

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

3 ABSTRACT

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

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

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

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

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

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

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

31 [PROSPERO registration: CRD42018089764]

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33 Word count: 299 words

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36 Introduction

37 Anticholinergic drugs act by blocking parasympathetic nerve impulses¹ and, hence, control
38 involuntary muscle movement². They are, therefore, commonly prescribed to treat
39 gastrointestinal disorders (e.g. diarrhoea, ulcers, spasms), overactive bladder (e.g.
40 incontinence) and to relieve symptoms of Parkinsonism. In addition, antidepressants and
41 antipsychotics used especially among older people also have anticholinergic properties. The
42 prevalence of their use is steadily increasing (estimates vary from 37-63%)³⁻⁵, particularly in
43 the ageing population. However, anticholinergics are associated with a wide range of adverse
44 effects, and there have been numerous calls for interventions to reduce the use of such drugs.
45 The challenge is to minimise the adverse effects of anticholinergic drugs whilst still retaining
46 the benefits.

47 The term “anticholinergic burden” refers to the cumulative anticholinergic action resulting
48 from concomitant use of multiple medications with anticholinergic properties¹. It is recognised
49 that high anticholinergic burden is linked to adverse events such as poor physical functioning,
50 dementia, and falls^{6,7}. However, to date there are few studies which examine the clinical and
51 cost effectiveness of using these tools in practice to change prescribing.

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

58 Methods

59 The systematic review protocol was registered in PROSPERO (CRD42018089764). The
60 literature search was systematically conducted in accordance with the general principles of the
61 Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in healthcare⁸
62 and the Cochrane Handbook for Systematic Reviews of Interventions⁹, and is reported in
63 accordance with the PRISMA statement¹⁰. The studies and interventions are described
64 according to the TIDieR, CONSORT or STROBE checklists¹¹⁻¹³, as appropriate.

65 *Search strategy, inclusion and exclusion criteria*

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

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

82 *Methods for identification of studies*

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

93 *Data collection and analysis*

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

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

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

105 *Quality assessment*

106 Two reviewers (AN and MC) independently assessed risk of bias of included studies. The RCTs
107 were assessed by the Cochrane Collaboration tool for assessing risk of bias⁹. Non randomised
108 studies were assessed using the Critical Appraisal notes and checklists from the Scottish
109 Intercollegiate Guidelines Network (SIGN), UK ¹⁴.

110 *Strategy for data synthesis*

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

114 Results

115 *Description of included studies*

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

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124 *Study characteristics*

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

135 Studies were conducted in various settings including hospital ^{17, 20-22}, the community ^{18, 19},
136 nursing homes ¹⁶ and self-care retirement village ¹⁵. The majority of studies had small sample
137 sizes (n=50-115 participants) with the exception of one community-based PPI that included
138 372 participants ¹⁹. The mean age of participants in all eight studies was over 75 years. Study
139 design and participant characteristics for each included study are presented in Appendix 1.
140 None of the studies mentioned the involvement of patients and/or other stakeholders (e.g.
141 health professionals, policy makers) with regards to study/intervention design.

142 *Risk of bias assessment*

143 None of the four RCTs complied fully with the Cochrane Collaboration tool for risk of bias
144 assessment, and one study met only one criterion ¹⁵. Blinding of participants and outcomes
145 had the lowest compliance. Sequence generation was judged to be adequate in only one study
146 ¹⁷, whilst the remaining three studies did not report sufficient detail to enable an assessment.

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

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

155 *Contents of the interventions*

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

163 The interventions that included recommendations to the prescriber adopted a range of
164 different approaches, for example, in one hospital study conducted in Spain, pharmacists
165 conducted clinical interviews, followed by medicine reconciliation and checking of medicine
166 appropriateness against the STOPP/START criteria before providing recommendations to the
167 prescriber²¹. In other studies, a clinical pharmacist performed a note based medication review
168 and then provided verbal recommendations to respective physicians in nursing homes

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

177 *Outcomes of interventions*

178 A summary of results of clinical effectiveness of individual studies is presented in Table 2. A
179 meta-analysis was not possible due to heterogeneity of the studies with regard to study designs
180 (e.g. use of different measures of anticholinergic burden) and outcome measures. Almost all
181 the studies chose to focus on measures of anticholinergic use as their main outcome ^{15, 17, 20-}
182 ²².

