Interventions to improve the appropriate use of polypharmacy for older people

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[Intervention Review]

Interventions to improve the appropriate use of polypharmacy for older people

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ABSTRACT

Background

Inappropriate polypharmacy is a particular concern in older people and is associated with negative health outcomes. Choosing the best interventions to improve appropriate polypharmacy is a priority, hence interest in appropriate polypharmacy, where many medicines may be used to achieve better clinical outcomes for patients, is growing.

Objectives

This review sought to determine which interventions, alone or in combination, are effective in improving the appropriate use of polypharmacy and reducing medication-related problems in older people.

Search methods

In November 2013, for this first update, a range of literature databases including MEDLINE and EMBASE were searched, and handsearching of reference lists was performed. Search terms included 'polypharmacy', 'medication appropriateness' and 'inappropriate prescribing'.

Selection criteria

A range of study designs were eligible. Eligible studies described interventions affecting prescribing aimed at improving appropriate polypharmacy in people 65 years of age and older in which a validated measure of appropriateness was used (e.g. Beers criteria, Medication Appropriateness Index (MAI)).

Data collection and analysis

Two review authors independently reviewed abstracts of eligible studies, extracted data and assessed risk of bias of included studies. Study-specific estimates were pooled, and a random-effects model was used to yield summary estimates of effect and 95% confidence intervals (CIs). The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach was used to assess the overall quality of evidence for each pooled outcome.

Main results

Two studies were added to this review to bring the total number of included studies to 12. One intervention consisted of computerised decision support; 11 complex, multi-faceted pharmaceutical approaches to interventions were provided in a variety of settings. Interventions were delivered by healthcare professionals, such as prescribers and pharmacists. Appropriateness of prescribing was measured using validated tools, including the MAI score post intervention (eight studies), Beers criteria (four studies), STOPP criteria (two studies) and START criteria (one study). Interventions included in this review resulted in a reduction in inappropriate medication usage. Based on the GRADE approach, the overall quality of evidence for all pooled outcomes ranged from very low to low. A greater reduction in MAI scores between baseline and follow-up was seen in the intervention group when compared with the control group (four studies; mean difference -6.78, 95% CI -12.34 to -1.22). Postintervention pooled data showed a lower summated MAI score (five studies; mean difference -3.88, 95% CI -5.40 to -2.35) and fewer Beers drugs per participant (two studies; mean difference -0.1, 95% CI -0.28 to 0.09) in the intervention group compared with the control group. Evidence of the effects of interventions on hospital admissions (five studies) and of medication-related problems (six studies) was conflicting.

Authors' conclusions

It is unclear whether interventions to improve appropriate polypharmacy, such as pharmaceutical care, resulted in clinically significant improvement; however, they appear beneficial in terms of reducing inappropriate prescribing.

PLAIN LANGUAGE SUMMARY

A review of the ways that healthcare professionals can improve the use of suitable medicines for older people

Taking medicine to treat symptoms of chronic illness and to prevent worsening of disease is common in older people. However, taking too many medicines can cause harm. This review examines studies in which healthcare professionals have taken action to make sure that older people are receiving the most effective and safest medication for their illness. Actions taken included providing pharmaceutical care, a service provided by pharmacists that involves identifying, preventing and resolving medication-related problems, as well as promoting the correct use of medications and encouraging health promotion and education. Another strategy was computerised decision support, which involves a programme on the doctor's computer that helps him/her to select appropriate treatment.

This review provides limited evidence that interventions, such as pharmaceutical care, may be successful in ensuring that older people are receiving the right medicines, but it is not clear whether this always results in clinical improvement.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Patient or population: older people receiving polypharmacy
Settings: community, nursing home, hospital

Intervention: pharmaceutical care
Comparison: usual care

Outcomes	Effect estimate		No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Usual care	Pharmaceutical care			
Summated MAI score Summated MAI score post intervention Follow-up: 0 to 12 months	Mean summated MAI score ranged across control groups from **6.5 to 19.3**	Mean summated MAI score in the intervention groups was **3.88 lower** (5.4 to 2.35 lower)	965 (5 studies)	⊕⊕◯◯ **low**[a,b]	
Change in MAI score Change in MAI score from baseline to follow-up Follow-up: 0 to 3 months	Mean change in MAI score ranged across control groups from **0.41 to 2.86**	Mean change in MAI score in the intervention groups was **6.78 lower** (12.34 to 1.22 lower)	424 (4 studies)	⊕◯◯◯ **very low**[a,b,c,d]	A sensitivity analysis showed that the mean change in MAI score in the intervention group was 1.79 lower (3.73 lower to 0.16 higher)[e]
Number of Beers drugs per participant The number of Beers drugs per participant post intervention Follow-up: 0 to 12 months	Mean number of Beers drugs per participant ranged across control groups from **0.04 to 0.4**	Mean number of Beers drugs per participant in the intervention groups was **0.1 lower** (0.28 lower to 0.09 higher)	586 (2 studies)	⊕◯◯◯ **very low**[a,c,d]	

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

MAI: Medication Appropriateness Index.

[a]Limitations in the design of studies included in the analysis such as lack of protection against contamination and lack of allocation concealment resulted in downgrading of the quality of evidence.

[b]A validated assessment of under-prescribing was not included in all studies; therefore, the findings answered a restricted version of the research question. This resulted in downgrading of the quality of evidence.

[c]Statistically significant heterogeneity, variation in effect estimates and non-overlapping CIs between studies resulted in downgrading of the quality of evidence.

[d]Imprecision in effect estimates was observed whereby CIs were wide and/or crossed the line of no effect.

[e]Two studies were excluded from the analysis because of a unit of analysis error (Crotty 2004a) and an outlying effect estimate with a high risk of bias (Spinewine 2007).

BACKGROUND

Prescribing for older people is complex because of factors such as age-related changes in body composition and multiple pathologies. Finding the balance between aggressively treating diseases and avoiding medication-related harm is a critical objective often set by healthcare professionals, yet rarely achieved (Steinman 2007). This review updates a Cochrane review of interventions to improve the appropriate use of polypharmacy for older people (Patterson 2012). The previous version of this review (Patterson 2012) found that, despite the potential to reduce inappropriate prescribing, it was unclear whether interventions to improve appropriate polypharmacy in older people resulted in clinically significant improvement.

Polypharmacy has a range of definitions that refer to the use of multiple medication regimens, but no standard definition is used consistently (King's Fund 2013; Stewart 1990). A simple definition-'the administration of more medicines than are clinically indicated, representing unnecessary drug use' (Montamat 2004)-has been used, but for the purpose of this review, we have used the common definition of 'the concomitant ingestion of four or more medications' (DoH 2001; Rollason 2003).

Polypharmacy is common in older people, conventionally defined as those aged 65 years and over, as this age group often suffers from multiple morbidities (Barnett 2012) such as heart disease and diabetes that require multiple medications for treatment and prophylaxis. In the USA, the prevalence of polypharmacy, defined in the Slone Survey as five or more medicines, in older people has increased over time, and the most recent available data indicate that approximately 28% of older people in the USA are receiving polypharmacy (Slone Survey 2007). This is relatively consistent with data from The Irish Longitudinal Study on Ageing, which has reported polypharmacy in 31% of the older population using the same definition of five or more medicines (Richardson 2012). Hence, older people use a disproportionate quantity of health service resources. For example, in 2013, patients aged 60 and older accounted for 23% of the population in England and were dispensed 60% of all prescription items (Information Centre 2014).

Inappropriate medications can be defined, in terms of older people, as 'medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available' (Beers 1991). The term 'inappropriate prescribing' also encompasses the use of medicines that lead to a significant risk of adverse drug events (ADEs) arising from prescribing practices such as continuing therapy for longer than necessary, in addition to unnecessary polypharmacy.

Reasons for the occurrence of polypharmacy in older patients have been described in the literature and can be broadly classified into three groups: demographic factors such as race and education (Fillenbaum 1996); health status factors such as poor health including depression, hypertension, anaemia, asthma, angina, diverticulosis, osteoarthritis, gout, diabetes mellitus, poor self-perceived health and poor life satisfaction; and factors related to access to health care such as number of healthcare visits, use of supplemental insurance and access to multiple providers of health care (Espino 1998; Hajar 2007).

Recent promotion of the use of clinical guidelines has influenced prescribing patterns, which often advocate the use of more than one drug to manage common diseases. Many guidelines for prevention and management of diseases common in older people recommend adding medications for secondary prevention. For example, within Europe, guidelines developed by a joint task force on cardiovascular disease prevention in clinical practice, which involved the European Society of Cardiology (Joint Task Force 2012), advocate this approach. However, it has been reported that some clinical guidelines do not modify or discuss the applicability of their recommendations for older patients with multiple morbidities, nor do they take account of patient preferences or comment on the quality of evidence supporting the guideline (Boyd 2005). Use of clinical guidelines may therefore promote polypharmacy and increase the risk of adverse events such as drug-drug and drug-disease interactions. In light of this, the National Institute for Health and Care Excellence (NICE) is considering the development of guidelines for the clinical treatment of patients with multiple morbidities (NICE 2012).

Appropriate or therapeutic polypharmacy also occurs when the results of clinical trials suggest that multiple medications should be used to treat specific diseases (Gurwitz 2004). Acceptance of the idea that such appropriate polypharmacy may be beneficial is increasing, and the combined use of multiple medications is beneficial and appropriate for many conditions, especially those in older people with multiple morbidities. For example, diabetes mellitus is often treated with several drugs at once (Standl 2003). However, it is important to consider whether each drug has been prescribed appropriately or inappropriately, both individually and in the context of the whole prescription (Aronson 2006). Improving appropriate polypharmacy involves encouraging use of the correct drugs under appropriate conditions to treat the right diseases. In certain circumstances, this may include the removal of unnecessary drugs or those with no valid clinical indication and the addition of useful ones.

However, polypharmacy is associated with negative health outcomes including adverse drug reactions, poor adherence and geriatric syndromes such as urinary incontinence, cognitive impairment and impaired balance leading to falls (Hajar 2007). The chance of occurrence of medication-related problems is increased in older age because the ageing process reduces the efficiency of the body's organs in eliminating drugs (Mangoni 2003). The risk of an ADE is 13% with the use of two medications, but when five medications are used, it increases to 58% (Fulton 2005). If seven or more medications are used, the incidence increases to

82% (Prybys 2002). In addition, the number of medicines prescribed predicts the number of drug interactions likely to occur (Gallagher 2001). Poor understanding of causes of certain disorders makes prescribing drug combinations more difficult. Treating poorly understood diseases may increase the risk for inappropriate polypharmacy (Werder 2003).

Under-prescribing is defined as lack of drug treatment for a clinical condition for which drug therapy is indicated according to clinical practice guidelines (Lipton 1992). Under-prescribing can be as challenging as polypharmacy in older people, and it has only recently gained recognition as a matter of concern. Under-prescribing has been shown to be associated with polypharmacy, whereby the probability of under-prescription increases with the number of medicines used (Kuijpers 2007). Using a sample of 150 older study participants, Kuijpers 2007 reported that the prevalence of polypharmacy and under-prescribing was 61% and 31%, respectively. Among participants receiving polypharmacy, 42.9% were under-treated, in contrast to 13.5% of those using four or fewer medicines (odds ratio (OR) 4.8, 95% confidence interval (CI) 2.0 to 11.2).

These findings may be explained by the unwillingness of general practitioners (GPs) to prescribe additional drugs for patients with polypharmacy (for reasons such as complexity of drug regimens, fear of ADEs and drug-drug interactions and poor adherence) (Kuijpers 2007). This so-called treatment/risk paradox or risk/treatment mismatch is seen when patients with the highest risk of complications are determined to have the lowest probability of receiving the recommended medications (Ko 2004; Lee 2005).

Thus, 'polypharmacy' can refer to the prescribing of many drugs (appropriately) or too many drugs (inappropriately) (Aronson 2004). What constitutes 'many' or 'too many' drugs is a prescriber's dilemma, and choosing the best interventions aimed at ensuring appropriate polypharmacy remains a challenge for healthcare practitioners and organisations.

Description of the condition

Inappropriate polypharmacy, as described above, occurs when older people are prescribed more medicines than are clinically indicated. As under-prescribing is also inappropriate therapy for older people, we have included in this review interventions provided to address this problem, such as the promotion of appropriate polypharmacy.

Inappropriate polypharmacy has been measured by using validated instruments or screening tools such as a validated list of medicines considered inappropriate for older people (AGS 2012; Beers 1991; Fick 2003), a list of clinically significant criteria for potentially inappropriate prescribing in older people (Gallagher 2008) or the Medication Appropriateness Index (MAI) (Knight 2001). Other methods of assessment of inappropriate polypharmacy include examining patient adherence to prescribed medications to identify target areas for intervention (Barat 2001; Bedell 2000).

Description of the intervention

Improvement in appropriate polypharmacy can be achieved through a wide range of interventions. These can be classified as professional, for example, educational programmes for prescribers or consumers; organisational, for example, medication review clinics and specific audits on benzodiazepine use; or financial, for example, prescribed incentive schemes and regulatory interventions. Interventions that reduce the risk of medication-related problems are important to consider (Fick 2008). These may be provided by healthcare professionals, educators, policy makers and healthcare service planners. The traditional approach to intervention in polypharmacy, based on the assumption that polypharmacy is harmful, has been to reduce inappropriate medication. By identifying risk factors for polypharmacy, it is possible to decrease its associated morbidity, mortality and cost (Werder 2003).

Methods recommended in many intervention studies include use of computer data entry and feedback procedures, which have been shown to decrease polypharmacy and drug-drug interactions (Werder 2003); visual identification of medicines; continuous medication review and thorough patient education to optimise polypharmacy (Fulton 2005).

This review seeks to identify evidence regarding which types of interventions can improve appropriate polypharmacy.

How the intervention might work

Interventions to improve polypharmacy are likely to achieve the following outcomes.

- Improved appropriate polypharmacy through removal of inappropriately prescribed medication.
- Increased appropriate medications by promotion of adherence to evidence-based therapy.

Computerised decision support (CDS) aimed at prescribers, whereby electronic alerts are produced to guide the prescriber to the right treatment, has been successful in reducing inappropriate prescribing for older people. Pharmacist-led interventions such as medication review, co-ordinated transition from hospital to long-term care facility and pharmacist consultations with patients and physicians have been shown to effectively reduce inappropriate prescribing and ADEs (Hanlon 1996; Kaur 2009). Multi-disciplinary case conferences involving GPs, geriatricians, pharmacists and residential care staff, wherein individual patient cases are discussed, have reduced the use of inappropriate medications in residential care (Crotty 2004a)

Why it is important to do this review

A systematic review may help to identify how we can improve appropriate polypharmacy in older people. Inappropriate prescribing for older people is both highly prevalent and commonly associated with polypharmacy (Bradley 2012; Cahir 2010). It is important that the gap in current evidence be addressed, so that interventions that are effective in managing disease with appropriate polypharmacy may be identified and put into practice.

OBJECTIVES

This review sought to determine which interventions, alone or in combination, are effective in improving the appropriate use of polypharmacy and reducing medication-related problems in older people.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs), including cluster-randomised controlled trials (cRCTs), non-randomised controlled clinical trials (CCTs), controlled before-and-after studies (CBAs) and interrupted time series (ITS) studies meeting the Effective Practice and Organisation of Care (EPOC) specification (EPOC 2009) in the review.

We classified trials eligible for inclusion according to the reader's degree of certainty that random allocation was used to form comparison groups in the trial. If study author(s) stated explicitly that groups compared in the trial were established by random allocation, we classified the trial as an RCT. If study author(s) did not state explicitly that the trial was randomised, but randomisation could not be ruled out, we classified the report as a CCT.

Types of participants

The review included studies of older people aged 65 years and older, who had more than one long-term medical condition, including those for whom polypharmacy (classified as four or more medicines) was common practice, for example, those with Parkinson's disease or diabetes. We considered trials for inclusion if they included a majority (80% or more) of participants aged 65 years and older, or if the mean age of study participants was over 65 years. If studies included both older and younger people, we included them if we were able to extract relevant data. We contacted study authors to check the availability of relevant data.

We excluded studies in which the intervention focused on people with a single long-term medical condition or who were receiving short-term polypharmacy, for example, those who were terminally ill or were receiving cancer chemotherapy.

Types of interventions

We examined all types of interventions aimed at improving appropriate polypharmacy in any setting compared with usual care as defined by the study. We included all unifaceted interventions, for example, those targeted solely at drug prescription, and multifaceted interventions, for example, specialist clinics involving comprehensive geriatric assessment, in studies in which most outcomes were related to polypharmacy. We included studies of interventions for which the target was polypharmacy across all ages, provided results for those aged 65 years and over were available separately. We examined all types of interventions that directly or indirectly affected prescribing and were aimed at improving appropriate polypharmacy. These included the following.

- Professional interventions such as educational programmes aimed at prescribers.
- Organisational interventions such as skill-mix changes, pharmacist-led medication review services or specialist clinics, information and communication technology (ICT) interventions such as clinical decision support systems or use of risk screening tools.
- Financial interventions such as incentive schemes for changes in prescribing practice.
- Regulatory interventions such as changes in government policy or legislation affecting prescribing.

Types of outcome measures

Validated measures of inappropriate prescribing were the main outcome measures considered in the review. Increasing appropriate polypharmacy could improve indicators of morbidity such as reduction in ADEs or hospital admissions, but clinical outcomes were not clearly reported because of confounding factors such as multi-morbidity in older people. We excluded studies in which expert opinion was used to determine medication appropriateness.

Primary outcomes

The primary outcome was change in the prevalence of appropriate use of polypharmacy, as measured by a validated instrument. This was defined as meeting one or more of the following criteria.

- Appropriateness of medications prescribed, as measured by a validated instrument, for example, Beers criteria (Fick 2003) or MAI (Knight 2001).
- Prevalence of appropriate medication, for example, an increase in the number of appropriate drugs, as defined by a validated tool, for example, Screening Tool to Alert doctors to the Right Treatment (START) criteria (Barry 2007).

- Hospital admissions.

Secondary outcomes

Secondary outcomes included the following.

- Medication-related problems in older people, for example, adverse drug reactions, drug-drug interactions and medication errors.
- Adherence to medication.
- Quality of life (as assessed by a validated method).

Search methods for identification of studies

Michelle Fiander, Trials Search Co-ordinator (TSC) for the EPOC Group, developed search strategies in consultation with the review authors. The TSC searched the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects (DARE) for related systematic reviews, as well as the databases listed below for primary studies. Searches were conducted in November 2013; exact search dates for each database are included with the search strategies, which are provided in Appendix 2

Databases

- Evidence-Based Medicine (EBM) Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), November 2013, Ovid SP.
- EBM Reviews, Health Technology Assessment, Fourth Quarter 2013, Ovid SP.
- EBM Reviews, NHS Economic Evaluation Database, Fourth Quarter 2013, Ovid SP.
- EBM Reviews, Cochrane Methodology Register, Third Quarter 2012, Ovid SP.
- EBM Reviews, ACP Journal Club, 1991 to November 2013, Ovid SP.
- The Joanna Briggs Institute EBP Database, current to November 2013, Ovid SP.
- MEDLINE, 1947 to November 2013, In-Process and other non-indexed citations, Ovid SP.
- EMBASE, 1947 to November 2013, Ovid SP.
- CINAHL (Cumulative Index to Nursing and Allied Health Literature), 1980 to November 2013, EBSCO Host.
- PsycINFO, 1806 to November week 2 2013, Ovid SP.

