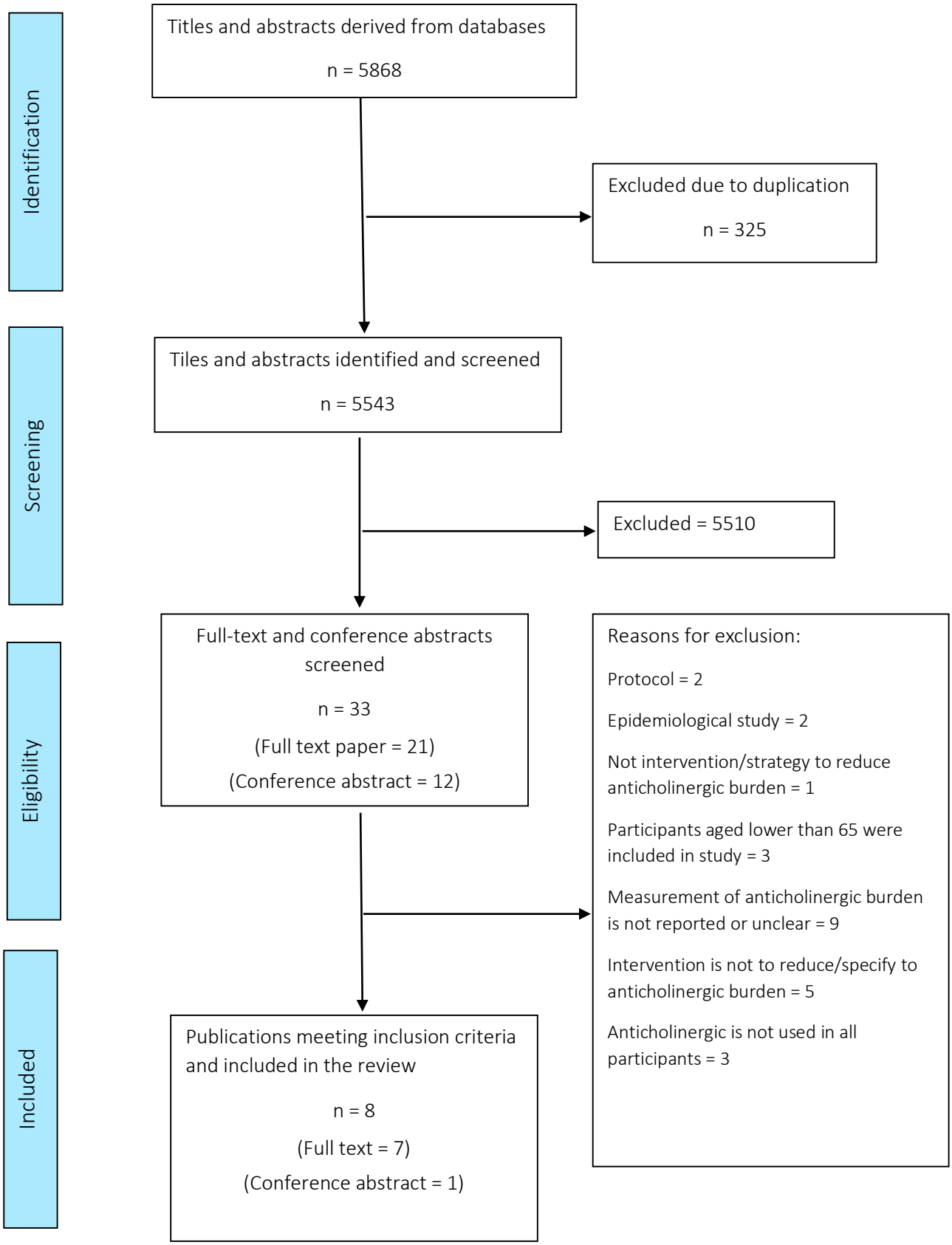

Figure 1: PRISMA Flow Diagram

Figure

