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.

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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 used especially 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 study [17], whilst the remaining three studies did not report sufficient detail to enable an assessment.

The conference abstract [18] included little methodological detail resulting in a high proportion of 'unclear' judgements. The risk of bias assessments of the RCTs are displayed in Figure 2.

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

Contents of the interventions

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

The interventions that included recommendations to the prescriber adopted a range of different approaches, for example, in one hospital study conducted in Spain, pharmacists conducted clinical interviews, followed by medicine reconciliation and checking of medicine 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

192 significantly different between the intervention and control group. [15] Furthermore, the RCT
193 that involved a medication review by a pharmacist in the community (n= 157, with 4.3%
194 attrition rate over 3 months duration) showed no difference between the groups in the
195 proportion of patients having a decrease in DBI ≥0.5 (14.7% vs. 15.9%; OR=0.91, 95%CI=0.38-
196 2.18), although there was a reduction in sedative side effect [18].

197 *Non-randomised PPI studies*

198 All four pre-post intervention studies (PPIs) showed significant reductions in anticholinergic
199 burden following the intervention [19-22]. In the study in Australia conducted in the community,
200 the total DBI was significantly reduced (p<0.001) and pharmacists' recommendations were
201 associated with a decrease in the use of Potential Inappropriate Medications (PIMs) [19]. In the
202 Electronic Health Record (EHR) medication review study, the acceptance rate of pharmacists'
203 recommendations by primary care physicians was 50% (95%CI:37-63%) and the Anticholinergic
204 Risk Scale (ARS) score was reduced significantly (p=0.0003) after intervention [20]. In the
205 STOPP/START study, both the ADS and ARS scores decreased significantly (p=0.001 and
206 p=0.047 respectively) between admission and discharge [21]. Finally, in the feedback audit and
207 feedback study, the ARS scores were significantly decreased and there was a higher proportion
208 of patients on anticholinergics who had their medications either stopped or reduced (OR=5.0,
209 95%CI:1.4-17.8) compared to pre-intervention [22].

210 *Clinical and Cost effectiveness of interventions*

211 One RCT reported no significant differences in the results of cognitive function tests between
212 groups, despite a significant decrease in anticholinergic use following the intervention [16]. None
213 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 outcome measurement in ACB scores or scales [21]. Current knowledge gaps identified in this review and recommendations for future research are presented in Table 3.

Conclusions and Implications

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

Conflict of Interest

There are no conflicts of interest.

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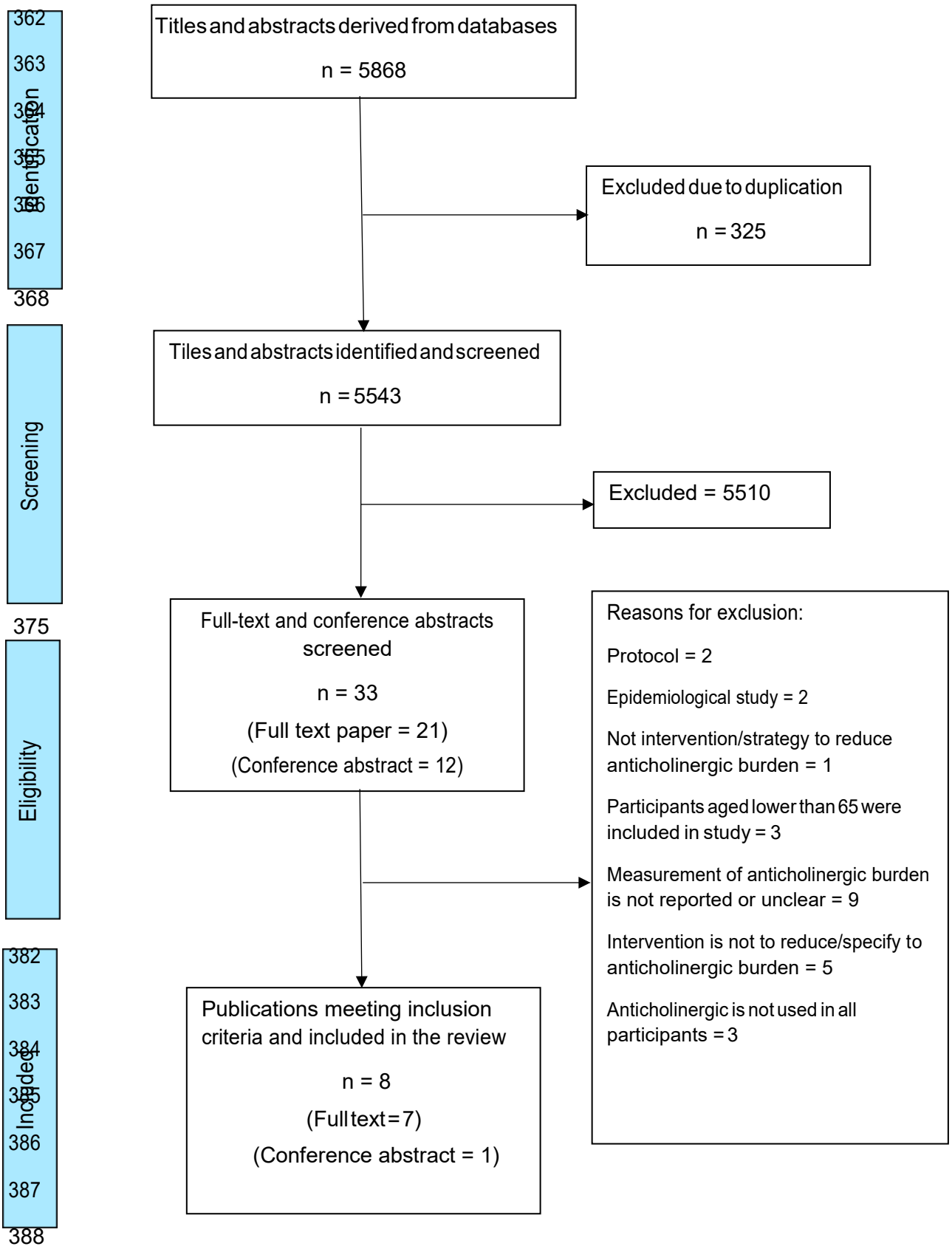