Trial registries

- ClinicalTrials.gov, US National Institutes of Health (NIH) (http://clinicaltrials.gov/), November 2013.

Search strategies comprised keywords and, when available, controlled vocabulary such as MeSH (medical subject headings). All databases were searched for articles indexed between May 2010 and November 2013. Two methodological search filters were used to limit retrieval to appropriate study designs: the Cochrane Highly Sensitive Search Strategy (sensitivity- and precision-maximising version, 2008) (Lefebvre 2011) to identify randomised trials; and an EPOC methodology filter to identify studies using non-RCT designs. No language restrictions were applied. All search strategies used for this review are provided in Appendix 2.

Searching other resources

- Screened selected issues of the *Journal of the American Geriatrics Society* (e.g. handsearching).
- Reviewed reference lists of relevant systematic reviews.
- Contacted authors of relevant studies and reviews to ask that they clarify reported published information or to seek unpublished results/data.
- Contacted researchers with expertise relevant to the review topic or to EPOC interventions.
- Conducted cited reference searches on studies selected for inclusion in this review, related reviews and other relevant citations as listed on the Institute for Scientific Information (ISI) Web of Science/Web of Knowledge.

Data collection and analysis

Selection of studies

For this update, two review authors (CH and CC) independently screened titles and abstracts identified in searches to assess which studies met the inclusion criteria of the review. At this stage, we excluded papers that did not meet the inclusion criteria. If uncertainty or disagreement arose at this stage, we obtained full-text articles and assessed them independently to determine whether they met previously defined inclusion criteria. Any remaining disagreement or uncertainty was resolved by consensus through discussion with another review author (CR).

Data extraction and management

Two review authors (CH and CC) independently extracted details of articles included in this update, including study design, study population, intervention, usual care, outcome measures used and length of follow-up data, using a specially designed data extraction form based on the EPOC template (EPOC 2009). We contacted study authors to ask for missing information or clarification. We used information from data extraction forms to guide the extraction of numerical data for meta-analysis in Review Manager 5.2 (RevMan 2012).

We presented data from RCT and CBA studies using the format suggested in the EPOC Working Paper on presentation of data (EPOC 2009).

Assessment of risk of bias in included studies

Two review authors (CH and CC) independently assessed the internal validity of each study included in this update and resolved discrepancies by discussion.

We used the tool of The Cochrane Collaboration for assessing risk of bias (Higgins 2011) based on six standard criteria: adequate sequence generation, concealment of allocation, blinded or objective assessment of primary outcome(s), adequately addressed incomplete outcome data, freedom from selective reporting and freedom from other risks of bias. We used three additional criteria specified by EPOC (EPOC 2009): similar baseline characteristics, reliable primary outcome measures and adequate protection against contamination. We reported all included studies in the Cochrane 'Risk of bias' tables.

Two review authors (CH and CC) used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach to assess the quality of the body of evidence for each primary outcome included in the 'Summary of findings' table (Guyatt 2008). The quality of the body of evidence for each primary outcome was rated according to the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias).

Measures of treatment effect

We measured the effect of the intervention by referencing published tools used to measure inappropriate prescribing as well as tools used to assess appropriateness of prescribing as outlined above, for example, MAI and Beers criteria. We reported outcomes for each study in natural units. When baseline results were available from studies, both preinterventionand postintervention means and proportions for study and control groups were reported. We analysed data using RevMan 5.2. When possible, results were presented with 95% CIs and estimates for dichotomous outcomes (e.g. number of participants receiving appropriate polypharmacy) as risk ratios.

Unit of analysis issues

We critically examined the methods of analysis of all study types. When studies with a unit of analysis error were identified, the data were reanalysed with exclusion of such studies (sensitivity analysis).

Dealing with missing data

We assessed the methods used in each included study to deal with missing data. Any study with a differential loss to follow-up between groups greater than 20% was excluded from meta-analysis.

Assessment of reporting biases

We assessed reporting bias by scrutinising study results using the 'Risk of bias' tables provided in RevMan 5.2. We examined funnel plots corresponding to meta-analysis of the primary outcome to assess the potential for small-study effects such as publication bias.

Data synthesis and investigation of heterogeneity

Methods utilised to synthesise the studies depended on their quality, design and heterogeneity. We pooled the results of studies if at least two studies were homogeneous regarding participants, interventions and outcomes. We grouped studies and described them according to type of intervention, setting and study design, and we performed an assessment of evidence on the theoretical basis for each of the approaches described.

In the presence of statistical heterogeneity (greater than 50%, as estimated by the I^2 statistic), we applied a random-effects model for meta-analysis. For pooling, we considered only groups of studies of the same design (RCTs and CCTs).

When it was not possible to combine outcome data because of differences in reporting or substantive heterogeneity, we provided a narrative summary.

Sensitivity analysis

We performed a sensitivity analysis for pooled results based on methodological quality to assess the overall effect. For example, studies with a unit of analysis error or high risk of bias were excluded from the analysis.

Ongoing studies

We described ongoing studies identified during completion of the review and provided details such as primary author, research question(s) and methods and outcome measures, together with an estimate of the reporting date in the Characteristics of ongoing studies table appended to this review.

Studies awaiting classification

Studies for which sufficient information was not available to determine eligibility for inclusion in this review have been allocated to the Studies awaiting classification section.

Summary of findings

We used Summary of findings for the main comparison for the main comparisons in the review to interpret results and draw conclusions about the effects of different interventions, including size of the effects and quality of the evidence.

RESULTS

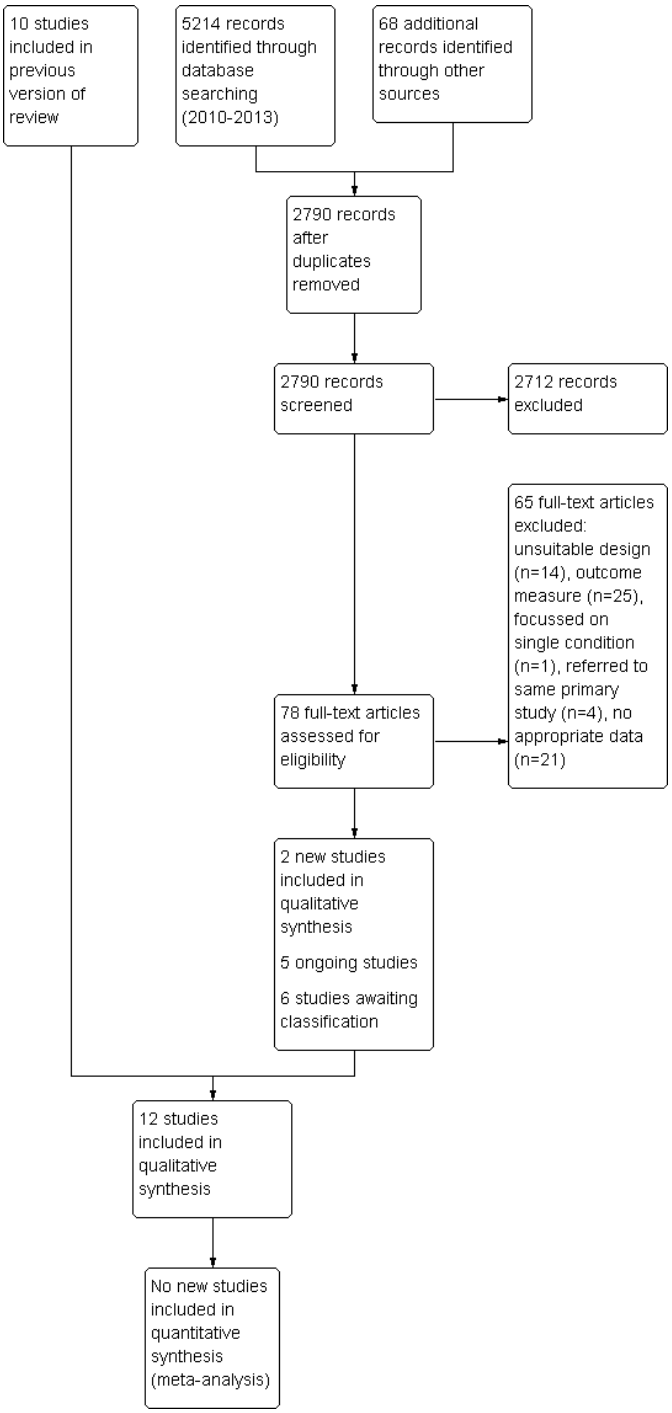
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies; and Characteristics of studies awaiting classification.

Results of the search

Updated electronic searches identified 2722 potentially relevant citations (Figure 1). Following review of titles and abstracts, 67 full-text publications were retrieved for more detailed assessment. Through searches of other sources, such as relevant reviews (Appendix 3), including the list of ongoing studies provided in the previous review (Patterson 2012) and the Clinical Trials Registry, as well as through contact with study authors, 11 additional potentially relevant citations were identified and assessed.

Figure 1. Study flow diagram.



Of these, two studies met all other inclusion criteria (including study design, study population, types of interventions examined) and were added to the review.

Four pairs of publications referred to the same studies (see Characteristics of excluded studies). Fourteen studies were excluded primarily because of an unsuitable design, for example, observational study, no control group. Twenty-five studies were excluded because of the outcome measure used (the primary outcome being the change in prevalence of appropriate use of polypharmacy, as measured by a validated instrument). One study was excluded because it focused on a single long-term medical condition.

We excluded a further 21 citations consisting of conference abstracts, protocols and summary reports because of the outcome measure used and/or the absence of appropriate data. Based on identified conference abstracts and published protocols, five ongoing studies were identified (see Characteristics of ongoing studies). Six additional studies are awaiting classification (see Characteristics of studies awaiting classification).

Included studies

Two studies were added to this review (Dalleur 2014; Gallagher 2011), hence the total number of studies included is 12: Bucci 2003; Crotty 2004a; Crotty 2004b; Hanlon 1996; Schmader 2004; Spinewine 2007; Tamblyn 2003; Taylor 2003; Trygstad 2005 and Trygstad 2009. The North Carolina Long-Term Care Polypharmacy Initiative was published as three studies (Christensen 2004; Trygstad 2005; Trygstad 2009), but only two of these studies (Trygstad 2005; Trygstad 2009) met the inclusion criteria. As outlined below, data from each of the studies that were added to the review could not be included in any form of meta-analysis; therefore narrative descriptions of results are presented. Details are provided in the Characteristics of included studies table and are briefly summarised below.

Study design

Included studies consisted of eight RCTs (Bucci 2003; Crotty 2004b; Dalleur 2014; Gallagher 2011; Hanlon 1996; Schmader 2004; Spinewine 2007; Taylor 2003), two cluster RCTs (Crotty 2004a; Tamblyn 2003) and two controlled before and after studies (Trygstad 2005; Trygstad 2009).

Settings

Of the seven studies (1489 participants) conducted in hospital settings, three were conducted in hospital outpatient clinics (general medicine, Hanlon 1996; heart function, Bucci 2003; geriatric evaluation and management (GEM), Schmader 2004), one at the hospital/home care interface (Crotty 2004b) and three in an inpatient setting (Dalleur 2014; Gallagher 2011; Spinewine 2007). Two studies (12,629 participants) were conducted in the primary care setting at community-based family medicine clinics (Taylor 2003) and in GP practices (Tamblyn 2003). Three studies (8320 participants) took place in nursing homes (Crotty 2004a; Trygstad 2005; Trygstad 2009).

The included studies were carried out in five countries: Australia (two studies), Belgium (two studies), Canada (two studies), Ireland (one study) and the USA (five studies).

Participants

A total of 22,438 participants were included in this review. The mean age of intervention group participants was 76.4 years and of control group participants was 76.3 years. Equal proportions of intervention and control group participants were female (65.6%). Ethnicity was not reported in most of the studies; in the four studies (8685 participants) that did report this, 71.7% of participants were white.

All study participants had more than one long-term medical condition, and, on average, participants were receiving more than four medicines at baseline. In 11 of the 12 studies for which data were available (9878 participants), participants were prescribed a mean of 9.4 (intervention) and 8.9 (control) medicines.

Common long-term care conditions among participants in the studies included in this review were asthma, diabetes, dyslipidaemia, hypertension, cardiovascular disease (including congestive heart failure) and dementia.

Interventions

In all cases, interventions were classified as organisational according to EPOC definitions; none of the included studies was classified as professional, financial or regulatory.

Eleven studies examined complex, multi-faceted interventions of pharmaceutical care in a variety of settings. Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definitive outcomes that improve a patient's quality of life (Hepler 1990). Pharmaceutical care reflects a systematic approach that ensures patients receive the correct medicines, at an appropriate dose, for appropriate indications. It involves pharmacists moderating drug management in collaboration with physician, patient and carer (Hepler 1990). One unifaceted study (Tamblyn 2003) examined CDS provided to GPs in their own practices.

Pharmaceutical care was commonly provided by pharmacists working closely with other healthcare professionals in a variety of settings. In hospital settings, pharmacists worked as part of a multidisciplinary team in outpatient clinics (Bucci 2003; Hanlon 1996; Schmader 2004), in inpatient services on hospital wards as a clinical pharmacy service (Spinewine 2007) or as part of the hospital discharge process (Crotty 2004b). In community settings, pharmaceutical care services, including medication reviews, patient interviews and counselling, were provided by pharmacists in community-based family medicine clinics (Taylor 2003). In nursing homes, multi-disciplinary case conferences combined with staff education were provided by pharmacists (Crotty 2004a), as was a drug therapy management service (Trygstad 2005; Trygstad 2009).

Physicians delivered the intervention via a computerised support programme in one study (Tamblyn 2003), whereas in all other studies, criteria-based processes were used to develop recommendations for improving the appropriateness of prescribing to prescribers.

Models of pharmaceutical care provided in the included studies were complex and variable. In seven studies, the pharmacist(s) conducted an independent medication review using participant notes (Crotty 2004a; Crotty 2004b) or together with participants during a face-to-face encounter (Bucci 2003; Hanlon 1996; Schmader 2004; Spinewine 2007; Tamblyn 2003; Taylor 2003). Following medication review, recommendations were discussed with a multidisciplinary team during case conferences (Crotty 2004a; Crotty 2004b) or were discussed with prescribers and followed up by written recommendations (Hanlon 1996) from multi-disciplinary team members at the same outpatient clinic (Bucci 2003) or during inpatient ward rounds (Spinewine 2007). In one study, the pharmacist was an integral member of the multi-disciplinary team (Schmader 2004) and contributed to the pharmaceutical aspect of the care plan of participants at the point of decision making. In two studies, consultant pharmacists performed a comprehensive profile review of the computerised drug profiles of selected participants using a range of tools such as the Beers criteria and made recommendations to prescribers in nursing homes by fax, telephone or written communication (Trygstad 2005; Trygstad 2009).

In two studies, participants' medication lists were screened by a geriatrician (Dalleur 2014) or by the primary research physician (Gallagher 2011) upon admission to hospital, and oral and written recommendations outlining appropriate prescribing changes were then provided to the attending physicians. In the Dalleur 2014 study, no pharmacist was available to collaborate with the inpatient geriatric consultation team owing to lack of resources within the hospital.

Participant education was provided as part of the pharmaceutical care intervention in four of six studies in which the intervention was conducted face-to-face, and these participants were given 'directive guidance' and specialised medication scheduling tools (e.g. monitored dosage systems) to encourage adherence to their prescribed medication regimens (Bucci 2003; Hanlon 1996; Spinewine 2007; Taylor 2003). Directive guidance describes pharmaceutical care activities such as provision of information about medications, their administration and their adverse effects (Bucci 2003).

Education was provided to prescribers and other healthcare professionals included in the multi-disciplinary team as part of the intervention in five studies (Bucci 2003; Crotty 2004a; Crotty 2004b; Hanlon 1996; Spinewine 2007); this occurred at case conferences, during ward rounds or when evidence-based information and answers to specific medication-related queries were presented. In two studies in which the pharmacist was part of a multi-disciplinary team, no educational intervention was specified in the methodology (Schmader 2004; Taylor 2003).

The timing of provision of the intervention was variable. Interventions were delivered over a period of time, for example, during the hospital inpatient stay and at discharge (Schmader 2004; Spinewine 2007) or over several clinic visits and over several months on an ongoing basis (Tamblyn 2003). Interventions were also delivered at the time of an event, for example, following hospital admission (Dalleur 2014; Gallagher 2011), during attendance at outpatient clinics (Bucci 2003; Hanlon 1996; Schmader 2004; Taylor 2003), at nursing home visits (Crotty 2004a; Trygstad 2005; Trygstad 2009) or at hospital discharge to a nursing home (Crotty 2004b). In studies for which details of intervention administration were provided, interventions were most commonly administered during a single episode of care (Bucci 2003; Crotty 2004a; Hanlon 1996; Tamblyn 2003; Taylor 2003; Trygstad 2005; Trygstad 2009). Interventions were provided over varying durations, ranging from five or six months (Bucci 2003; Trygstad 2005) to three years and three months (Schmader 2004). Further details of the interventions are detailed in the Characteristics of included studies tables.

Outcomes

The primary outcome of interest in this review was the change in prevalence of appropriate use of polypharmacy, as measured by a validated instrument. Validated assessments of appropriateness reported in all included studies were measured independently by pharmacists, geriatricians or the research team, who had access to participants' charts and medication records, except in Trygstad 2005 and Trygstad 2009, where the Medicaid dispensed prescription claims database was used. Time between delivery of the intervention and follow-up outcome measurement varied from immediately post intervention (e.g. post hospital discharge or clinic visit) (Schmader 2004; Spinewine 2007; Tamblyn 2003) to at least one month (Bucci 2003), eight weeks (Crotty 2004b), zero to three months (Crotty 2004a; Trygstad 2005; Trygstad 2009), six months (Gallagher 2011) and up to one year (Dalleur 2014; Hanlon 1996; Taylor 2003).

Eight studies measured appropriateness using the summated MAI score post intervention (Bucci 2003; Crotty 2004a; Crotty 2004b; Gallagher 2011; Hanlon 1996; Schmader 2004; Spinewine 2007; Taylor 2003). If it was not possible to calculate the change in MAI from the results presented, study authors were contacted to provide the change in the summated MAI score. One study reported the MAI score in terms of the number of prescriptions with inappropriate medications; this was unsuitable for inclusion in the meta-analysis (Taylor 2003). The Beers list of criteria was used to assess the appropriateness of medications post intervention in four studies (Schmader 2004; Spinewine 2007; Trygstad 2005; Trygstad 2009), and one study reported the number of participants with one or more Beers criteria drugs post intervention (Spinewine 2007). Data for the change in the number of Beers drugs were not reported by the Spinewine 2007 study authors. Two studies used the STOPP (Screening Tool of Older Person's Prescriptions) criteria to screen for potentially inappropriate prescribing

in hospitalised study participants (Dalleur 2014; Gallagher 2011). Both studies reported the proportions of participants with at least one potentially inappropriate medication, as identified using the STOPP criteria post intervention. In the Gallagher 2011 study, the START criteria were also applied, and the proportions of participants with at least one potentially inappropriate prescribing omission, as identified using the START criteria post intervention, were reported.

One study measured appropriateness using the McLeod criteria and reported the rate of inappropriate medications prescribed per physician visit post intervention (Tamblyn 2003). No other validated criteria (e.g. Zhan) were reported.