183 *RCTs*

184 Two of the four RCTs reported that anticholinergic burden decreased significantly following
185 the intervention ¹⁶⁻¹⁷. The trial carried out in the nursing home setting resulted in a statistically
186 significant reduction in the median Anticholinergic Drug Scale (ADS) from baseline for the
187 intervention group and remained unchanged in the control group ($p < 0.0001$) ¹⁶. The trial in the
188 Alzheimer's Disease Centre showed a statistically significant improvement in the Medication
189 Appropriateness Index (MAI) ($p = 0.04$) and reduced ADS score ($p = 0.03$) in the intervention
190 group compared with the control group ¹⁷. However, the changes in DBI following the
191 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.

214 Discussion

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

223 Two of the four identified RCTs ¹⁶⁻¹⁷ and all four PPIs ¹⁹⁻²² demonstrated that the intervention
224 reduced anticholinergic burden effectively. These findings are in line with two systematic
225 reviews (including randomised and non-randomised studies) of general deprescribing in
226 people aged 65 and over, which reported that deprescribing reduced medication use ^{24, 25}. The
227 two RCTs that reduced anticholinergic burden were both small trials of short duration ^{16, 17}. The
228 RCT conducted in the Alzheimer's Disease Centre was the only study to report a clinical
229 outcome (i.e. cognitive function; the Consortium to Establish a Registry for Alzheimer's Disease
230 10-wordlist test for immediate recall) but showed no statistical differences between the
231 intervention and control group ¹⁶. Loss to follow-up rate in three of the four RCTs was low ^{15,}
232 ^{17, 18}, suggesting that the interventions were acceptable and feasible, in line with the findings
233 of a systematic review of general deprescribing in older adults ²⁴.

234 However, no studies in the review reported costs or cost-effectiveness and the majority of the
235 studies did not include an objective clinical outcome such as physical function, cardiovascular
236 diseases, falls and mortality. Recent systematic reviews have found the evidence on the impact

237 of general deprescribing on clinical outcomes to be ambiguous²³⁻²⁵. Therefore, it appears that
238 the current evidence base on the impact of deprescribing in older adults is inconclusive.

239 Strengths of the review included a comprehensive search of all potentially relevant articles and
240 the use of explicit, reproducible criteria in the selection of articles included. The search was
241 limited to 2010 onwards, providing contemporary practice relevant to the current ageing
242 population with multi-morbidity and polypharmacy as well as the growing number of ACB
243 medications in the literature. The search strategy was conducted on more than one database
244 and a minimum of two researchers screened abstracts and full texts independently to select
245 eligible publications. Furthermore, the review was conducted rigorously according to
246 published guidelines⁹. Whilst emphasizing the need for RCT evidence - the 'gold standard' for
247 health research - this review has also summarised evidence from other types of studies.

248 However, overall the studies included had many limitations. Sample sizes were small, and two
249 self-identified as pilot studies. Most had considerable methodological limitations introducing
250 bias, and there were only four randomised controlled trials. In the RCTs, it was not possible to
251 blind participants or personnel due to the nature of the interventions. The inclusion of non-
252 randomised PPIs in the review increased the available body of evidence but the limitations of
253 this study design should be borne in mind and their findings interpreted with caution. In
254 addition, interpretation of PPI studies is not straight forward. Changes in the outcome of
255 interest may be due to the intervention; however, it may also reflect disease natural history
256 (as the condition improves over time or clinical therapy improves with experience), patient
257 selection (patients before and after the intervention may have differed in clinically important
258 attributes), or placebo effects (because neither patient nor provider is blinded). In addition,

259 there is a natural tendency for processes to regress to the mean, which may occur without
260 intervention.