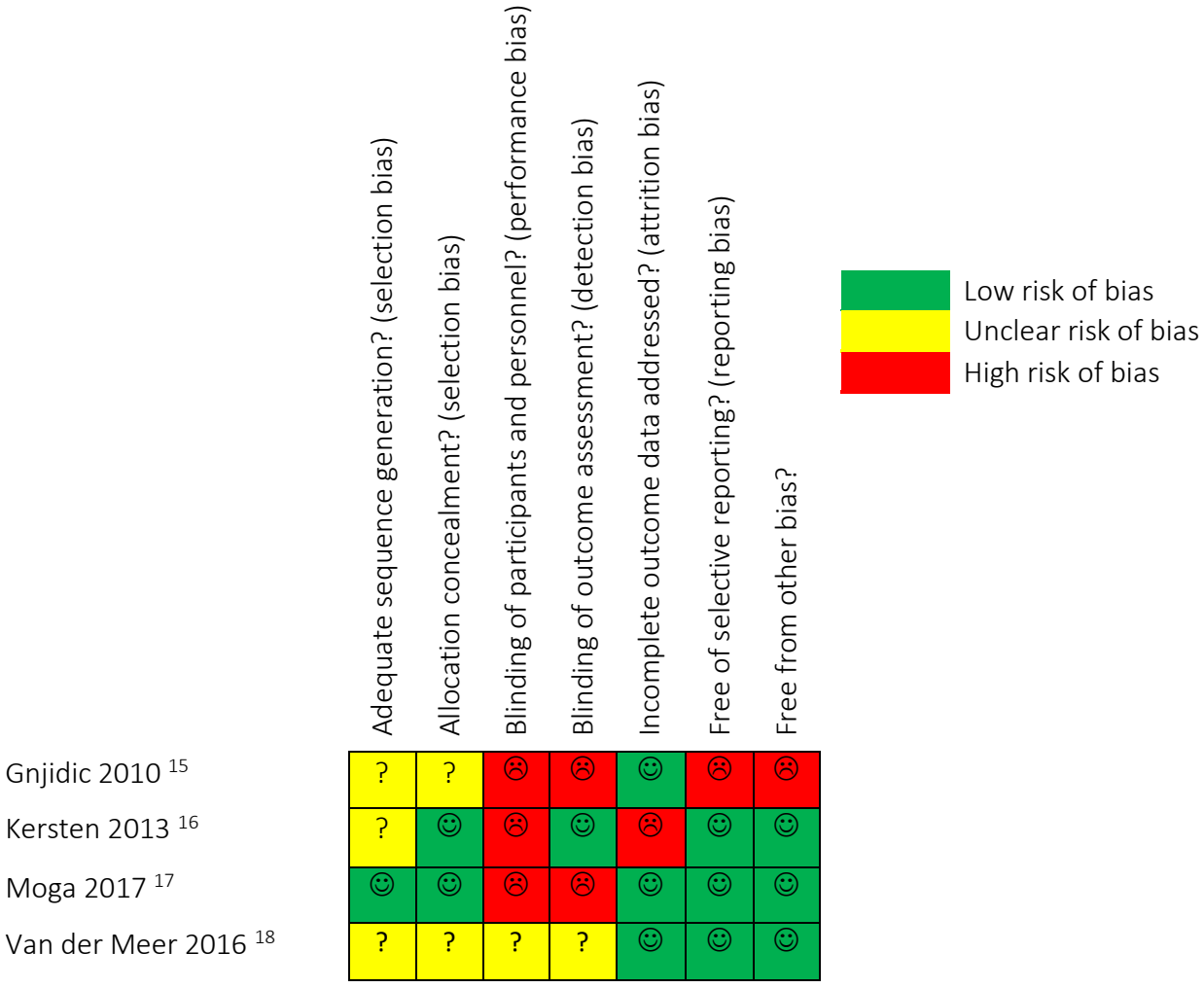

Figure 2: Risk of bias in individual RCT studies