Under-use of medication was reported in three studies (Gallagher 2011; Schmader 2004; Spinewine 2007). Under-use defined as 'the omission of drug therapy indicated for the treatment or prevention of established diseases' (Lipton 1992) was measured using the Assessment of Under-utilisation of Medication (AUM) instrument (Jeffery 1999) in two studies (Gallagher 2011; Schmader 2004), whereas Spinewine 2007 used seven process measures from the full range of Assessing Care of Vulnerable Elderly (ACOVE) criteria (Wenger 2001), which relate to the inappropriate under-use of medication.

Five studies measured hospital admissions by examining hospital records at varying time points post intervention (Crotty 2004b; Gallagher 2011; Spinewine 2007; Taylor 2003; Trygstad 2005) ranging from eight weeks (Crotty 2004b; Spinewine 2007) to one year (Taylor 2003).

Medication-related problems, a secondary outcome, were measured in six studies and were reported as medication misadventures (defined as iatrogenic incidents that occur as a result of error, immunological response or idiosyncratic response and are always unexpected or undesirable to the participant) (Taylor 2003), potential drug therapy problems (Trygstad 2005; Trygstad 2009) or postintervention ADEs (Crotty 2004b; Hanlon 1996; Schmader 2004).

One study assessed adherence to medication via participant self-report (Taylor 2003).

Health-related quality of life (HRQoL) was assessed using the Medical Outcomes Study 36-item Short Form health survey (SF-36) in two studies (Hanlon 1996; Taylor 2003).

Excluded studies

Excluded publications that were read in full are summarised along with the reasons for exclusion in the Characteristics of excluded studies table.

Studies of unsuitable design were excluded from this review (14 studies). Twenty-five studies were excluded because of the outcome measure used (the primary outcome was change in the prevalence of appropriate use of polypharmacy, as measured by a validated instrument). One study was excluded because it focused on a single long-term medical condition.

A further 21 citations consisting of conference abstracts, protocols and summary reports were excluded because of the outcome measure used and/or the absence of appropriate data.

Risk of bias in included studies

Details of the risk of bias are presented in Figure 2 and Figure 3 and in the Characteristics of included studies tables.

Figure 2. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.

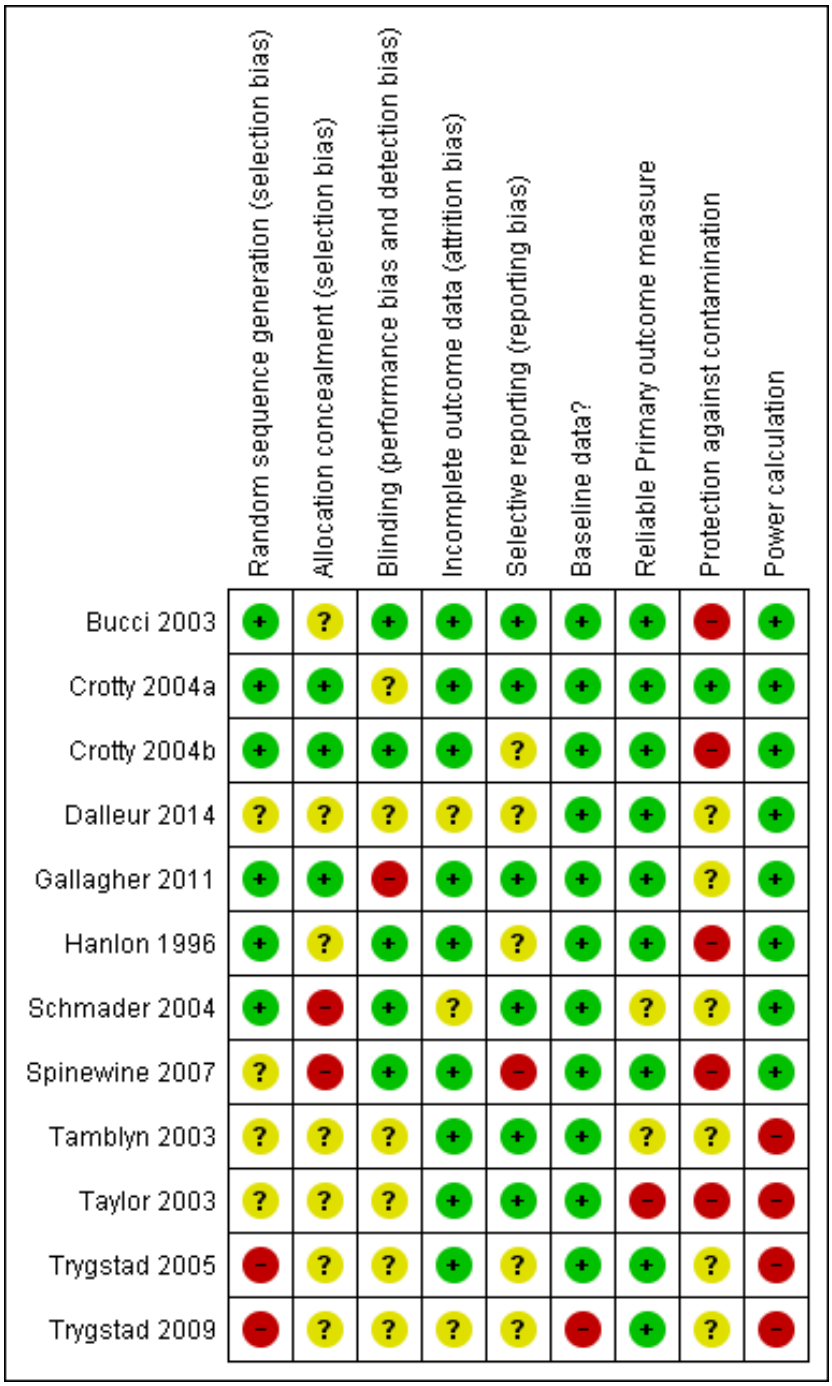
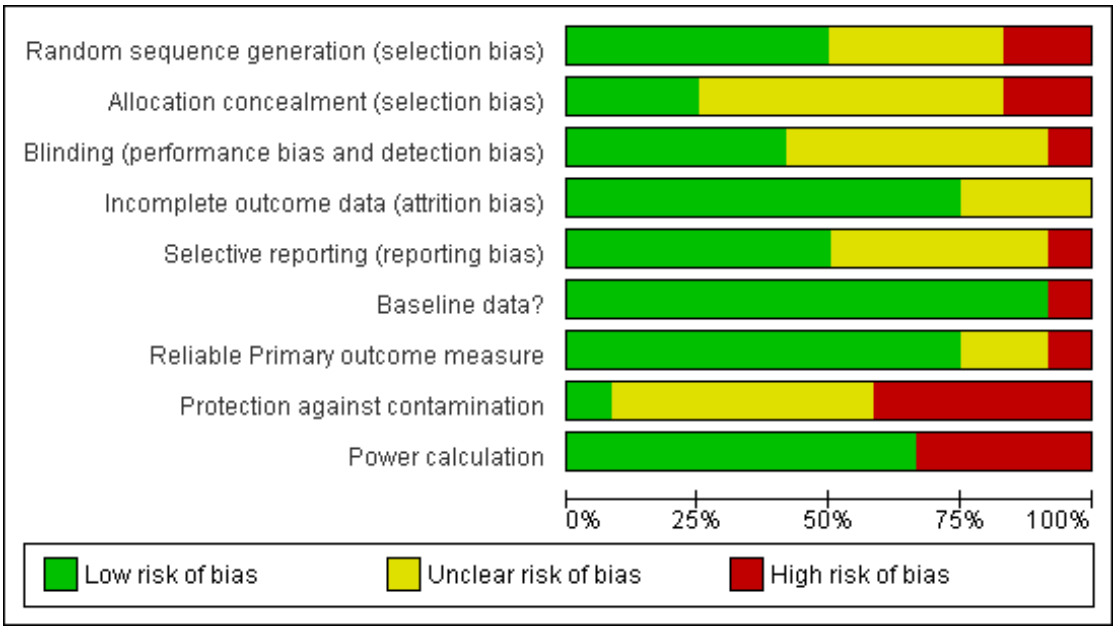


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



No major differences were noted in the risk of bias of studies included in the review.

Allocation

Six trials reported adequate sequence generation (Bucci 2003; Crotty 2004a; Crotty 2004b; Gallagher 2011; Hanlon 1996; Schmader 2004), and three reported concealment of allocation (Crotty 2004a; Crotty 2004b; Gallagher 2011).

Blinding

In six studies, blinded measurement of outcomes had taken place to ensure that primary outcome assessors had no knowledge of the intervention received by participants (Bucci 2003; Crotty 2004b; Hanlon 1996; Schmader 2004; Spinewine 2007; Trygstad 2009).

Incomplete outcome data

Incomplete outcome data were adequately addressed in nine studies. In one study (Schmader 2004), 864 participants were randomly assigned but only 834 were included in the analysis, and no intention-to-treat analysis was reported. Therefore, it was unclear whether all outcome data were included.

Selective reporting

One study (Trygstad 2009) did not report baseline data, and in the Spinewine 2007 study, the authors failed to report one of the secondary outcomes-'medications taken.'

Other potential sources of bias

The primary outcome measures used were reliable instruments in all studies, for example, MAI kappa value = 0.84.

Participants in one study were protected from contamination (Crotty 2004a). In six studies it was unclear whether protection against contamination had been provided (Dalleur 2014; Gallagher 2011; Schmader 2004; Tamblyn 2003; Trygstad 2005; Trygstad 2009), and the remaining studies were determined to have high risk of contamination (Bucci 2003; Crotty 2004b; Hanlon 1996; Spinewine 2007; Taylor 2003). Contamination bias occurs when members of the control group are inadvertently exposed to the intervention, thus potentially minimising differences in outcomes between the two groups (Higgins 2011). This is an important limitation for this review, where, in some studies, for example, a pharmacist involved in the provision of pharmaceutical

care to members of the intervention group may have inadvertently modified the treatment of those in the control group as a result of having knowledge of the intervention. The possible influence of contamination bias should be considered when the results of this review are interpreted.

Seven studies (Bucci 2003; Crotty 2004a; Crotty 2004b; Dalleur 2014; Gallagher 2011; Hanlon 1996; Schmader 2004) had sufficient power to detect a meaningful effect size. Funnel plots of postintervention estimates of the change in MAI and summated MAI showed little evidence of publication bias (Figure 4; Figure 5).

Figure 4. Funnel plot of comparison: 1 Postintervention analysis, outcome: 1.1 Change in MAI score.

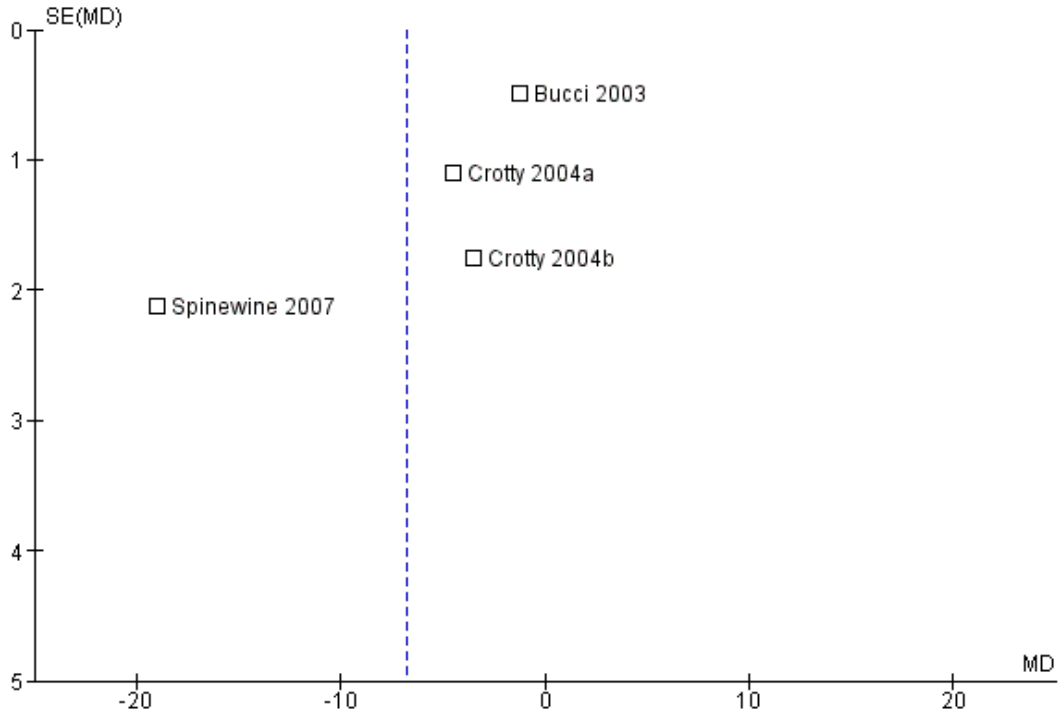
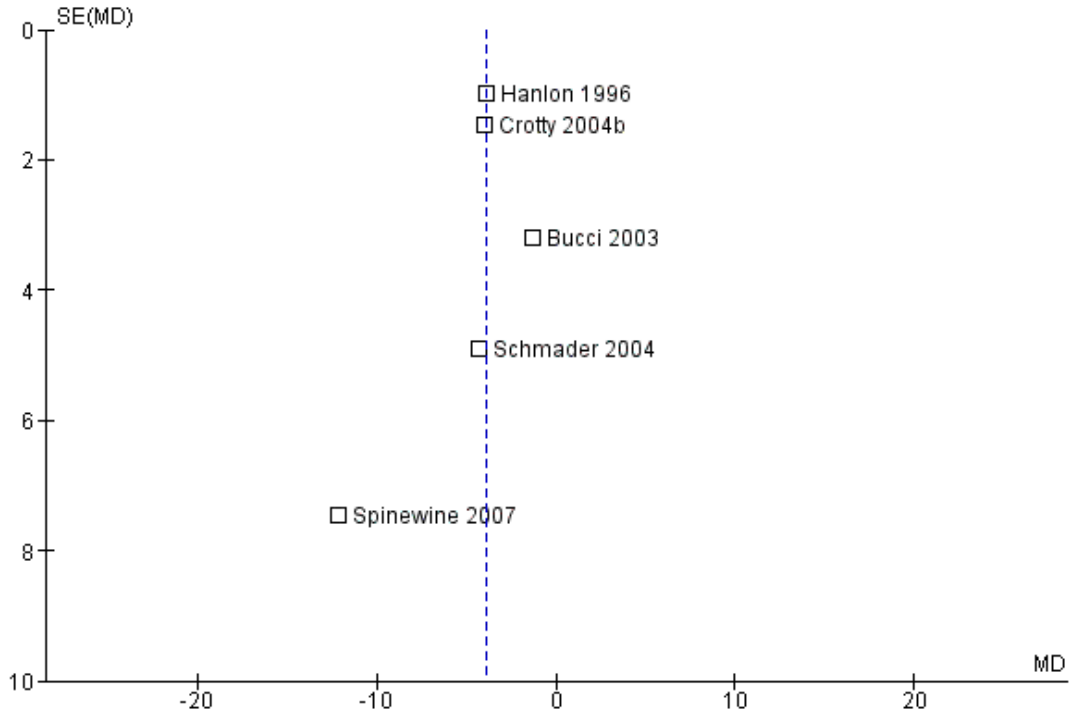


Figure 5. Funnel plot of comparison: 1 Postintervention analysis, outcome: 1.4 Summated MAI score.



Effects of interventions

See: **Summary of findings for the main comparison** Pharmaceutical care compared with usual care for older people receiving polypharmacy

Pharmaceutical care and CDS interventions included in this review demonstrated a reduction in inappropriate polypharmacy. Hospitalisations, as reported in five studies, were reduced in three studies (Crotty 2004b; Taylor 2003; Trygstad 2009) (in one cohort, but not in the remaining nine cohorts), and two studies (Gallagher 2011; Spinewine 2007) found no difference.

No consistent intervention effect on medication-related problems was observed across studies (six studies); these problems were reported in terms of ADEs (Crotty 2004b; Hanlon 1996; Schmader 2004), medication misadventures (Taylor 2003) and potential drug therapy problems (Trygstad 2005; Trygstad 2009). Improvement in adherence to medication was demonstrated (Taylor 2003), but no changes in HRQoL (Hanlon 1996; Taylor 2003) were detected.

Primary outcome results

As only one unifaceted study was included (Tamblyn 2003), a subgroup analysis was not possible. Tamblyn 2003 also was not included in the meta-analysis, as a different outcome measure was used (McLeod criteria; McLeod 1997) that was not considered similar enough to the other outcomes for data to be combined.

Change in the prevalence of appropriate use of polypharmacy, as measured by a validated instrument

Change in summated MAI score

Two studies reported appropriateness of polypharmacy as the change in the summated MAI score (Bucci 2003; Crotty 2004a), and further unpublished data were received from the authors of two studies (Crotty 2004b; Spinewine 2007). Two hundred ten intervention participants and 214 control participants were included in the analysis. Comparison of the change in summated MAI score from baseline to follow-up between the intervention group and the control group is shown in Analysis 1.1. Overall a greater reduction in the summated MAI score was seen in the intervention group compared with the control group (mean difference -6.78, 95% CI -12.34 to -1.22). Marked heterogeneity between studies was noted (I^2 = 96%; P value < 0.00001). Crotty 2004a reported a unit of analysis error; nursing homes were the unit of

randomisation, but the analysis was conducted at the participant level. A sensitivity analysis excluding Crotty 2004a showed a similar change in summated MAI score (mean difference -7.75, 95% CI -17.06 to 1.56, I^2 = 97%) in favour of the intervention group (Analysis 1.2) based on 178 intervention participants and 175 control participants. A further sensitivity analysis removing both Crotty 2004a and Spinewine 2007 (an outlying study with a large effect size that had a high risk of bias with respect to contamination, allocation concealment and selective outcome reporting) also showed a greater reduction in the summated MAI score of the intervention group, but the magnitude of the difference was smaller compared with previous analyses (mean difference -1.79, 95% CI -3.73 to 0.16, I^2 = 39%) (Analysis 1.3).

Prevalence of appropriate use of polypharmacy post intervention

Summated MAI score post intervention

Postintervention pooled data from five studies (Bucci 2003; Crotty 2004b; Hanlon 1996; Schmader 2004; Spinewine 2007) with 488 intervention participants and 477 control participants showed a lower summated MAI score (mean difference -3.88, 95% CI -5.40 to -2.35) in the intervention group compared with the control group (see Data and analyses, Postintervention; Analysis 1.4). Little evidence of heterogeneity between these estimates was found (I^2 = 0%). Gallagher 2011 also reported the summated MAI score post intervention. These data were not included in the meta-analysis because it was skewed. Compared with the control group, the median summated MAI score was lower in the intervention group at discharge and at each assessment during the six-month follow-up period (P value < 0.001).

MAI score-other

One study (Taylor 2003) expressed the MAI score as the number of inappropriate prescriptions and thus could not be included in the meta-analysis. The percentage of inappropriate prescriptions decreased in all 10 MAI domains in the intervention group and increased in five domains in the control group.