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

270 Only one study examined a clinical outcome. In that study, participants' cognitive function did
271 not change despite the median ADS score decreasing by 2 units in the intervention group ¹⁶.
272 However, a previous study suggested that performance of individuals with higher
273 anticholinergic burden in cognitive tasks was poorer than that of those with lower ACB ²⁶. This
274 may be due to the fact that detection of the impact of reducing ACB on cognition could require
275 a longer follow-up. A study with 8 week of follow up was not of sufficient length to assess the
276 long-term impact of the intervention ¹⁷. One study did not include short-term medications
277 when calculating anticholinergic burden, and that might have influenced the outcome
278 measurement in ACB scores or scales ²¹. Current knowledge gaps identified in this review and
279 recommendations for future research are presented in Table 3.

280

281 Conclusions and Implications

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

286 *Conflict of Interest*

287 There are no conflicts of interest.

288

- 290 1. Kersten H, Wyller TB. Anticholinergic drug burden in older people's brain - how well is it
291 measured? *Basic Clin Pharmacol Toxicol* 2014;114:151-9.
- 292 2. Carnahan RM, Lund BC, Perry PJ, et al. The anticholinergic drug scale as a measure of drug-
293 related anticholinergic burden: associations with serum anticholinergic activity, *The Journal of*
294 *Clinical Pharmacology* 2006;46:1481-1486.
- 295 3. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and
296 anticholinergic adverse effects in older persons, *Arch Intern Med* 2008;168:508-513.
- 297 4. Ancelin ML, Artero S, Portet F, et al. Non-degenerative mild cognitive impairment in elderly
298 people and use of anticholinergic drugs: longitudinal cohort study, *British Medical Journal*
299 2006;332:455-459.
- 300 5. Ehrt U, Broich K, Larsen JP. Use of drugs with anticholinergic effect and impact on cognition
301 in Parkinson's disease: A cohort study, *Journal of Neurology, Neurosurgery, and Psychiatry*
302 2010;81:160-165.
- 303 6. Fox C., Smith T., Maidment I., et al. Effect of medications with anti-cholinergic properties
304 on cognitive function, delirium, physical function and mortality: a systematic review, *Age*
305 *Ageing* 2014;43:604-615.
- 306 7. Ablett AD, Wood AD, Barr R, et al. A high anticholinergic burden is associated with a history
307 of falls in the previous year in middle-aged women: findings from the Aberdeen prospective
308 osteoporosis screening study, *Annals of Epidemiology* 2018;28:557-562.
- 309 8. Centre for Review and Dissemination Ed. *Systematic Reviews CRD's Guidance for*
310 *Undertaking Review in Health Care*, 1st Ed. York: York Publishing Services Ltd, 2009.
- 311 9. Higgins JPT, Green S Eds. *Cochrane Handbook for Systematic Reviews of Interventions*, 1st
312 Ed. West Sussex: John Wiley & Sons Ltd., 2008.
- 313 10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic
314 reviews and meta-analyses:
315 The PRISMA statement, *Annals of Internal Medicine* 2009;151:264-269.
- 316 11. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for
317 intervention description and replication (TIDieR) checklist and guide, *BMJ* 2014;348:1-12.
- 318 12. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for
319 reporting parallel group randomised trials, *Journal of clinical epidemiology* 2010;63:834-840.
- 320 13. Elm EV, Altman DG, Egger M, et al. The strengthening the reporting of observational
321 studies in epidemiology (STROBE) statement: guidelines for reporting observational studies,
322 *Ann Intern Med* 2007;147:573-577.