Figure 1: PRISMA Flow Diagram

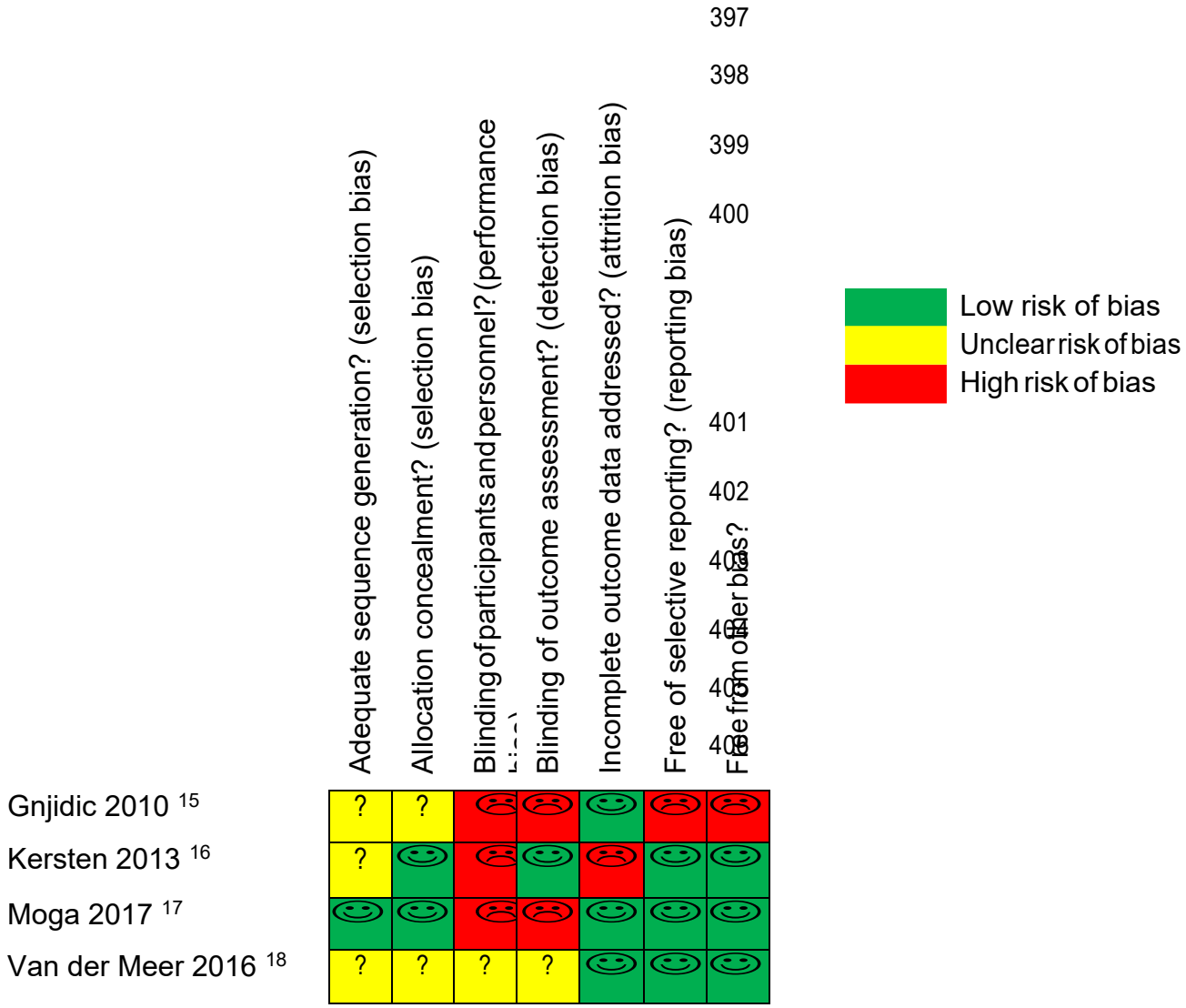

Figure 2: Risk of bias in individual RCT studies

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. No studies in the review reported costs or cost-effectiveness. No long-term follow-up of clinical outcome(s).	Patients and other stakeholders should be involved from the design until evaluation and implementation of any future interventions. We recommend the assessment of costs or cost-effectiveness in future studies. Longer-term follow up of clinical outcomes, such as cognitive function, is recommended.