Beers criteria

Number of Beers drugs post intervention

Pooled data from two studies (Schmader 2004; Spinewine 2007) with 298 intervention participants and 288 control participants showed that intervention group participants were prescribed fewer Beers drugs compared with control group participants post intervention (mean difference -0.1, 95% CI -0.28 to 0.09, I^2 = 89%) (Analysis 1.5). The Trygstad 2009 study, which also reported the number of Beers list drugs, comprised 10 cohorts. It was not included in the meta-analysis, as study design, analysis and reporting (e.g. using propensity matching, reporting results as difference-in-difference) differed from the others, resulting in estimates that were not sufficiently similar to support inclusion. We were unable to ascertain the standard deviation of the results for Trygstad 2005, which also was not included in the meta-analysis.

Number of participants with one or more Beers drugs

As well as the total number of Beers list drugs post intervention, Spinewine 2007 reported the proportions of participants taking one or more Beers list drugs before and after intervention. Similar improvements were reported in the proportions of intervention and control group participants receiving one or more Beers list drugs between the time of hospital admission and discharge (OR 0.6, 95% CI 0.3 to 1.1). As this was the only study to report this measure of appropriate polypharmacy, meta-analysis was not possible.

McLeod criteria

The McLeod criteria were used in one study (Tamblyn 2003) to identify initiation and discontinuation rates of 159 prescription-related problems. During the 13-month study period, the number of inappropriate medications started by study physicians per 1000 visits was 43.8 (intervention) and 53.2 (control). The relative rate of initiation of an inappropriate prescription for the intervention group was 0.82 (95% CI 0.69 to 0.98). Meta-analysis was not possible, as these criteria were not used in other studies.

STOPP and START criteria

Two studies (Dalleur 2014; Gallagher 2011) used the STOPP criteria to screen for potentially inappropriate prescribing in older study participants admitted to hospital. Gallagher 2011 reported lower (P value < 0.001) proportions of participants in the intervention group compared with the control group, with one or more STOPP criteria medications given for each of the postintervention assessments (discharge; two, four and six months post discharge). Dalleur 2014 reported that the reduction in the proportions of participants with one or more STOPP criteria medications between the time of hospital admission and discharge did not differ between intervention and control groups (OR 1.5, 95% CI 0.49 to 4.89; P value 0.454). However, at group level, the discontinuation rate of potentially inappropriate medications, as identified using STOPP criteria, was higher in the intervention group compared with the control group (OR 2.75, 95% CI 1.22 to 6.24; P value 0.013). Data from these two studies were not pooled because included participants were not considered to be homogenous. Dalleur 2014 specifically targeted frail patients aged 75 years

and older, whereas Gallagher 2011 included patients aged 65 years and above.

In the Gallagher 2011 study, the START criteria were also used to screen participants' medication lists. For each of the postintervention assessments (discharge, two, four and six months post discharge), lower proportions of participants with one or more START criteria medications were reported in the intervention group compared with the control group (P value < 0.001). As this was the only study to report the use of these criteria, meta-analysis was not possible.

Under-use of medication

Two studies assessed under-use of medication using the AUM index (Gallagher 2011; Schmader 2004). In the Gallagher 2011 study, a greater reduction was seen in the proportion of intervention group participants with prescribing omissions post intervention, as identified using the AUM index, compared with the control group (absolute risk reduction 21.2%, 95% CI 13.3 to 29.1). In the Schmader 2004 study, a reduction in the number of conditions with omitted drugs was observed post intervention in the intervention group relative to the control group; the difference in change in AUM score was -0.3 (P value < 0.0001). As the two studies assessed under-prescribing on two different levels (i.e. participant, medical condition), meta-analysis was not possible.

In the Spinewine 2007 study, the magnitude of the reduction in ACOVE scores was greater in the intervention group (baseline score 50.0, postintervention score 14.6; P value < 0.001) compared with the control group (baseline score 58.9, postintervention score 44.4, P value 0.02), and intervention participants were six times more likely than control participants to show at least one improvement in appropriate prescribing based on these criteria (OR 6.1, 95% CI 2.2 to 17.0). No meta-analysis was possible, as this outcome measure was assessed differently from those in the above two studies, and under-use was not reported in the other studies.

Hospital admissions

Five studies measured hospital admissions post intervention (Crotty 2004b; Gallagher 2011; Spinewine 2007; Taylor 2003, Trygstad 2009). Two studies (Gallagher 2011; Spinewine 2007) reported no difference in hospitalisations between intervention and control group participants, and the remaining studies reported some overall reductions in hospital admissions using a variety of measurements, as detailed below.

Taylor 2003 reported a reduction in both the number of hospital admissions (P value 0.003) and the number of emergency department visits (P value 0.044) during the intervention year compared with preintervention. Crotty 2004b reported less hospital usage among participants who received the intervention and were still alive at eight weeks post intervention compared with control group participants (risk ratio (RR) 0.38, 95% CI 0.15 to 0.99). However, analysis of all participants including deaths and losses to follow-up showed similar hospital usage in the intervention and control groups (-9 (16.7%) with intervention vs -15 (26.8%) with control; RR 0.58, 95% CI 0.28 to 1.21). Trygstad 2009 showed a reduction in the RR of hospitalisation in one cohort of nursing home residents receiving retrospective-only-type medication reviews (RR 0.84, 95% CI 0.71 to 1.00; P value 0.04). The remaining eight cohorts also had an RR below 1.0; however, confidence intervals for the individual point estimates crossed the line of no effect.

Because of differences in methodology in the measurement of hospital admissions and the expression of results, a meta-analysis was not possible for studies reporting hospital admissions.

Inappropriate medication was also reported by these studies. In the study by Trygstad 2009, the Beers list was used to measure inappropriate medication, but no reductions were observed in the cohorts receiving retrospective medication review. In the remaining four studies, appropriateness of prescribing improved, as shown by reductions in MAI scores, but the association with hospitalisations was inconsistent.

Secondary outcome results

Medication-related problems in older people (e.g. adverse drug reactions, drug-drug interactions, medication errors)

Medication-related problems were reported in six studies using different terms. No consistent intervention effect on medication-related problems was noted across studies.

Three studies reported medication-related problems as ADEs (Crotty 2004b; Hanlon 1996; Schmader 2004). Schmader 2004 showed that the risk of a serious ADE was reduced (RR 0.65, 95% CI 0.45 to 0.93; P value 0.02) in a geriatric outpatient clinic compared with usual outpatient care; however, no difference in the risk of an ADE was noted when all types of ADEs were considered (RR 1.03, 95% CI 0.86 to 1.23; P value 0.75). The other two studies (Crotty 2004b; Hanlon 1996) showed no differences between proportions of intervention and control group participants with ADEs at follow-up.

Taylor 2003 reported medication-related problems as medication misadventures. Proportions of intervention group (2.8%) and control group (3.0%) participants with at least one medication misadventure at 12 months were similar (P value 0.73).

Potential medication problems categorised as 'consider duration' (of therapy), 'clinical initiatives' and 'therapeutic duplication' were reported in the two North Carolina initiative studies (see Characteristics of included studies tables; Trygstad 2005; Trygstad 2009). At three months, duration alert rates were reduced by 6.3% in the intervention group (n = 5160) and by 16.7% in the control group (n = 2202); clinical initiatives were reduced by 10.8%

in the intervention group and 0.7% in the control group, and therapeutic duplication was reduced in the intervention group by 9.4% and in the control group by 8.8% (Trygstad 2005). Control group results were not reported separately in Trygstad 2009. At three months, duration of therapy alerts were reduced by 27.8% (mean difference in the difference (mDID) = -0.023; P value > 0.05); clinical initiative alerts were reduced by 13.9% (mDID = -0.24; P < 0.05); and therapeutic duplication alerts were reduced by 5.6% (mDID = -0.087; P value > 0.05) (Trygstad 2009).

Adherence to medication

One study (Taylor 2003) reported adherence to medication in terms of compliance scores, calculated through assessment of participants' reports of missed doses. Those with medication compliance scores of 80% to 100% increased by 15% at 12 months from a mean (± standard deviation (SD)) of 84.9 ± 6.7% to 100% in the intervention group (n = 33), but the control group (n = 36) did not change from 88.9% ± 5.8% at baseline to 88.9% ± 6.3% at 12 months (P value 0.115).

Quality of life (as assessed by a validated method)

Two studies (Hanlon 1996; Taylor 2003) assessed HRQoL. No differences in HRQoL scores (SF-36) were observed between groups at baseline or at endpoint.

Quality assessment-the GRADE approach

Based on the GRADE approach (Guyatt 2008), the overall quality of the body of evidence for each primary outcome for which data were included in a meta-analysis was deemed to be low or very low. Although each study included in the meta-analyses was of a randomised design, and, where assessed, no evidence of publication bias was found (Figure 4; Figure 5), the quality of the body of evidence was downgraded for each outcome based on other GRADE considerations (i.*e.* study limitations, consistency of effect, imprecision, indirectness).

The quality of the body of evidence for the summated MAI score post intervention was downgraded to low. Serious design limitations with implications in terms of selection bias, reporting bias and risk of contamination bias were identified in several studies. It was also found that some studies answered a restricted version of the research question, as a validated assessment of under-prescribing was not included as part of the overall assessment of prescribing appropriateness. Therefore, interventions did not directly target appropriate polypharmacy.

The quality of the body of evidence for the change in MAI score was downgraded to very low. Similar issues were identified to those in studies evaluating the summated MAI score post intervention in terms of design limitations and a restricted version of the research question. Evidence showed heterogeneity (I^2 = 89%) and imprecision, whereby the pooled effect estimate had a 95% CI that was wide and/or crossed the line of no effect.

The quality of the body of evidence for the number of Beers drugs per participant post intervention was downgraded to very low. Serious design limitations were identified in both studies, with implications in terms of risks of selection bias and contamination bias. Evidence showed heterogeneity (I^2 = 96%) and imprecision in the pooled effect estimate.

DISCUSSION

Summary of main results

The addition of only two studies to this updated review highlights the lack of intervention studies of suitable quality that have been conducted to date aimed at improving appropriate polypharmacy in older people. The two studies that were added to this update had little impact on the overall findings of the review, as it was not possible to include data from either study in a meta-analysis. Overall, the studies included in this review were limited by their small sample sizes and poor quality.

The summated MAI was one of the measures of appropriate medication used in the studies to indicate appropriateness of polypharmacy in older people. Four of the 10 included studies were pooled in a meta-analysis of the change in the summated MAI; this showed improvement in the appropriateness of polypharmacy (Analysis 1.1). Postintervention summated MAI results of five studies that were pooled in a meta-analysis (Analysis 1.4) also appeared to indicate that pharmaceutical care interventions improved appropriate polypharmacy. This was consistent with postintervention results of the Gallagher 2011 study, which were not included in the meta-analysis because the summated MAI scores were skewed. Little evidence of heterogeneity was noted in the effect of the interventions on the summated MAI score (I^2 = 0).

Changes in summated MAI score results were normally distributed and were more suitable for meta-analysis, but greater heterogeneity was noted among the included studies (I^2 = 96%), largely because of the influence of the results of one study (Spinewine 2007). Overall, the reduction in the intervention group summated MAI score was greater than that in the control group. A sensitivity analysis in which Crotty 2004a was removed because of a unit of analysis error showed further improvement in the effect estimate when compared with the meta-analysis. Furthermore, removal of an outlying study with a large effect size (Spinewine 2007) reduced heterogeneity but also reduced the effect estimate. This may have been related to the small sample size for this meta-analysis (82 intervention participants and 85 control participants). When the two studies were combined using the number of Beers list drugs per participant as a measure of appropriateness (Schmader 2004; Spinewine 2007), differences between intervention and control

groups in the number of Beers list drugs per participant favoured the intervention group. However,this difference is unlikely to have any clinical significance. Data from two studies (Dalleur 2014; Gallagher 2011) that used the STOPP criteria to screen for potentially inappropriate medications could not be included in a meta-analysis because participants were not considered to be homogenous. No consistent intervention effect was seen between the two studies in terms of the proportions of intervention and control group participants with one or more STOPP criteria medications. Only one study (Gallagher 2011) used the START criteria to screen for potentially inappropriate prescribing omissions. Three studies measured the under-usage of medication using two different assessment tools; the AUM index (Gallagher 2011; Schmader 2004) and the ACOVE criteria (Spinewine 2007). Each of these studies reported improvement in the under-usage of medication, but study results could not be included in a meta-analysis because of differences in the assessment measures used and in reporting of results.

The various endpoints of inappropriate medication score considered in this review are surrogate markers; future studies should focus on clinical outcomes such as hospital admissions. Only five studies reported hospitalisations, and we were unable to combine these results, as the reporting styles were different.

Overall completeness and applicability of evidence

Types of interventions included in the review were limited. Few trials aimed to improve the skills of the prescriber. Most interventions were pharmaceutical care interventions, which included outreach by pharmacists, screening of automated drug alerts by consultant pharmacists visiting nursing homes and clinical pharmacist interventions in various settings. Only one trial that involved CDS was identified. The interventions were complex and most were multi-faceted. Variation in heterogeneity observed in the pooled estimates should be treated cautiously as the interventions did not seem to work consistently across all studies, perhaps because of differences in how the interventions were provided, background practice and culture and variable processes in delivery of care. In addition, study-specific factors, such as variation in the quality of studies, may have played a role. The methods sections of studies provided little detail on how complex interventions were developed, how trials were designed and how staff were trained in delivery of the intervention. Other information pertinent to the success of pharmaceutical care interventions including documentation, communication and sharing of information and extent of access to clinical records given to intervention pharmacists was not stated clearly in the papers.

Although a promising result was obtained, suggesting that the interventions described in this review were successful in improving appropriateness of polypharmacy, the clinical impact of this is not known. The summated MAI score is a weighted average of the individual process scores of 10 criteria for each prescribed drug. For each criterion, the index includes operational definitions, explicit instructions and examples, and the evaluator rates whether the particular medication is 'appropriate,' 'marginally appropriate' or 'inappropriate'. Each medication can score between zero and 18, representing the range of medication appropriateness from completely appropriate to completely inappropriate. Although the removal of any inappropriate medication (with a resultant improvement in appropriate polypharmacy) is beneficial, it is unclear to what extent a reduction in the magnitude of 3.88 in the summated MAI score represents a clinically significant reduction in the risk of harm. However, improvement in validated assessment scales, such as the MAI, is important, as the quality of prescribing is assuming increasing importance as a means of preventing avoidable medication-related harm.

Evidence of potential bias was found in some studies, for example, only three studies reported adequate concealment of allocation, and only two reported appropriate protection from contamination, both of which may have influenced the effect estimate in these studies and therefore the overall pooled estimate.

Few rigourously conducted studies have tested interventions and examined clinically relevant outcomes such as hospital admissions or ADEs. Five studies in this review reported hospital admissions post intervention (Crotty 2004b; Gallagher 2011; Spinewine 2007; Taylor 2003; Trygstad 2009), and four studies (Crotty 2004b; Gallagher 2011; Spinewine 2007; Taylor 2003) reported that the appropriateness of prescribing improved, as was shown by reductions in the MAI, although the association with hospital admissions was inconsistent. In the fourth study (Trygstad 2009), no difference was found in the number of Beers list alerts post intervention, but the relative risk of hospitalisation was reduced. Use of different appropriateness scales in the included studies made it difficult for researchers to assess the impact of any improvement in medication appropriateness on hospital admissions. Similarly, some associations between measures of appropriateness and medication-related problems appeared to exist but were difficult to assess because of variation in scales used to measure outcomes and in reporting methods.

The aim of the intervention studies included in this review was to reduce harm subsequent to the prescription of too many medicines and to ensure that older people are prescribed appropriate medications that enhance their quality of life. However, several studies focused on reducing the number of medications, rather than improving overall appropriateness of prescribing, including underprescribing, that is, recommending medications that are clinically indicated yet are currently missing. Such under-treatment is a relevant outcome with clinical relevance (Aronson 2004; Gurwitz 2004) that is not often studied.

Limitations of the data

Quality of the evidence and potential biases in the review process

A limited number of studies were included in this review, as a paucity of studies in this area used validated instruments to measure the appropriateness of prescribing. The number of studies that could be combined in the meta-analyses was small. For example, the meta-analysis based on the number of Beers drugs per participant included just two studies (Analysis 1.5). As shown in the Summary of findings for the main comparison, the quality of evidence presented in this review, as described by the GRADE approach, was low or very low. Despite inclusion of data from randomised trial designs in the meta-analyses, the quality of the body of evidence was subsequently downgraded when each of the GRADE considerations (i.*e.* study limitations, consistency of effect, imprecision, indirectness, publication bias) was taken into account. This limits our confidence in the pooled effect estimates. Based on observed heterogeneity in the pooled effect estimates (Analysis 1.1; Analysis 1.4), the findings of meta-analyses related to MAI scores (change in MAI, summmated MAI post intervention) should be treated cautiously, as the interventions did not seem to work consistently across all studies. Factors contributing to this heterogeneity could have included variation in type, intensity and duration of interventions, as well as differences in the timing of follow-up assessments. In addition, study-specific factors such as variation in study quality may have played a role. However, no systematic approach was used to ensure a consistent level of detail in published reports of the interventions. For example, the methods sections of the studies provided little detail on the development of complex interventions, trial design or staff training in delivery of interventions. Other information pertinent to intervention success, such as documentation, communication and intervention pharmacists' level of access to clinical records, was not clearly reported in the papers. The specific processes that constituted successful interventions was often unclear, which may have contributed to heterogeneity in effect estimates.

No language restrictions were placed on the search strategy, but all of the included trials were published in English and were conducted in developed countries. Despite the limited number of studies included in the meta-analyses, funnel plots of studies reporting MAI-related outcomes revealed no apparent publication bias (Figure 4; Figure 5).

Agreements and disagreements with other studies or reviews

Other systematic reviews have reported that the most influential factor affecting the results of pharmaceutical care interventions is the way that interventions were conducted, for example, face-to-face consultations with physicians achieved a greater reduction in the number of medications taken than was achieved by written recommendations (Rollason 2003). Another narrative review reported that timely provision of the intervention, that is, prospective advice at the time of prescription rather than at the time of dispensing of medication, is more effective (Spinewine 2007a). A recent and related Cochrane review of interventions to optimise prescribing for older people in care homes (Alldred 2013) found no evidence of an intervention effect on any of the primary outcomes, which included adverse drug events and hospital admissions. Other studies of interventions conducted across a variety of settings have also been unable to detect the effects of pharmaceutical care on these outcome measures (Holland 2007; Spinewine 2007a). One systematic review (Kaur 2009) revealed that the most successful types of interventions used to reduce inappropriate prescribing in older people were those that had multidisciplinary involvement including a geriatrician, utilised CDS or had mandatory pharmaceutical services or drug restriction policies in place. Results of this current review largely support the findings described above, as most of the pharmaceutical care interventions involved a multi-disciplinary component, and the CDS intervention study (Tamblyn 2003) reported a positive result.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence obtained when results of these studies were combined is rather weak, and it is unclear whether interventions provided to improve appropriate polypharmacy, such as pharmaceutical care, resulted in clinically significant improvement. Uncertainty surrounds the effects of such interventions on hospital admissions and medication-related problems, and it could be argued that these are the critical outcomes for patients. However, these interventions appear beneficial in terms of reducing inappropriate prescribing and encouraging proper use of medications.

From the results of this review, we can recommend that pharmaceutical care appears to improve prescribing for older patients receiving polypharmacy, especially when a multi-disciplinary element is included in the provision of care (Bucci 2003; Crotty 2004a; Crotty 2004b; Gallagher 2011; Hanlon 1996; Schmader 2004; Spinewine 2007; Taylor 2003). In addition, although only one study was included in this review, CDS appears to be a helpful intervention for improving appropriate polypharmacy (Tamblyn 2003).