- 323 14. Scottish Intercollegiate Guidelines Network. Critical appraisal notes and checklists,
324 2018;2018:.
- 325 15. Gnjidic D, Le CD, Abernethy DR, Hilmer SN. A pilot randomised clinical trial utilising the
326 drug burden index to reduce exposure to anticholinergic and sedative medications in older
327 people, *Ann Pharmacother*2010;44:1725-1732.
- 328 16. Kersten H, Molden E, Tolo IK, et al. Cognitive effects of reducing anticholinergic drug
329 burden in a frail elderly population: a randomised controlled trial, *J Gerontol A Biol Sci Med*
330 *Sci* 2013;68:271-278.
- 331 17. Moga DC, Abner EL, Rigsby DN, et al. Optimising medication appropriateness in older
332 adults: a randomised clinical interventional trial to decrease anticholinergic burden,
333 *Alzheimers Res Ther* 2017;9:36.
- 334 18. Van Der Meer HG, Wouters H, Pras N, Taxis K. Reducing patients' cumulative exposure to
335 anticholinergic and sedative medication with medication reviews: A randomised controlled
336 trial. *Pharmacoepidemiology and Drug Safety. Conference: 32nd International Conference on*
337 *Pharmacoepidemiology and Therapeutic Risk Management. Ireland* 2016;25:266.
- 338 19. Castelino RL, Hilmer SN, Bajorek BV, et al. Drug burden index and potentially
339 inappropriate medications in community-dwelling older people: The impact of home
340 medicines review, *Drugs Aging* 2010;27:135-148.
- 341 20. Hanus RJ, Lisowe KS, Eickhoff JC, et al. Evaluation of a pharmacist-led pilot service based
342 on the anticholinergic risk scale, *J Am Pharm Assoc* 2016;56:555-561.
- 343 21. Rojo-Sanchis AM, Velez-Diaz-Pallares M, Munoz GM, et al. Reduction of anticholinergic
344 burden in older patients admitted to a multidisciplinary geriatric acute care unit, *Eur Geriatr*
345 *Med* 2017;8:492-495.
- 346 22. Tay HS, Soiza RL, Mangoni AA. Minimising anticholinergic drug prescribing in older
347 hospitalised patients: a full audit cycle. *Therapeutic Advances in Drug Safety* 2014;5:121-128.
- 348 23. Thillainadesan J, Gnjidic D, Green S, Hilmer SN.
349 Impact of deprescribing interventions in older hospitalised patients on prescribing and clinical
350 outcomes: a systematic review of randomised trials. *Drugs Aging* 2018;35:303-319.
- 351 24. Page AT, Clifford RM, Potter K, et al. The feasibility and effect of deprescribing in older
352 adults on mortality and health: a systematic review and meta-analysis. *British Journal of*
353 *Clinical Pharmacology* 2016;82:583-623.
- 354 25. Johansson T, Abuzahra ME, Keller S, et al. Impact of strategies to reduce polypharmacy on
355 clinically relevant endpoints: a systematic review and meta-analysis. *British Journal of Clinical*
356 *Pharmacology* 2016;82:532-548.

357 26. Swami S, Cohen RA, Kairalla JA, Manini TM. Anticholinergic drug use and risk of cognitive
358 performance in older adults with questionable cognitive impairment: A cross-sectional
359 analysis, *Drugs Aging* 2016;33:809-818.

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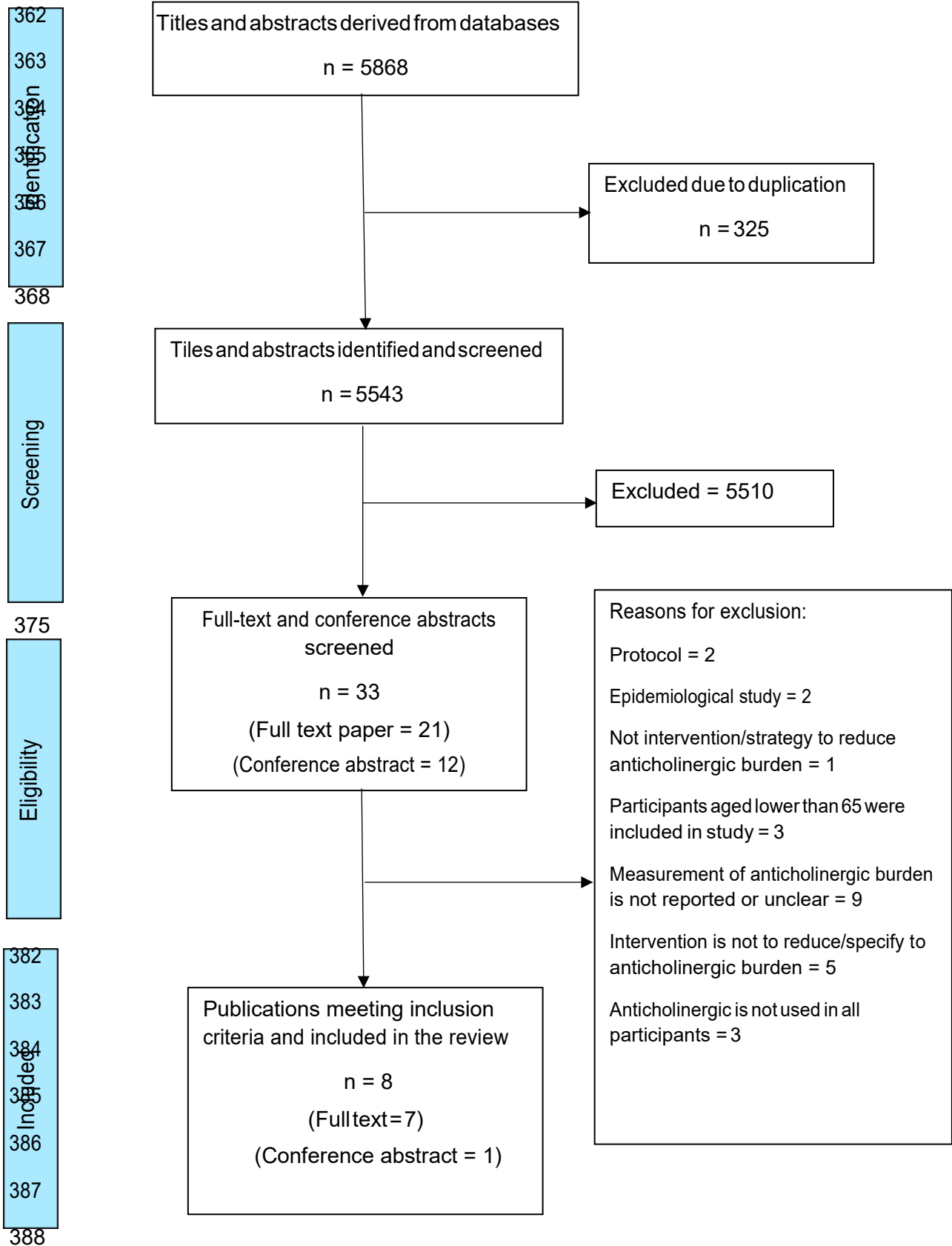