Given the difficulties involved in applying the results of clinical studies to older people, physicians should carefully consider their sources of evidence and recommendations to find the right balance between avoiding the 'risk/treatment paradox' (high-risk older patients denied safe medications capable of materially improving survival or quality of life) and avoiding inappropriate use of medications for which risks are likely to outweigh benefits (Scott 2010).

Based on the findings of our updated review, we are still uncertain about which elements of the intervention processes constitute

success in improving appropriate polypharmacy, and a number of questions remain unanswered. For example, is it sufficient to provide the intervention during a single episode of care, or should patients be exposed to the intervention on a daily/weekly or monthly basis? What is the optimal duration of an intervention, and should interventions ideally be multi-faceted or unifaceted? It is clear that control of processes to support fidelity and control of the chosen interventions is critical. Staff training is important to ensure consistency; the receptiveness of prescribers, patients and staff in various settings will have an impact on the uptake and effectiveness of interventions in older people.

Implications for research

Overall, the quality of the studies in this review was poor, and further research should attend to rigour in study design. More research is needed to test whether existing tools for comprehensive medication review (e.g. the hyperpharmacotherapy assessment tool (HAT tool) (Bushardt 2008) and other similar interventions) can improve appropriate polypharmacy. A two-stage process of simple screening at drug level only (this could be automatically generated by computer, e.g. Christensen 2004) followed by application of a more comprehensive tool such as the MAI by clinically trained personnel, allowing detection of clinical problems through clinical knowledge and access to patients and/or medical records, may be beneficial.

Uncertainty about which elements of the intervention are critical to successful outcomes needs to be addressed. On the basis of the studies included in this review, this poses challenges, as details of intervention development and delivery were lacking. Methods of specifying and reporting complex interventions, as well as their implementation strategies, are necessary to strengthen the evidence base required for interventions to be more effective, implementable and replicable across different settings (Michie 2011; Proctor 2013). Future intervention studies targeting appropriate polypharmacy could benefit from guidance provided by the framework of the Medical Research Council on the design of complex interventions (MRC 2008). This framework recognises the importance of the initial stage of intervention development, in which evidence and theory are used to inform the selection of relevant components before the intervention is piloted, and the feasibility of delivering it in practice is assessed. These initial stages precede formal evaluations seeking to establish the effectiveness of the intervention. Careful documentation of development of the intervention and of the training and background of providers that may be critical to the effectiveness of the intervention is essential for facilitating replication of successful interventions in practice. The recently published TIDieR (Template for Intervention Description and Replication) checklist offers useful guidance that may assist the reporting and replication of future interventions (Hoffmann 2014). A systematic approach to the reporting of future interventions could facilitate comparisons between studies and could help to reduce, or account for, heterogeneity between effect estimates.

The framework of the Medical Research Council (MRC 2008) also outlines the potential application of qualitative methodologies, such as semi-structured interviews, to involve users and to gain insights into the processes of change that underlie the intervention. For example, establishing the reasons why not all interventions are accepted may be enlightening and may support research into the development of more successful interventions. There appears to be a ceiling effect (approximately 75%) whereby inappropriate prescribing continues despite the evidence base of interventions (Furniss 2000; Zermansky 2006). Qualitative interviews of prescribers may uncover reasons as to why they did not accept interventions (e.g. timing or appropriateness of provision of the intervention, the expertise of providers). Additionally, poor prescribing practice must be explored and understood with the goal of learning how to improve it and how to enhance patient safety by reducing the need for intervention. The importance of these investigations extends beyond the research context alone. Given the high financial expenditure that has been attributed to potentially inappropriate prescribing in older people (Bradley 2012; Cahir 2010), it is likely that policy makers will continue to be interested in the costs of these types of interventions.

The importance of behaviour change in increasing the uptake of evidence into practice is increasingly recognised. For example, an overarching theoretical framework known as the theoretical domains framework (TDF) has been developed to simplify psychological theory relevant to behaviour change to make it accessible to those involved in implementation research (Michie 2005). The TDF has been used in a number of different contexts to date, including exploratory interview studies conducted to identify beliefs that reflect barriers to, and enablers of, behaviour change, which can be used to guide behavioural change intervention design (Francis 2012). Such an approach could potentially serve to address the notable lack of theoretically informed interventions that has been identified in this review and in other reviews related to healthcare practice (Colquhoun 2013; Davies 2010).

In the previous version of this review (Patterson 2012), we recommended that future studies could consider relevant risk factors for polypharmacy including demographic factors, such as race and education (Fillenbaum 1996); health status, poorer health and access to health care (Hajar 2007); and multiple providers of health care (Espino 1998) and numbers of healthcare visits (Jörgensen 2001), in designing interventions. We recommended that future studies should utilise clearer definitions of appropriate polypharmacy because the term 'polypharmacy' can be both negative and positive, and this duality of meaning makes objective research difficult (Bushardt 2008). This subject has recently drawn attention with publication of a report by the King's Fund in the UK (King's Fund 2013). This report discussed the need to reconsider current definitions of polypharmacy on account of the increasing numbers of medications being prescribed to patients and recommended that

polypharmacy should be defined as appropriate (i.e. medicine use has been optimised and medicines prescribed according to best evidence) or problematic (i.e. medicines have been prescribed inappropriately or intended benefits have not been realised). Although the potential benefit of having a simple means of identifying patients at particular risk for inappropriate prescribing and adverse effects was acknowledged, the authors of the King's Fund report noted that existing thresholds used to define polypharmacy, such as four or five or more medicines, may be too low. A pragmatic approach was proposed to identify patients warranting medication review, which focused on particular patient groups (e.g. patients receiving $\geq$ 10 regular medicines, patients receiving four to nine medicines with other risk factors).

Publication of the King's Fund report (King's Fund 2013) coincided with the abstract screening process in the update of this review. Therefore, for the purpose of this update, the definition of polypharmacy was not changed from that used in the original review. Future updates of this review may reconsider the criteria used to define polypharmacy while taking into consideration that the threshold of four or more regular medicines may be too low, and that it would be preferable to consider the overall appropriateness of therapy as opposed to the number of medications alone. Using the definition of appropriate polypharmacy proposed in the King's Fund report (King's Fund 2013), we recommend that, in seeking to improve appropriate polypharmacy in older people, future intervention studies should ensure that under-prescribing is also targeted. It should be accepted that appropriate polypharmacy is not just about reductions in numbers of drugs but rather includes the prescription of medication appropriate to the needs of patients. However, many of the studies included in this review focused solely on reducing the numbers of medications prescribed without assessing prescribing omissions. As validated tools to assess potentially inappropriate prescribing in older people, such as Beers criteria, are not specifically designed to measure appropriate polypharmacy, it is important that future interventions should include assessments of potentially inappropriate omissions/under-prescribing with the goal of improving appropriate polypharmacy.

Perhaps most critically, the selection of clinical and humanistic outcomes appropriate for older people (e.g. hospitalisations, ADEs) will be important to consider in future studies. Quality of life is difficult to measure in the older co-morbid population, especially given longitudinal changes in this outcome, and the SF-36 may not be the most appropriate tool (McHorney 1996). Strategies for improving the evidence base for older patient care have been reviewed by Scott 2010.

The judgement as to whether many (appropriate polypharmacy) or too many (inappropriate polypharmacy) medications are used is difficult. The complexity of the clinical situation, patient attributes and wishes and the individuality of prescribing for older complex patients will remain a challenge in this regard. Development of a new, universal, easily applied, valid and reliable outcome measure to evaluate effectiveness of interventions should be a priority for future research. Ideally this measure should be globally applicable across various healthcare and cultural settings; for example, STOPP and START are validated instruments that may go some way toward fulfilling this need (Gallagher 2008). Although research on the use of STOPP and START criteria is still at a relatively early stage, these criteria have received support from the European Union Geriatric Medicine Society and are posed for wider application in future research (Hill-Taylor 2013). Both of the studies included in this update applied the STOPP criteria (Dalleur 2014; Gallagher 2011). Gallagher 2011 also applied the START criteria. The START criteria offer a promising strategy to decrease under-prescribing (Cherubini 2012) and, combined with the STOPP criteria, could serve to improve appropriate polypharmacy in older people.

A number of other important developments have occurred regarding screening tools to assess prescribing in older people since the original version of this review was published. Two new tools-the RASP (Rationalisation of Home Medication by an Adjusted STOPP list in Older Patients) instrument (Van der Linden 2014 [pers comm]) and the FORTA (Fit fOR The Aged) list (Kuhn-Thiel 2014)-have been validated. Two studies that are awaiting classification (Muth 2010; Van Der Linden 2013) employed screening tools that were not used previously in studies included in this review (i.e. PRISCUS list, RASP instrument). Data from such research will aid practitioners in identifying preferred criteria (Levy 2010).

Finally, it is important that sufficient detail about the context in which complex interventions are conducted, such as those included in this review, is reported and understood, so the transferability of complex interventions can be assessed (Wells 2012). For example, heterogeneity among the fitness levels of older people (Spinewine 2007a) means that translational research and retesting of successful interventions may be necessary in dissemination to new populations, as a population of quite healthy 70-year-old people may respond differently to an intervention compared with a group of very frail 92-year-old individuals.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bucci 2003

Methods	Study design: RCT (block design, using a computerised randomisation scheme) Unit of allocation/analysis: participant Follow-up: 1 month after intervention Duration: unclear Providers: pharmacists
Participants	Setting/participants: 80 participants (39 intervention and 41 control) enrolled at a hospital clinic at the University Health Network Toronto General Hospital, Canada Focus on polypharmacy: mean number of medications at baseline 7.6 intervention, 6.0 control Age (mean): 56.4 years intervention, 60.2 years control Male: 78.9% intervention, 78% control Ethnicity: no information given
Interventions	The intervention involved receipt of pharmacist services, that is, functioning as part of a healthcare team, meeting participants' drug-related needs and ensuring continuity of care. Specifically, this involved the pharmacist reviewing the appropriateness of drug therapy, making recommendations for change and providing information about medications, their administration and their adverse effects Those randomly assigned to the non-intervention group received usual care from other clinic staff
Outcomes	Participant outcomes were assessed by the research assistant pharmacist at baseline and at follow-up using the MAI and the directive guidance scale Appropriateness of prescribing was determined by preintervention and postintervention mean MAI scores The Purdue Pharmacist Directive Guidance score rated the guidance provided by the pharmacist. Directive guidance is described as pharmaceutical care activities such as providing information about medicines, their administration and their potential to cause adverse effects
Notes	The participant chart was reviewed by a research assistant pharmacist who was blinded to the intervention, and information required to assess the appropriateness of medications was abstracted. A summated MAI score was determined for each participant at least 1 month after the intervention. Follow-up took place at a scheduled clinic visit or by telephone

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a computerised randomisation scheme

Bucci 2003 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge yes/no
Blinding (performance bias and detection bias) All outcomes	Low risk	The research assistant was blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant in the intervention group had died at follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Baseline data?	Low risk	Baseline participant characteristics were reported
Reliable Primary outcome measure	Low risk	The MAI has good (kappa value = 0.59) to excellent (kappa value = 0.83) reproducibility
Protection against contamination	High risk	The presence of the pharmacist in the clinic may have contaminated medication appropriateness results of the non-intervention group
Power calculation	Low risk	Assuming a change of 25% between groups using the MAI with an alpha of 0.05, a power of 80% and a 10% dropout rate requires a sample size of 76 participants

Crotty 2004a

Methods	Study design: RCT (cluster) Unit of allocation: 10 residential facilities Unit of analysis: participant Follow-up: 3 months Duration: 2 case conferences 6 to 12 weeks apart Providers: resident's GP, geriatrician, pharmacist, home care staff and Alzheimer's Society representative
Participants	Setting/participants: 154 residents (100 intervention and internal control and 54 external control) from 10 high-level residential aged care facilities (nursing homes) in Southern Adelaide Focus on polypharmacy: Residents were prescribed more than 5 medications Age (mean): 85.3 years (95% CI 84.0 to 86.6) intervention, 83.6 years (95% CI 81.3 to 85.9) external control Male: 44% intervention, 43% external control Ethnicity: no information given

Crotty 2004a (*Continued*)

Interventions	A medication review was conducted before a multi-disciplinary case conference. The resident's GP, a geriatrician, a pharmacist, carers and a representative from the Alzheimer's Association of South Australia attended the case conferences, which were held at the nursing home. At the case conference, care staff expanded on any issues in the case notes that required discussion, and the Alzheimer's representative discussed non-pharmacological management of dementia-related behaviour. A problem list was developed by the GP in collaboration with the care staff A half-day training workshop examining use of a toolkit in the management of challenging behaviours was provided to all facilities in the study, including control facilities
Outcomes	Medication appropriateness was assessed using the MAI. Change in MAI was reported. All residents had their medication charts reviewed before and after the intervention by an independent pharmacist The Nursing Home Behaviour Problem Scale (NHBPS) was used to assess the effect of the intervention on residents' behaviour Monthly drug costs for all regular medications on the government's pharmaceutical benefits scheme were calculated for all residents in the intervention and control groups
Notes	Mean MAI score at baseline and at follow-up (3 months) Unit of analysis error

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers were used by a researcher independent of investigators
Allocation concealment (selection bias)	Low risk	Randomly allocated by the pharmacy department using sequential sealed opaque envelopes to receive the case conferences
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to judge yes/no
Incomplete outcome data (attrition bias) All outcomes	Low risk	Those lost to follow-up were stated, and an ITT analysis was used
Selective reporting (reporting bias)	Low risk	The impact of case conferences on appropriateness of medication and participant behaviours were stated as the objectives
Baseline data?	Low risk	Characteristics of residents at baseline were reported

Crotty 2004a (*Continued*)

Reliable Primary outcome measure	Low risk	The MAI has good to excellent reproducibility (kappa value = 0.59 to 0.83)
Protection against contamination	Low risk	No evidence was found of a carryover effect to other residents within the facilities
Power calculation	Low risk	An effect size of 0.9 in the MAI between intervention and control groups would be detected with 28 residents in each group

Crotty 2004b

Methods	Study design: single-blind RCT Unit of allocation/analysis:participants Follow-up: at 8 weeks Duration: unclear Providers: transition co-ordinator pharmacist, nurses
Participants	Setting/participants: 110 (56 intervention and 54 control) eligible patients making first-time transition from a hospital to 1 of 85 long-term residential care facilities in Southern Adelaide South Australia. Patients were eligible if they or their carer gave consent and they had a life expectancy > 1 month Focus on polypharmacy: the number of preadmission medicines was 6.6 intervention group and 7.7 control group Age (mean): 82 years (95% CI 80.2 to 83.7) intervention, 83.4 years (95% CI 81.7 to 85.1) control Female: 58.9% intervention, 63% control Ethnicity: non-English speaking background: 8.9% intervention, 5.6% control
Interventions	The intervention focussed on transferring information on medications to care providers in long-term care facilities (first-time transition). When discharged from hospital to long-term care facilities, participants' family physicians and community pharmacists were faxed a medication transfer summary compiled by the transition pharmacist. After transfer, the transition pharmacist co-ordinated an evidence-based medication review that was conducted by community pharmacists within 10 to 14 days of transfer A case conference that involved the transition co-coordinator, the family physician, the community pharmacist and the nurse was held within 14 to 28 days of transfer Usual hospital discharge process was received by controls and included a standard hospital discharge summary
Outcomes	The appropriateness of prescribing was measured using the MAI. A single score was determined for each medication received. A total MAI score for each resident was calculated as a sum of MAI scores Secondary outcome measures included unplanned visits to the emergency department or hospital readmissions (grouped together as hospital usage), ADEs, falls, worsening of mobility, behaviours, pain and increasing confusion
Notes	

Crotty 2004b (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer-generated allocation sequence that used block randomisation
Allocation concealment (selection bias)	Low risk	Centralised hospital pharmacy service used for randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Independent pharmacists who were blinded to the study group allocation assessed participant medication charts and case notes
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 participants in the intervention group and 10 in the control group died or did not complete the study for other reasons
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of yes/no
Baseline data?	Low risk	At baseline, no significant difference in the mean MAI was noted
Reliable Primary outcome measure	Low risk	The validity of the MAI has been reported previously
Protection against contamination	High risk	The transition pharmacist also co-ordinated a case conference involving himself or herself, the family physician, the community pharmacist and a registered nurse at the facility within 14 to 28 days of the transfer. At this case conference, the transition pharmacist provided information concerning medication usage and appropriateness
Power calculation	Low risk	90% power to detect a mean (± SD) difference in MAI of 4.0 (± 4.5) between groups at 8-week follow-up

Dalleur 2014

Methods	Study design: RCT Unit of allocation/analysis: participant Follow-up: at discharge and 1 year after discharge Duration: unclear Provider: inpatient geriatric consultation team (IGCT)
Participants	Setting/participants: 146 (74 intervention and 72 control) frail patients ≥ 75 years of age admitted to Cliniques Universitaires Saint-Luc, a 975-bed teaching hospital in Brussels, Belgium Focus on polypharmacy: mean number of medications at baseline: 7.2 intervention, 7.3 control Age (median (IQR)): 84 years (IQR 81 to 87) intervention, 86 years (IQR 81 to 89) control Female: 58.1% intervention, 68.1% control Ethnicity: no information given
Interventions	In the intervention group, geriatricians used 64 STOPP criteria ('Duplicate drug classes' was not considered) to systematically screen the list of medications being taken by participants on admission for potentially inappropriate medications and provided oral and written recommendations to the ward physician during hospitalisation for discontinuation of potentially inappropriate medications. Participants also received standard IGCT care Participants in the control group received standard care from the IGCT. Control participants' medications were routinely reviewed by the IGCT geriatrician, using an implicit approach (i.e. no explicit tool was used)
Outcomes	Discontinuation of potentially inappropriate medications identified using STOPP criteria Clinical significance of STOPP-related recommendations
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Eligible participants were allocated by the IGCT nurse to control or intervention group by drawing of lots-insufficient information to permit judgement of yes/no
Allocation concealment (selection bias)	Unclear risk	IGCT nurse assigned each participant to the geriatrician who had been allocated to the intended group after randomisation-insufficient information on nurse's involvement in IGCT to permit judgement of yes/no

Blinding (performance bias and detection bias) All outcomes	Unclear risk	The attending ward physician (who was responsible for prescriptions during hospitalisation and at discharge), the evaluator and participants were blinded to group assignment. However, the IGCT nurse was not blinded, and insufficient information was provided on nurses' involvement in the IGCT to permit judgement of yes/no
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants in the intervention group and 9 in the control group were not included in the primary outcome assessment because they did not receive the allocated intervention, or because data were missing from their discharge letters Subset of participants in each group was assessed at 1-year follow-up
Selective reporting (reporting bias)	Unclear risk	Characteristics associated with discontinuation of potentially inappropriate medications at discharge were listed as a secondary outcome measure but were not clearly reported in the results
Baseline data?	Low risk	Baseline participant characteristics were reported
Reliable Primary outcome measure	Low risk	STOPP criteria
Protection against contamination	Unclear risk	To avoid contamination bias, 2 of the 4 geriatricians involved in the IGCT during the study period were allocated to the intervention group because they used the STOPP criteria in their current practice; the other 2, who had never worked with the STOPP criteria, were allocated to the control group. However, this was a single-site study; therefore the possibility of contamination bias cannot be ruled out
Power calculation	Low risk	56 participants per group were required to have 80% power to detect a 30% difference in discontinuation rate of potentially inappropriate medications between groups at discharge