Figure 1: PRISMA Flow Diagram

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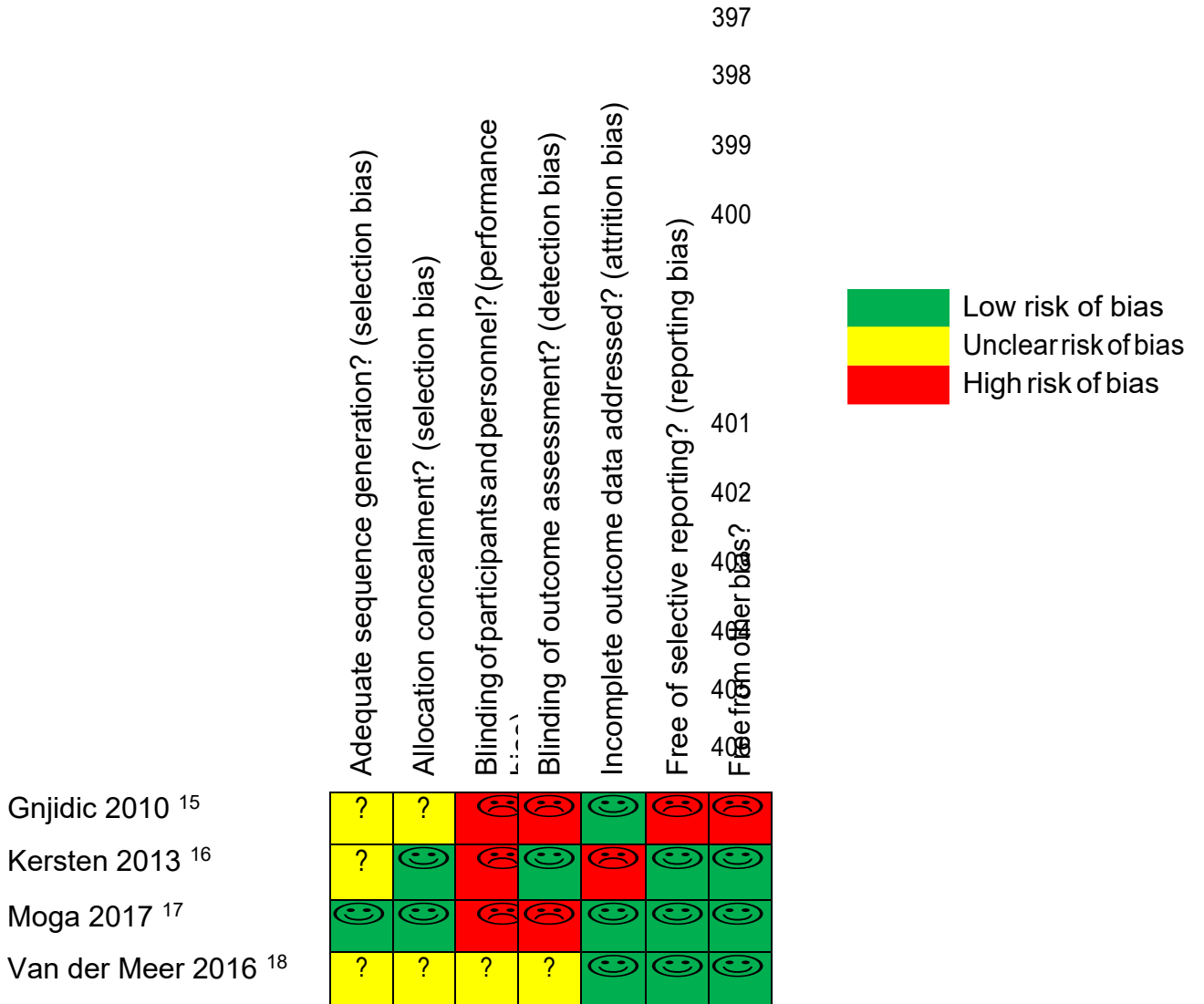


Figure 2: Risk of bias in individual RCT studies

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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 State 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	<p>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.</p> <p>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</p>	8 weeks	<p>ADS median Intervention group = 2.8 +/- 1.9, Control group 2.9 +/- 1.3</p>	<p>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</p>	<p>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)</p> <p>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.</p>
van der Meer 2016 ¹⁸	<p>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</p> <p>Exclusion criteria: NR</p>	3 months	NR	Mean DBI 2.6	<p>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</p> <p>Secondary: anticholinergic and sedative effects, falls, cognitive function, activities of daily living, quality of life, hospital admission and mortality</p>

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-Sanchis 2017 ²¹	<p>Inclusion criteria: Patients more than 80 years old who were admitted to the acute geriatric unit of tertiary hospital</p> <p>Exclusion criteria: Patients who were readmission in less than 3 months, receiving palliative care before or during admission, and death within the hospitalization period</p>	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 ward Exclusion criteria: NR	First phase: 25 th April 2011 to 9 th May; second phase: 5 th June 2011 to 20 th 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	<p>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.</p> <p>GPs identified the following barriers to reducing anticholinergic and sedative drugs: uncomfortable altering prescriptions initiated by specialists; unable to influence patients' attitudes; unaware of patients' medications and strong clinical indication.</p>
Kersten 2013 ¹⁶	<p>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.</p>
Moga 2017 ¹⁷	<p>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).</p>
van der Meer 2016 ¹⁸	<p>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.</p>
Non-randomised PPI studies	
Castelino 2010 ¹⁹	<p>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.</p>
Hanus 2016 ²⁰	<p>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.</p>

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