Gallagher 2011

Methods	Study design: RCT Unit of allocation/analysis: participant Follow-up: 2 months, 4 months and 6 months post discharge Duration: unclear Provider: attending medical team
Participants	Setting/participants: 382 hospital inpatients (190 intervention, 192 control) aged 65 years and older admitted to Cork University Hospital via the emergency department under the care of a general medical physician Focus on polypharmacy: mean number of medications at baseline: 7.4 intervention, 8. 0 control Age (median (IQR)): 74.5 years (71.0 to 80.0) intervention, 77.0 years (71.0 to 81.75) control Female: 53.2% intervention, 53.1% control Ethnicity: no information given
Interventions	The primary research physician applied STOPP/START criteria to baseline data of participants in the intervention group on admission to identify potentially inappropriate prescriptions and prescribing omissions. These were immediately discussed with the attending medical team, and discussion was followed up by written communication within 24 hours. Intervention recommendations comprised simple statements highlighting potentially inappropriate prescriptions according to relevant STOPP/START criteria. The attending physician judged whether these recommendations should be accepted and prescribing changes implemented. Medication changes were included in the discharge summary to the intervention participants' general practitioners
Outcomes	Prescribing appropriateness measured using the MAI and the AUM index Mortality, hospital readmissions, falls, frequency of general practitioner visits
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to the intervention group or the control group using a randomisation sequence that was determined by an independently generated random-numbers table using StatsDirect software, version 4.5
Allocation concealment (selection bias)	Low risk	The random-numbers table was retained, independent of researchers, by a physician external to the study, who assigned participants to groups using a sealed-envelope system. Group allocation was concealed from the research physician and from participants until baseline data had been collected

Gallagher 2011 (*Continued*)

		and inclusion criteria verified
Blinding (performance bias and detection bias) All outcomes	High risk	Because of the nature of the intervention, blinding of the research physician, attending physician and participating patients was not possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 participants (10 intervention, 8 control) died before the first outcome measure was assessed and were excluded from analysis; a further 24 participants (10 intervention, 14 control) died during the follow-up period
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Baseline data?	Low risk	Baseline participant characteristics were reported
Reliable Primary outcome measure	Low risk	MAI reported to have good content validity and good interrater and intrarater reliability when used in hospital settings AUM reported to have good interrater reliability and identified under-treatment in 25% to 64% of participants
Protection against contamination	Unclear risk	Insufficient information to permit judgement of yes/no; study conducted at a single hospital
Power calculation	Low risk	Power calculation involved a combined approach using estimates based on both AUM and MAI • 170 participants per group were required to ensure 90% power of detecting a 50% reduction in the proportion of participants with potentially inappropriate prescribing omissions according to the AUM • 28 participants per group would provide 90% power to detect an effect size of 0.9 on the MAI between groups post intervention

Hanlon 1996

Methods	Study design: RCT Unit of allocation/analysis: participant Follow-up: 3 months and 12 months after randomisation Duration: unclear Providers: geriatrician, clinical pharmacist, nurse
Participants	Setting/participants: 208 patients who were 65 years or older and were enrolled at the Veteran Affairs Medical Center, Durham, North Carolina, USA Focus on polypharmacy: Included participants were prescribed 5 or more regularly scheduled medications by a Veteran Affairs physician and were enrolled at the Veteran Affairs Medical Center, Durham, North Carolina Age (mean ± SD): 69.7 ± 3.5 years intervention, 69.9 ± 4.1 years control Male: 98.1% intervention, 100% control Ethnicity, white: 79% intervention, 74.8% control
Interventions	The clinical pharmacist monitored drug therapy outcomes by reviewing each participant's medical record and medication list, ascertained current medication use, identified drug-related problems by meeting with participants and carers and evaluated participants' medications by applying the MAI. The pharmacist then formulated prioritised written recommendations presented orally and in writing to the primary physician. After the physician visit, the clinical pharmacist educated the participant regarding drug-related problems and encouraged compliance In the control group, the clinic nurse reviewed participants' current medications before the visit
Outcomes	Participant MAI scores were determined by summing MAI medication scores across evaluated medications HRQoL Participant medication compliance and knowledge were assessed by participant self-report Potential ADEs Participant satisfaction
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to the control group or the intervention group using a computer-generated scheme
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of yes/no
Blinding (performance bias and detection bias) All outcomes	Low risk	Prescribing appropriateness was assessed by a blinded research clinical pharmacist. HRQoL was assessed by blinded interview-

Hanlon 1996 (*Continued*)

		ers
Incomplete outcome data (attrition bias) All outcomes	Low risk	36 participants were not interviewed. 5 in control and intervention groups were institutionalised. 5 from the intervention group and 1 from the control group were lost to follow-up. 7 from the intervention group and 10 from the control group died
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of yes/no
Baseline data?	Low risk	Characteristics at baseline reported
Reliable Primary outcome measure	Low risk	Previous MAI assessments made by a clinical pharmacist and a physician demonstrated excellent interrater (kappa value = 0.83) and intrarater reliability (kappa value = 0.92)
Protection against contamination	High risk	Potential for contamination because physicians had patients in both intervention and control groups
Power calculation	Low risk	100 participants per group were required to obtain 80% power to detect an effect size of 0.4. 84 participants per group were required to obtain 80% power to detect an effect size of 0.5

Schmader 2004

Methods	Study design: RCT (2 × 2 factorial design) Unit of allocation/analysis: participant Follow-up: closeout telephone interviews 12 months after randomisation Duration: Participants were followed for 12 months Provider: pharmacist/nurse/geriatrician/social worker
Participants	834 (430 intervention (inpatient), 404 control (inpatient)) participants who were 65 years of age or older, were hospitalised on a medical ward or surgical ward, had an expected stay of 3 or more days and met criteria for frailty, in 11 Veterans Affairs hospitals, in the USA Focus on polypharmacy: at baseline, the mean number of prescription drugs per participant in the geriatric inpatient unit was 7.7; number was 7.6 in the usual inpatient care group Age ranges: 65 to 73 years (196 people in intervention group, 191 people in control group), 74 years or older (234 people in intervention group, 213 people in control group) Male: 97% intervention, 98% control

Schmader 2004 (*Continued*)

	Ethnicity, white: 71% intervention, 75% control
Interventions	All 11 inpatient and outpatient geriatric evaluation management programmes had a core team that included a geriatrician, a social worker and a nurse. Pharmacists performed regular assessments and recommendations regarding medications in 7 inpatient and 6 outpatient teams. For participants assigned to the GEM unit or clinic, team members implemented evaluation and management protocols Usual inpatient care was the customary medical or surgical treatment provided by attending physicians Usual outpatient care was the customary care delivered by ambulatory care attending physicians or house staff under their direction
Outcomes	Adverse drug reactions and serious adverse drug reactions Inappropriate prescribing was assessed using the MAI and the Beers list at baseline and at discharge Polypharmacy and under-use were also measured
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation
Allocation concealment (selection bias)	High risk	The centre notified site research assistants of each participant's inpatient assignment by telephone. Outpatient assignment was revealed at hospital discharge
Blinding (performance bias and detection bias) All outcomes	Low risk	A trained research assistant blinded to group assignment conducted close-out telephone interviews 12 months after randomisation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement of yes/no
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Baseline data?	Low risk	Participant characteristics at baseline were reported
Reliable Primary outcome measure	Unclear risk	Primary outcomes were related to adverse drug reactions, which were assumed when an event and a drug were determined to be causally related. Disagreements on the item level were resolved by clinical consen-

Schmader 2004 (*Continued*)

		sus conference
Protection against contamination	Unclear risk	Insufficient information to permit judgement of yes/no
Power calculation	Low risk	376 participants per group (total of 752 participants) were required to obtain 80% power and a 95% confidence interval

Spinewine 2007

Methods	Study design: RCT Unit of allocation/analysis: participant Follow-up: 1 month, 3 months and 1 year Duration: from admission to discharge Provider: pharmacists
Participants	Setting/participants: 186 hospital inpatients (96 intervention, 90 controls) aged 70 years and older with acute geriatric problems in a GEM unit of a university teaching hospital, Mount-Godinne, Yvoir, Belgium Focus on polypharmacy: at baseline, mean (± SD) number of prescribed drugs was 7.9 (± 3.5) for participants in the intervention group and 7.3 (± 3.3) for those in the control group Age (mean ± SD): 82.4 ± 6.9 years intervention, 81.9 ± 6.2 years control Female: 71.9% intervention, 66.7% control Ethnicity: no information given
Interventions	The intervention consisted of the provision of pharmaceutical care from admission to discharge by a clinical pharmacist. A pharmacist was present 4 days per week and participated in medical and multi-disciplinary rounds, had direct contact with participants and carers and had access to participant medical records. For every participant, the pharmacist performed a medication history on admission and prepared a participant record with clinical and pharmaceutical data. Appropriateness of treatment was analysed, and a pharmaceutical care plan was prepared. Whenever an opportunity to optimise prescribing arose, the pharmacist discussed this with the prescriber, who could accept or reject the advice. The pharmacist answered all questions received from healthcare professionals about medications. At discharge the pharmacist provided written and oral information on treatment changes to the participant or carer, as well as written information to the GP
Outcomes	Prescribing appropriateness measured using MAI, Beers list, ACOVE Mortality, readmission (hospitalisation) or visit to an emergency department, medications taken, unnecessary drug use and satisfaction with information provided at admission and at discharge
Notes	

Risk of bias

Spinewine 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was alternate and was stratified for age, number of prescribed medicines and identity of the resident in charge of the participant. A pharmacist external to the main study checked the inclusion criteria and assigned participants to their groups
Allocation concealment (selection bias)	High risk	A pharmacist external to the main study checked inclusion criteria and assigned participants to their groups
Blinding (performance bias and detection bias) All outcomes	Low risk	Because of the nature of the project, physicians were not blinded to group assignment; however MAI, Beers, ACOVE and hospital admissions were carried out in a blinded manner
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 participants in both control and intervention groups were transferred to another unit 5 participants in each of the groups (10 people in total) died
Selective reporting (reporting bias)	High risk	A secondary outcome-'medications taken' was not reported
Baseline data?	Low risk	Baseline participant characteristics were reported
Reliable Primary outcome measure	Low risk	MAI, Beers criteria and ACOVE are validated measures
Protection against contamination	High risk	Some physicians cared for control and intervention participants
Power calculation	Low risk	90 participants per group were required to have 80% power to detect a 20% absolute improvement in ACOVE and Beers criteria. 28 participants per group would provide 90% power to detect an effect size of 0.9 on the MAI

Tamblyn 2003

Methods	Study design: RCT Unit of allocation: physicians Unit of analysis: participant Follow-up: terminated after an inappropriate prescription had been initiated or discontinued Duration: 13 months Provider: physician
Participants	Setting/participants: 107 primary care physicians with at least 100 participants, who were 30 years of age or older, had practices in Montreal and spent at least 70% of the week in fee-for-service practice were randomly assigned. Participants were 66 years of age or older, had been seen on 2 or more occasions by the study physician in the past year and were living in the community at the start of the study Focus on polypharmacy: implied 35.6 intervention/33.8 control prescriptions per elderly patient in the 18 months before the study date Age (mean ± SD): 75.4 ± 6.3 years intervention, 75.3 ± 6.2 years control Female: 61.2% intervention, 64.2% control Ethnicity: no information given
Interventions	Each physician was given a computer, a printer, health record software and dial-up access to the Internet. The software documented health problems and medications supplied. For each participant, trained personnel developed a health problem list and documented 26 health problems related to targeted drug-disease contraindications and other health problems CDS group physicians downloaded updates of dispensed prescriptions from the Quebec beneficiary, medical-service and prescription claims database (Regie de l'assurance maladie du Quebec (RAMQ)). Data were integrated into the participant's health record and were categorised as having been prescribed by the study physician or by another physician. Alerts were instituted to identify 159 clinically relevant prescribing problems among the elderly (McLeod 1997). Alerts appeared when the physician accessed the record, when prescription record updates were downloaded from RAMQ and when current health problems and prescriptions were recorded in the chart by the physician. They identified the nature of the problem, possible consequences and suggested alternative therapy in accordance with expert consensus
Outcomes	Initiation and discontinuation rates of 159 prescription-related problems (McLeod criteria)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Physicians were stratified by age, sex, language, location of medical school and number of elderly patients. Half of the physicians within each stratum were randomly assigned to the CDS group

Tamblyn 2003 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of yes/no
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of yes/no
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of inappropriate scripts started per 1000 visits and number of inappropriate scripts discontinued per 1000 visits were reported
Selective reporting (reporting bias)	Low risk	All results of outcomes specified in the methodology were reported
Baseline data?	Low risk	The prevalence of potentially inappropriate prescribing in the 2-month period before the study was reported
Reliable Primary outcome measure	Unclear risk	McLeod criteria were used
Protection against contamination	Unclear risk	To minimise the possibility of contamination, only 1 physician per group practice was included
Power calculation	High risk	No power calculation was given

Taylor 2003

Methods	Study design: RCT Unit of allocation/analysis: participant Follow-up: 12 months Duration: baseline until 12 months Provider: pharmacists
Participants	Setting/participants: adult patients (33 intervention, 36 control) who received care at 3 community-based family medicine clinics affiliated with the University of Alabama School of Medicine in Tuscaloosa and other towns in Pickens County, Alabama Focus on polypharmacy: Patients eligible for inclusion were taking 5 or more medications, 12 or more doses per day, or both Age (mean ± SD): 64.4 ± 13.37 years intervention, 66.7 ± 12.3 years control Male: 36.4% intervention, 27.8% control Ethnicity, white: 60.6% intervention, 61.1% control
Interventions	Participants received usual medical care along with pharmacotherapeutic interventions provided by a pharmacist during regularly scheduled clinic visits, based on the principles of pharmaceutical care. A participant typically met with a pharmacist for 20 minutes before seeing a physician. Published therapeutic algorithms and guidelines were used as

	the basis of the pharmacists' recommendations. Pharmacists were specifically trained to evaluate a therapy's indication, effectiveness and dosage, as well as the correctness and practicality of directions, drug-drug interactions, drug-disease interactions, therapeutic duplication and duration of treatment, untreated indications and expense The pharmacist reviewed the medical record for medication-related problems, conducted a chart review to ensure that information on drug therapy and allergies was accurately documented, examined the medication history to determine compliance with and complications of medications and provided comprehensive individualised participant education, which included a brief review of the disease, important lifestyle modifications and basic drug information. Pharmacists monitored participants' responses to drugs and attempted to improve compliance by consolidating medication regimens, reducing dosage frequency, devising medication reminders and teaching participants techniques for using devices such as inhalers. In addition to this, a system was developed in which the participant, the physician or the nurse reported suspected problems associated with drug therapy. Participants, nurses and physicians were educated about the signs and symptoms of medication misadventures The control group received standard medical care
Outcomes	Number of inappropriate prescriptions at baseline and at 12 months using the MAI Change in number of hospitalisations and emergency department visits at 12 months. Medication misadventures, medication compliance and quality of life were also assessed
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to a control group or an intervention group"; insufficient information to permit judgement of yes/no
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of yes/no
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of yes/no
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 participants were not included because they were lost to follow-up
Selective reporting (reporting bias)	Low risk	All outcomes described were reported
Baseline data?	Low risk	Baseline data were reported
Reliable Primary outcome measure	High risk	Insufficient information to permit judgement of yes/no

Taylor 2003 (*Continued*)

Protection against contamination	High risk	Although participants were randomly assigned, physicians were not because of the small number of physicians practising in the rural community
Power calculation	High risk	No power calculation was given

Trygstad 2005

Methods	Study design: controlled before and after study Unit of allocation/analysis: participant Follow-up: 3 months, March to June 2003 Duration: 6 months Providers: pharmacists
Participants	Setting/participants: Medicaid-dependent nursing home residents from 253 nursing homes in North Carolina Focus on polypharmacy: Participants had 18 or more prescription fills in the 90-day period before the start of the study Age (mean ± SD): 77.57 ± 12.72 years Male: 24.98%
Interventions	An on-site drug profile review was completed by pharmacists. A toolkit with instructions for documenting and screening criteria, used to flag drugs, was given to pharmacists. Pharmacists were also provided with computer-generated drug profiles from Medicaid pharmacy claims that displayed flags for patients and suggestions for modification of drugs and classes of drugs. Drug profiles were a compilation of all drugs for which a claim was paid in the 90 days before generation. regardless of the presence of an alert. The first alert criterion was receipt of a drug widely considered to be inappropriate for use in the elderly (Beers list drug). The second criterion was receipt of a drug on the community care of North Carolina prescription advantage list (PAL), which encourages substitution of a less expensive drug within a therapeutic class. The third criterion was appearance of a drug on the clinical initiatives list, which includes 16 drugs that had potential for quality improvement and cost savings. Pharmacists were asked to record the result of the review and the result of the consultation with the prescribing physician. If an intervention resulted in a drug therapy change of any type, the new drug, dose and quantity were noted. Drug dose and quantity were also reported for each new drug added for previously untreated indications
Outcomes	Number of Beers list drugs per participant, number of PAL list alerts, potential medication problems categorised as 'consider duration' (of therapy), 'clinical initiatives' and 'therapeutic duplication'
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Trygstad 2005 (*Continued*)

Random sequence generation (selection bias)	High risk	The comparison group consisted of patients in nursing homes not responding to the invitation for inclusion in phase 1 of the intervention
Allocation concealment (selection bias)	Unclear risk	Pharmacist and physician prescriber knew the allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Prescription profiles were generated and were sent to consultant pharmacists. However, authors do not state whether the participant knew the status of the nursing home (intervention or control)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates were similar between groups
Selective reporting (reporting bias)	Unclear risk	Not stated, not registered, so insufficient information to permit judgement of yes/no
Baseline data?	Low risk	Beers list drugs and number of prescription fills measured in 3 months before intervention
Reliable Primary outcome measure	Low risk	The Beers drug list, which is a validated instrument, was used
Protection against contamination	Unclear risk	Unclear as study authors stated that comparison group homes participated after 6 months
Power calculation	High risk	No power calculation was given

Trygstad 2009

Methods	Study design: controlled before and after Unit of allocation/analysis: participant Follow-up: 3 months Duration: 3 months Providers: pharmacists
Participants	Setting/participants: Medicaid-dependent nursing home residents in North Carolina Focus on polypharmacy: Patients were included if they had 18 or more drug fills in the 90 days immediately preceding the intervention Age (mean): 77.6 years Male: 24.9%

Interventions	Prescription drug records of all North Carolina nursing facilities were retrieved from Medicaid claims databases for the period August 2002 to April 2003. This period encompassed the 90-day baseline, the 90-day intervention and the 90-day postintervention periods to allow for a difference in difference (DID) with a comparison group study method. Targeted ('value added') drug regimen reviews (DRRs) were performed during the routine monthly DRRs required by Omnibus Budget Reconciliation Act (OBRA) nursing facility guidelines. Drug claims data were used to create drug profiles that contained cost- and quality-focussed alerts for patients with 18 or more drug fills in the 90 days immediately preceding the intervention. Computer algorithms were used to screen profiles for 5 types of drug alerts: Beers drug alerts, prescription advantage list (PAL) alerts, Clinical Initiatives alerts, duration alerts for specific drugs and therapeutic duplication alerts. Alerts were generated retrospectively from claims data and were provided to consultant pharmacists for their retrospective reviews, together with residents' most recent drug claims profiles. These profiles were comprehensive in nature and considered all drugs on a resident's profile regardless of the presence or absence of an alert. The prospective component of the study allowed a pharmacist to intervene and request a drug change for new medication orders that came into the dispensing facility, using the same alerting-targeting criteria developed for the retrospective, computer-generated drug profiles. Some residents received only retrospective reviews and interventions, some received only prospective interventions and some received both
Outcomes	Number of Beers list drugs per participant, number of PAL list alerts, potential medication problems categorised as "consider duration" (of therapy), "clinical initiatives" and "therapeutic duplication"
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Comparison group residents were drawn from non-participating long-term care facilities
Allocation concealment (selection bias)	Unclear risk	Consultant pharmacists performed targeted, value-added drug regimen reviews for selected Medicaid-dependent residents. It is not clear whether consultant pharmacists worked in both intervention and control homes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of yes/no
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	63 residents had a prospective review

Trygstad 2009 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of yes/no
Baseline data?	High risk	Baseline measures not reported for the comparison group
Reliable Primary outcome measure	Low risk	Beers criteria
Protection against contamination	Unclear risk	Not clear whether consultant pharmacists worked in both intervention and control homes
Power calculation	High risk	No power calculation given

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alexopoulos 2008	Not polypharmacy focus. No measure of appropriateness
Alkema 2006	Unsuitable study design. No measure of appropriateness
Allard 2001	Outcome measure. Appropriateness criteria not validated (expert opinion)
Allen 1986	Outcome measure. No measure of appropriateness
Allen 2011	No data. Outcome measure: appropriateness criteria not validated (structured around ACOVE guidelines but also included evidence-based protocols developed by the research team based on literature review)
Allen 2012	No data. Outcome measure. No measure of appropriateness
Altiner 2012	No data. Outcome measure. No measure of appropriateness
Anonymous 2005	No appropriate data
Anonymous 2011	No data. Erratum referred to list of multiple choice questions published in *Journal of the American Academy of Physician Assistants*
Anonymous 2012	No appropriate data
Atkin 1996	Outcome measure. No measure of appropriateness
Avorn 1992	Outcome measure. Appropriateness criteria not validated (expert opinion)

(*Continued*)

Bakken 2012	Unsuitable design
Bartlett 2008	Unsuitable study design. No measure of appropriateness
Beckett 2012	Outcome measure. Appropriateness criteria not validated (expert opinion)
Beer 2011	Outcome measure. No measure of appropriateness
Bell 2011	No appropriate data. No measure of appropriateness
Bergkvist 2009	Unsuitable study design
Bilyeu 2011	Unsuitable design
Bladh 2011	Outcome measure. Appropriateness criteria not validated (guidelines published by the Swedish National Board of Health)
Blais 2008	Participants too young. Not polypharmacy focus. Appropriateness of asthma medication only
Bloomfield 2005	Not polypharmacy focus. No measure of appropriateness
Bosma 2008	Unsuitable study design. Appropriateness criteria not validated (WinAP High Risk Medicines;list of 14 high-risk medicines based on a list compiled by the Dutch Scientific Institute for Pharmacy)
Buckmaster 2006	Not polypharmacy focus. Participants too young. No measure of appropriateness
Burnett 2009	Participants too young
Burns 1995	Outcome measure. No measure of appropriateness
Carey 2008	Unsuitable study design. No measure of appropriateness
Christensen 2004	Unsuitable study design
Claesson 1998	Outcome measure. Appropriateness criteria not validated (expert opinion)
Clyne 2013	No data. Not polypharmacy focus
Coleman 1999	Outcome measure. Appropriateness criteria not validated (expert opinion)
Colpaert 2006	Unsuitable study design. No measure of appropriateness
Courtenay 2007	Not polypharmacy focus. No measure of appropriateness
Davis 2007	Unsuitable study design

(*Continued*)

Delate 2008	Unsuitable study design. No measure of appropriateness
Denneboom 2007	Outcome measure. No measure of appropriateness
Der 1997	Outcome measure. Appropriateness criteria not validated (unnecessary drugs)
Diaz 2003	Unsuitable study design. No measure of appropriateness
Dresden 2013	Unsuitable design. No appropriate data
Eckert 1991	No appropriate data
Edmans 2013	Outcome measure. No measure of appropriateness
Elliott 2012	Outcome measure. No measure of appropriateness
Eriksson 2012	No appropriate data
Essock 2011	Outcome measure. No measure of appropriateness. Antipsychotic polypharmacy
Feder 1999	Not polypharmacy focus. Outcome measure. No measure of appropriateness
Feldstein 2006	Unsuitable study design. No measure of appropriateness
Fick 2004	Unsuitable study design
Flanagan 2002	Unsuitable study design. No measure of appropriateness
Fontaine 2006	Not polypharmacy focus. No measure of appropriateness
Gaede 2008	Not polypharmacy focus. No measure of appropriateness
Ganz 2010	Unsuitable design. Not polypharmacy focus
Garfinkel 2007	Unsuitable study design. No measure of appropriateness
Gerber 2008	Unsuitable study design. No measure of appropriateness
Gill 2001	Unsuitable study design. Appropriateness criteria not validated (Improved Prescribing in the Elderly Tool (IPET)-improved prescriptions in the elderly tool)
Gillespie 2009	Outcome measure. No prospective assessment of appropriateness
Ginzburg 2012	No appropriate data
Gislason 2007	Unsuitable study design. No measure of appropriateness

(*Continued*)

Gorup 2012	No data. Protocol changed
Gradman 2002	Unsuitable study design. No measure of appropriateness
Graffen 2004	Outcome measure. No measure of appropriateness
Guptha 2003	Unsuitable study design. Appropriateness criteria not validated (algorithms to assess appropriateness)
Gwadry-Sridhar 2005	Outcome measure. No measure of appropriateness
Hamilton 2007	Not polypharmacy focus. Participants too young. No measure of appropriateness
Hellstrom 2011	Unsuitable design
Hobbs 2006	Unsuitable study design. No measure of appropriateness
Hogg 2009	Outcome measure. Validated appropriateness criteria not applied to control group
Humphries 2007	Unsuitable study design. No measure of appropriateness
Hung 2012	Not polypharmacy focus. Outcome measure. No measure of appropriateness
Izquierdo 2007	Not polypharmacy focus. No measure of appropriateness
Jabalquinto 2007	Unsuitable study design. No measure of appropriateness
Jensen 2003	Unsuitable study design. No measure of appropriateness
Kairuz 2008	Unsuitable study design. No measure of appropriateness
Kassam 2001	Unsuitable study design. No measure of appropriateness
Kassam 2003	Unsuitable study design
Kastrissios 1998	Outcome measure. No measure of appropriateness
Keith 2013	Unsuitable design
Keller 2012	Outcome measure. Appropriateness criteria not validated (baseline risk strategy). Participants too young
Key 2010	Unsuitable design
Kjekshus 2005	Unsuitable study design. No measure of appropriateness
Klopotowska 2011	No data. Outcome measure. Appropriatenes criteria not validated (expert opinion)

(*Continued*)

Kojima 2012	Unsuitable design. Outcome measure. No measure of appropriateness
Kroenke 1990	Outcome measure. No measure of appropriateness
Kwan 2007	Outcome measure. No measure of appropriateness
Lacaille 2010	Outcome measure. Appropriateness criteria not validated (expert opinion)
Lalonde 2008	Outcome measure. No measure of appropriateness
Lapane 2007	Unsuitable study design. No measure of appropriateness
Lapane 2011	Not polypharmacy focus. No measure of appropriateness
Laroche 2006	Unsuitable study design
Leach 2013	No data
Ledwidge 2004	Unsuitable study design. Appropriateness criteria not validated (expert opinion)
Lee 2006	Outcome measure. No measure of appropriateness
Lenaghan 2007	Outcome measure. No measure of appropriateness
Lim 2004	Outcome measure. No measure of appropriateness
Linton 2010	Unsuitable design
Lipton 1992	Outcome measure. Appropriateness criteria not validated (expert opinion)
Lipton 1994	Outcome measure. No measure of appropriateness
Logue 2002	No data. Not polypharmacy focus
Lourens 1994	Outcome measure. No measure of appropriateness
Mador 2004	Not polypharmacy focus. Only appropriateness of psychoactive drugs measured
Majumdar 2007	Outcome measure. Appropriateness criteria not validated (efficacious medicine)
Mannheimer 2006	Not polypharmacy focus. Appropriateness criteria not validated (Drug Related Problems- PharmCareNetwork Europe)
Mansur 2008	Unsuitable study design. No measure of appropriateness
Martin 2013	No data. Outcome measure. Rate of change in benzodiazepine use

(*Continued*)

Masoudi 2005	Unsuitable study design. No measure of appropriateness
Mattison 2010	Unsuitable design. Outcome measure. Appropriateness criteria not validated (subset of Beers medications)
Meredith 2002	Outcome measure. Appropriateness criteria not validated (expert opinion)
Meyer 1991	Outcome measure. No measure of appropriateness
Midlov 2002	Unsuitable study design. No measure of appropriateness
Miller 2008	Outcome measure. No measure of appropriateness
Mills 2008	Unsuitable study design. No measure of appropriateness
Milos 2013	Outcome measure. Appropriateness criteria not validated (guidelines published by the Swedish National Board of Health and Welfare)
Mistler 2009	Unsuitable study design. Appropriateness criteria not validated (medication reduction algorithm)
Moczygemba 2011	Unsuitable design. Outcome measure. No measure of appropriateness
Monane 1998	Unsuitable study design
Moore 1998	Outcome measure. No measure of appropriateness
Muir 2001	Outcome measure. No measure of appropriateness
Muller-Mundt 2011	Outcome measure. No measure of appropriateness
Muntinga 2012	No data. Outcome measure. No measure of appropriateness
Murray 2004	Unsuitable study design. No measure of appropriateness
Murray 2007	Not polypharmacy focus. No measure of appropriateness
Murray 2009	Not polypharmacy focus. No measure of appropriateness
Neutel 2007	Unsuitable study design. No measure of appropriateness
Nickerson 2005	Participants too young. No measure of appropriateness
Ogihara 2008	Outcome measure. No measure of appropriateness
Olsson 2012	Outcome measure. Appropriateness criteria not validated (adapted from literature and guidelines published by the Swedish National Board of Health and Welfare)

(*Continued*)

Ortega 2013	Outcome measure. No measure of appropriateness
Owens 1990	Outcome measure. Appropriateness criteria not validated (" problem pairs")
Pagaiya 2005	Participants too young. Appropriateness criteria not validated (guideline adherence)
Paluch 2007	Unsuitable study design. No measure of appropriateness
Patterson 2010	Not polypharmacy focus. Approriateness of psychoactive drugs only. Appropriateness criteria not validated (medication algorithm)
Pepine 1998	Unsuitable study design. No measure of appropriateness
Phelan 2008	Unsuitable study design. No measure of appropriateness
Pimlott 2003	Not polypharmacy focus. No measure of appropriateness
Pit 2007	Appropriateness criteria not validated
Pitkala 2001	Outcome measure. No measure of appropriateness
Pitkala 2012	No data. Outcome measure. Appropriateness of anticholinergic and psychotropic drugs only
Pool 2007	Not polypharmacy focus. No measure of appropriateness
PRIMM 2012	No appropriate data
Pugh 2006	Unsuitable study design. Appropriateness criteria not validated (Health Plan Employer Data and Information Set (HEDIS) 2006 quality measure)
Raebel 2007	Outcome measure. Appropriateness criteria not validated (expert opinion)
RESPECT 2010	Outcome measure. Appropriateness criteria not validated (UK - MAI)
Reuben 2010	Unsuitable study design. Participants with single long-term condition
Rognstad 2013	Outcome measure. Appropriateness criteria not validated (adapted from Beers criteria and guidelines published by the Swedish National Board of Health and Welfare)
Rosenthal 2004	Outcome measure. No measure of appropriateness
Roughead 2007	Unsuitable study design
Roughead 2007	Unsuitable study design. No measure of appropriateness
Saltvedt 2002	Outcome measure. No measure of appropriateness

(*Continued*)

Schmidt 2008	Not polypharmacy focus. No measure of appropriateness
Schnipper 2006	Outcome measure. No measure of appropriateness. Participants too young
Schrader 1996	Unsuitable study design. No measure of appropriateness
Schroder 2012	Participants with single long-term condition
Sellors 2001	Outcome measure. No measure of appropriateness
Sellors 2003	Outcome measure. Appropriateness criteria not validated (expert opinion)
Shrestha 2006	Participants too young. No measure of appropriateness
Sicras Mainar 2004	Outcome measure. No measure of appropriateness
Sicras Mainar 2005	Unsuitable study design. No measure of appropriateness
Sicras Mainar 2007	Outcome measure. No measure of appropriateness
Silkey 2005	Unsuitable study design. No measure of appropriateness
Simon 2005	Not polypharmacy focus. No measure of appropriateness
Simon 2006	Outcome measure. Appropriateness criteria not validated (expert opinion)
Smith 1996	Outcome measure. No measure of appropriateness
Sorensen 2004	Outcome measure. No measure of appropriateness
Soumerai 1998	Not polypharmacy focus. No measure of appropriateness
Straand 2006	Unsuitable study design. No measure of appropriateness
Stuck 1995	Unsuitable study design. No measure of appropriateness
Sturgess 2003	Outcome measure. No measure of appropriateness
Teichert 2013	Unsuitable design
Terceros 2007	Unsuitable study design. No measure of appropriateness
Terrell 2009	Outcome measure. Appropriateness criteria not validated (expert panel selected subset of medications from Beers criteria)
Thiem 2011	No appropriate data

(*Continued*)

Thompson 2008	Outcome measure. No measure of appropriateness. Participants too young
Thurmann 2011	No appropriate data
Thyrian 2012	No data. Participants with single long-term condition
Touchette 2012	Outcome measure. Appropriateness criteria not validated (Drug Related Problems- Pharmaceutical Care Network Europe)
Tse 2008	Outcome measure. No measure of appropriateness
Van der Elst 2006	Outcome measure. Appropriateness criteria not validated (Peer Review Group consensus)
van Hees 2008	Outcome measure. No measure of appropriateness
Vetter 1992	Outcome measure. No measure of appropriateness
Viktil 2006	Unsuitable study design. No measure of appropriateness
Volume 2001	Outcome measure. No measure of appropriateness
Weber 2008	Outcome measure. No measure of appropriateness
Weingart 2008	Participants too young. No measure of appropriateness
Wenger 2007	Unsuitable study design. (ACOVE criteria development/assessment)
Wessell 2008	Unsuitable study design. Appropriateness criteria not validated (potentially inappropriate medication indicators based on Zhan criteria)
Willcox 1994	Unsuitable study design
Williams 2004	Outcome measure. No measure of appropriateness
Wu 2006	Outcome measure. No measure of appropriateness
Zermansky 2006	Outcome measure. No measure of appropriateness
Zuckerman 2005	Unsuitable study design

Characteristics of studies awaiting assessment *[ordered by study ID]*

Bosch-Lenders 2013

Methods	Cluster randomised controlled trial (RCT)
Participants	Not known
Interventions	Not known
Outcomes	Not known
Notes	

Carter 2008

Methods	RCT
Participants	Patient participants: English- or Spanish-speaking patients, aged 18 years or older, admitted to the general medicine, family medicine, cardiology or orthopaedics services within the University of Iowa Hospitals and Clinics (UIHC), a tertiary academic health sciences centre, with one of the following diagnoses: hypertension, hyperlipidaemia, heart failure, coronary artery disease, myocardial infarction, stroke, transient ischaemic attack, asthma, chronic obstructive pulmonary disease (COPD) or diabetes, or patients receiving oral anticoagulation
Interventions	Minimal intervention group: Participants will receive medication teaching throughout hospitalisation from the pharmacy case manager. On the day of discharge, participants will receive a discharge medication list and a wallet card containing all discharge medications. Participants will receive no further contact or intervention from the pharmacy case manager Enhanced intervention group: In addition to providing medication teaching to participants throughout hospitalisation, the pharmacy case manager will compile a detailed discharge care plan, which will be faxed to participants' community physicians and community pharmacists. Participants will also receive a follow-up phone call from the pharmacy case manager 3 to 5 days after hospital discharge. Problems identified during the follow-up phone call will be communicated to participants' community physicians or to the inpatient medical team, and an electronic report of the follow-up call will be faxed to the community physician and the community pharmacist. The pharmacy case manager will continue to communicate with participants and participants' community healthcare providers at least weekly until all identified problems have been resolved
Outcomes	Primary: medication appropriateness (modified version of Medication Appropriateness Index), guideline adherence, adverse drug events (ADEs), hospital readmissions, emergency department visits, billing records for university and community hospital admissions, unscheduled office visits, prescription costs Secondary: medication adherence (pharmacy and self-reported data), inappropriate medications (Beers criteria), physician and pharmacist feedback
Notes	

Desborough 2011

Methods	Cluster RCT
Participants	Care homes for older people (average age > 65 years), registered with the Care Quality Commission (CQC) for at least 6 months and not specifically for people (of all ages) with learning disability, sensory impairment, mental health problems, physical disabilities and alcohol dependence. Care homes will also be excluded if they have received a medication review service from the Primary Care Trust in the previous 6 months, if they receive the services of a community geriatrician or if they are subject to investigation of the safeguarding of vulnerable adults
Interventions	Intervention homes will receive a multi-professional medication review at baseline and at 6 months, with follow-up at 12 months. Control homes will receive usual care (support they currently receive from the National Health Service) with data collection at baseline and 12 months
Outcomes	Primary: number of falls (mean number per participant per month), potentially inappropriate prescribing (number of drugs matching STOPP criteria at each data collection point) Secondary: medication costs (mean drug cost per participant-net ingredient costs for 28 days); utilisation of primary care, secondary care and personal social services health professional time (general practitioner (GP), nurse and other); emergency hospital admissions and accident and emergency visits (number of admissions in 6 months per participant) , mortality
Notes	ISRCTN90761620

Muth 2010

Methods	Cluster RCT
Participants	Patient participants: patients aged 60 years and older, at least 3 chronic diseases affecting 2 or more organ systems which require pharmaceutical treatment, at least 5 long-term prescriptions with systemic effects, health care provided by general practitioner (at least 1 contact in most recent quarter), legally competent to sign any documents, able to understand and participate in trial of own free will, able to fill out questionnaires and participate in telephone interviews, able to provide written informed consent to participate in trial
Interventions	Complex intervention involving basic assessment of medicines (brown bag review) and checklist-based (MediMoL-Medication Monitoring List) preconsultation interview on problems related to medicines (technical handling, potential adverse drug reactions) and participants' therapeutic aims conducted by a general practice-based healthcare assistant; structured information provided by healthcare assistant to general practitioners to enable participants to discuss their problems; computerised decision support system used by general practitioners to optimise medication (to reduce number of inappropriate prescriptions, e.g. pharmaceutical interactions, renal dose adjustments, duplicate prescriptions) and to prioritise medication in the physician-participant consultation while taking participants' preferences into consideration
Outcomes	Primary: Medication Appropriateness Index score (time frame: 6 and 9 months from baseline) Secondary (time frame: 6 months and 9 months from baseline): generic health-related quality of life (EQ-5D), functional disability (VES-13), change in all-cause hospitalisation, observed and self-reported adherence, future life expectancy/years of desired life, medication complexity, Beliefs about Medicines Questionnaire, severity of chronic pain, satisfaction with shared decision making (Man Son Hing scale)
Notes	NCT01171339

Ryan 2012

Methods	Controlled clinical trial (CCT)
Participants	Patient participants: older hospitalised patients
Interventions	Participants' medications were screened by a clinical pharmacist using the STOPP/START criteria, and the medical team was alerted of any identified potentially inappropriate prescribing
Outcomes	Primary: medications most frequently implicated in cases of potentially inappropriate prescribing using STOPP/START criteria, impact of screening patients' medication lists on Medication Appropriateness Index scores
Notes	

Van Der Linden 2013

Methods	Cluster randomised controlled trial (RCT)
Participants	Patient participants: patients aged 65 years and older
Interventions	Pharmaceutical care plan based on RASP (rationalisation of home medication by an adjusted STOPP-list in older patients) list
Outcomes	Primary: number of drugs stopped or adjusted (time frame: duration of hospital stay) Secondary: number of potentially inappropriate drug prescriptions as defined by the RASP instrument (time frame: duration of hospital stay), actual drug use (time frame: 30 and 90 days post discharge), number and category of drugs adjusted on recommendations of the clinical pharmacist independent of RASP instrument (time frame: duration of hospital stay), mortality (time frame: duration of hospital stay and within 90 days post discharge), number of falls (time frame: duration of hospital stay and within 90 days post discharge), quality of Life (EQ-5D-3L) (time frame: duration of hospital stay), length of hospital, rehospitalisation (time frame: within 90 days post discharge), incidence of delirium (time frame: duration of hospital stay), number of falls post discharge (time frame: within 90 days post discharge)
Notes	NCT01513265

Characteristics of ongoing studies *[ordered by study ID]*

Canty

Trial name or title	Using Clinical Alerts in a Computerized Provider Order Entry System to Decrease Inappropriate Medication Prescribing Among Hospitalized Elders
Methods	Randomised controlled trial (RCT)
Participants	Patient participants: hospitalised patients over 65 years of age
Interventions	A series of clinical alerts will be developed in the hospital's computerised provider order entry system to reduce the use of potentially inappropriate medications among hospitalised older patients. A synchronous alert (i.e. a "pop-up") will appear whenever a physician attempts to place an order for a high-risk medication on the

Canty (*Continued*)

	Beers list and the intended recipient is over 65 years of age. The alert will inform the physician about the risks associated with the medication and will propose safer alternatives
Outcomes	Primary: percentage of older participants who received a specified high-risk medication from the Beer's list (time frame: earlier hospital stay or end of study) Secondary: average number of specified high-risk medications prescribed per participant (time frame: earlier hospital stay or end of study), restraint use (time frame: earlier hospital stay or end of study), falls (time frame: earlier hospital stay or end of study), length of stay (time frame: earlier hospital stay or end of study), total cost (time frame: earlier hospital stay or end of study), discharge status (time frame: 6 months)
Starting date	April 2013
Contact information	Linda Canty, MD, Assistant Clinical Professor of Medicine Baystate Medical Cente, Springfield, Massachusetts, United States
Notes	ClinicalTrials.gov identifier: NCT01034761

Cedilnik

Trial name or title	Use of Web-based Application to Improve Prescribing in Home-living Elderly
Methods	RCT
Participants	Patient participants: home-dwelling adults over 65 years of age
Interventions	Participants' data will be entered into a web-based application and screened for potentially inappropriate prescribing using STOPP and START criteria. Identified potentially inappropriate prescriptions will be presented to participants' physicians for consideration and change. Physicians of participants in the control group will not be informed about potentially inappropriate prescriptions
Outcomes	Primary: decrease in potentially inappropriate prescriptions Secondary: polypharmacy rate, frequency of physician visits, participant adherence
Starting date	Unknown
Contact information	Not provided
Notes	

Eisert

Trial name or title	Medication Safety of Elderly Patients in Hospital and Ambulatory Setting Considering the Transitions of Care for Home-cared Patients and Nursing Home Residents
Methods	RCT
Participants	Patients aged 65 years and older admitted to one of the project wards for a minimum period of 3 days

Eisert (*Continued*)

Interventions	Intensified pharmaceutical care: Participants in the intervention group will receive both traditional care provided by physician and nurse on the ward and additional pharmaceutical care provided by a pharmacist during hospitalisation
Outcomes	Primary: drug-related hospital readmission Secondary: adverse drug events, number of potentially inappropriate medications prescribed (PRISCUS-criteria), time to readmission, number of accepted recommendations in the intervention group, time for intervention, drug-related problems
Starting date	April 2012
Contact information	Albrecht Eisert University Hospital Aachen, Hospital Pharmacy, Steinbergweg 20, 52074 Aachen, Germany aeisert@ukaachen.de
Notes	ClinicalTrials.gov Identifier: NCT01578525

McElnay

Trial name or title	A Pharmacist-led Medicines Management Outpatient Service for Patients at High Risk of Medication Related Problems
Methods	RCT
Participants	Patients aged 18 years and older admitted to one of the study hospitals as acute/unscheduled medical admissions and meeting at least 1 of the following criteria: prescribed 5 or more regular long-term medications; have 3 or more changes to medications during hospital stay; past history of medication-related problems; referred to the medicines management clinic service by hospital doctor or clinical pharmacist because of concerns about ability to manage medicines in primary care
Interventions	Medicines management outpatient service: Participants assigned to the intervention group will receive a new customised clinical pharmacy service (medicines management clinic and follow-up phone calls)
Outcomes	Primary: time to hospital readmission (time frame: 12 months post discharge) Secondary: number of hospital readmissions (time frame: 12 months post discharge); number of GP consultations and GP home visits (time frame: 12 months post discharge); number of accident and emergency visits (time frame: 12 months post discharge); Medication Appropriateness Index score (time frame: 4, 8 and 12 months post discharge), health-related quality of life (EQ-5D) (time frame: every 4 months over 12 months post discharge); medication adherence assessments (time frame: 12 months post discharge), cost utility analysis (time frame: 12 months post discharge)
Starting date	November 2011
Contact information	James McElnay, PhD, Chief Investigator Queen's University, Belfast, Northern Ireland
Notes	ClinicalTrials.gov identifier: NCT01534559

Trampsich

Trial name or title	Reduction of Potentially Inappropriate Medication in the Elderly
Methods	Cluster RCT
Participants	Patient participants: aged 70 years and older, taking at least 6 different drugs on a regular basis, life expectancy of at least 6 months (at the discretion of the treating primary care physician), legal competence, willingness to comply with study arrangements (i.e. assessment in the primary care office, telephone interviews) and to provide written informed consent, accessible by phone
Interventions	Written information sources (pocket-sized quick reference guide and comprehensive manual) containing recommendations from the PRISCUS list of potentially inappropriate medications in the elderly will be provided to general practitioners in the intervention arm. General practitioners will also be offered different training opportunities, depending on their needs and requirements, to allow them to get familiar with recommendations and to practice their application
Outcomes	Primary: proportion of participants per office with potentially inappropriate medication as defined by PRISCUS list (time frame: after 12 months of follow-up)
Starting date	May 2012
Contact information	Prof. Hans-Joachim Trampsich Department of Medical Informatics, Biometry and Epidemiology, University of Bochum, Bochum, Germany hans.j.trampisch@ruhr-uni-bochum.de
Notes	DRKS-ID: DRKS00003610

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Trial name or title	Pharmaceutical Care and Clinical Outcomes for the Elderly Taking Potentially Inappropriate Medication: A Randomized-Controlled Trial
Methods	Randomised controlled trial
Participants	Elderly with chronic disease. 65 to 90 years old, hospitalised
Interventions	Behavioural: pharmacist intervention Participants in the intervention group will receive pharmaceutical care delivered by a clinical pharmacist, including medication review, medication reconciliation, participant education and recommended actions
Outcomes	Primary outcome measures: number of unsolved drug-related problems (time frame: 14 days after randomisation) Secondary outcome measures: rate of ADE during hospitalisation (time frame: 14 days after randomisation) Number of potentially inappropriate medications (time frame: 14 days after randomisation)
Starting date	February 2009
Contact information	Liu Jen Wei, MS, Principal Investigator, Shin Kong Wo Ho-Su Memorial Hospital, Department of Pharmacy, Taipei,111, Taiwan

Notes	Clinical Trials.gov identifier: NCT00844025

DATA AND ANALYSES

Comparison 1. Postintervention analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in MAI score	4	424	Mean Difference (IV, Random, 95% CI)	-6.78 [-12.34, -1.22]
2 Change in MAI (excl Crotty 2004a)	3	353	Mean Difference (IV, Random, 95% CI)	-7.75 [-17.06, 1.56]
3 Change in MAI (excl Crotty 2004a and Spinewine 2007)	2	167	Mean Difference (IV, Random, 95% CI)	-1.79 [-3.73, 0.16]
4 Summated MAI score	5	965	Mean Difference (IV, Random, 95% CI)	-3.88 [-5.40, -2.35]
5 Number of Beers drugs per patient	2	586	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.28, 0.09]

Analysis 1.1. Comparison 1 Postintervention analysis, Outcome 1 Change in MAI score.

Review: Interventions to improve the appropriate use of polypharmacy for older people

Comparison: 1 Postintervention analysis

Outcome: 1 Change in MAI score

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bucci 2003	38	-0.74 (2.42)	41	0.49 (1.82)		26.6 %	-1.23 [-2.18, -0.28]
Crotty 2004a	32	-4.1 (5.76)	39	0.41 (2.63)		25.8 %	-4.51 [-6.67, -2.35]
Crotty 2004b	44	-0.7 (5.28)	44	2.86 (10.36)		24.3 %	-3.56 [-7.00, -0.12]
Spinewine 2007	96	-17 (15.68)	90	1.98 (13.21)		23.3 %	-18.98 [-23.14, -14.82]
Total (95% CI)	**210**		**214**			**100.0 %**	**-6.78 [-12.34, -1.22]**

Heterogeneity: Tau^2 = 30.04; Chi^2 = 70.90, df = 3 (P<0.00001); I^2 =96%

Test for overall effect: Z = 2.39 (P = 0.017)

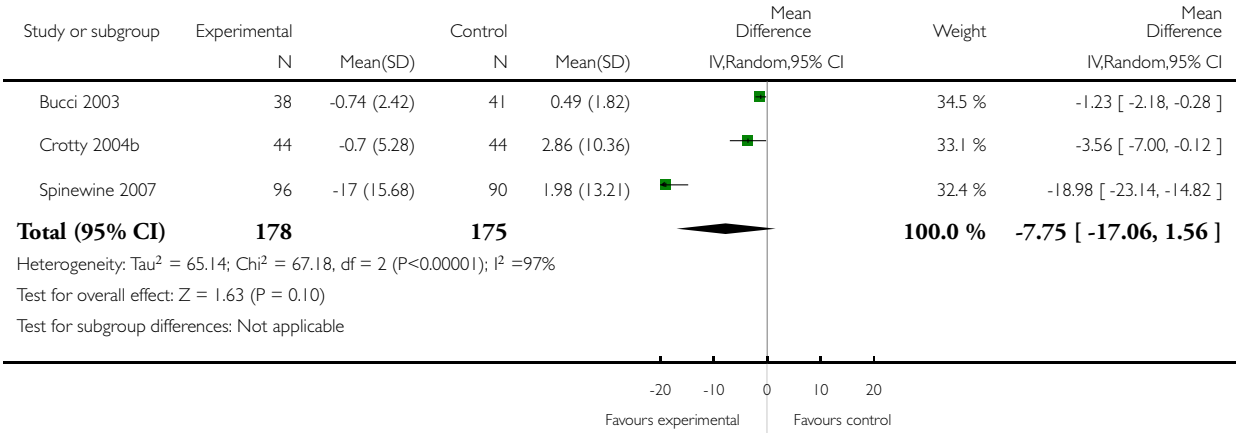
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Postintervention analysis, Outcome 2 Change in MAI (excl Crotty 2004a).

Review: Interventions to improve the appropriate use of polypharmacy for older people

Comparison: 1 Postintervention analysis

Outcome: 2 Change in MAI (excl Crotty 2004a)

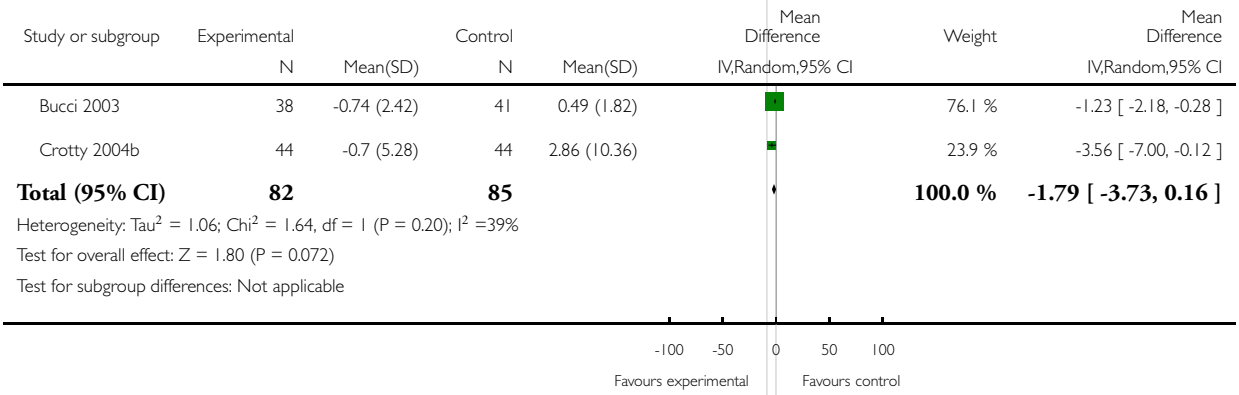


Analysis 1.3. Comparison 1 Postintervention analysis, Outcome 3 Change in MAI (excl Crotty 2004a and Spinewine 2007).

Review: Interventions to improve the appropriate use of polypharmacy for older people

Comparison: 1 Postintervention analysis

Outcome: 3 Change in MAI (excl Crotty 2004a and Spinewine 2007)



Analysis 1.4. Comparison 1 Postintervention analysis, Outcome 4 Summated MAI score.

Review: Interventions to improve the appropriate use of polypharmacy for older people

Comparison: 1 Postintervention analysis

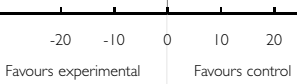
Outcome: 4 Summated MAI score

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bucci 2003	41	7.03 (20.29)	38	8.37 (2.58)		5.9 %	-1.34 [-7.60, 4.92]
Crotty 2004b	44	2.5 (3.89)	44	6.5 (8.8)		28.7 %	-4.00 [-6.84, -1.16]
Hanlon 1996	105	12.8 (7.17)	107	16.7 (7.24)		61.7 %	-3.90 [-5.84, -1.96]
Schmader 2004	202	5.3 (35.53)	198	9.6 (58.87)		2.5 %	-4.30 [-13.85, 5.25]
Spinewine 2007	96	7.1 (37.49)	90	19.3 (60.5)		1.1 %	-12.20 [-26.78, 2.38]
Total (95% CI)	**488**		**477**			**100.0 %**	**-3.88 [-5.40, -2.35]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.90$, df = 4 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 4.99 (P < 0.00001)

Test for subgroup differences: Not applicable

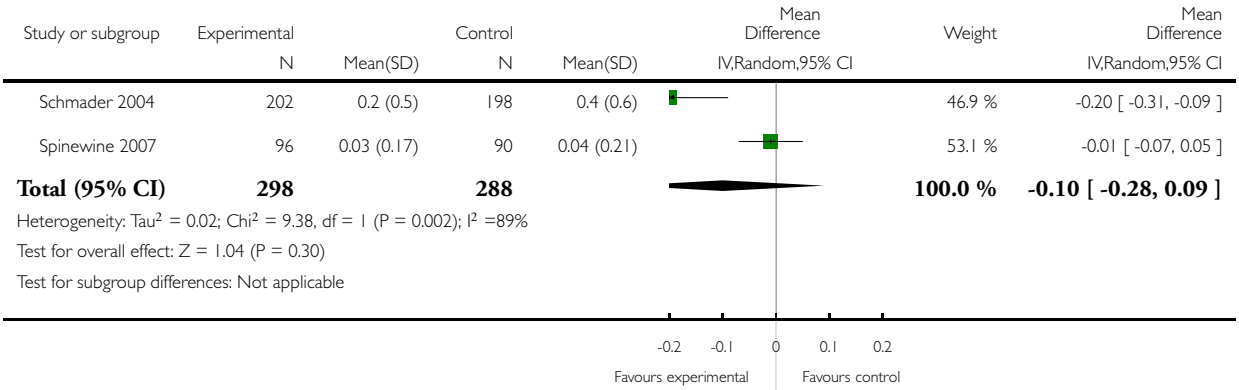


Analysis 1.5. Comparison 1 Postintervention analysis, Outcome 5 Number of Beers drugs per patient.

Review: Interventions to improve the appropriate use of polypharmacy for older people

Comparison: 1 Postintervention analysis

Outcome: 5 Number of Beers drugs per patient



ADDITIONAL TABLES

Table 1. Medication Appropriateness Index

To assess the appropriateness of the drug, please answer the following questions and circle the applicable score					
1. Is there an indication for the drug? Comments:	1 Indicated	2	3 Not Indicated		9 DK
2. Is the medication effective for the condition? Comments:	1 Effective	2	3 Ineffective		9 DK
3. Is the dosage correct? Comments:	1 Correct	2	3 Incorrect		9 DK
4. Are the directions correct? Comments:	1 Correct	2	3 Incorrect		9 DK
5. Are the directions practical? Comments:	1	2	3		9 DK

Table 1. Medication Appropriateness Index (*Continued*)

	Practical		Impractical	
6. Are there clinically significant drug-drug interactions? Comments:	1	2	3	9 DK
	Insignificant		Significant	
7. Are there clinically significant drug-disease/condition interactions? Comments:	1	2	3	9 DK
	Insignificant		Significant	
8. Is there unnecessary duplication with other drug(s)? Comments:	1	2	3	9 DK
	Necessary		Unnecessary	
9. Is the duration of therapy acceptable? Comments:	1	2	3	9 DK
	Acceptable		Unacceptable	
10. Is this drug the least expensive alternative compared with others of equal utility? Comments:	1	2	3	9 DK
	Least expensive		Most expensive	

ACOVE: Assessing Care of Vulnerable Elders.
AUM: Assessment of Under-utilisation of Medication.
CDS: computerised decision support.
CI: confidence interval.
DID: difference in difference.
DK: Don't know.
DRR: drug regimen review.
GP: general practitioner.
HRQoL: health-related quality of life.
IGCT: inpatient geriatric consultation team.
IQR: interquartile range.
ITT: intention-to-treat.
MAI: Medication Appropriateness Index.
NHBPS: Nursing Home Behavior Problem Scale.
OBRA: Omnibus Budget Reconciliation Act.
PAL: Prescription Advantage List.
RAMQ: Régie de l'assurance maladie du Québec
RCT: randomised controlled trial.
SD: standard deviation.
START: Screening Tool to Alert doctors to Right Treatment.

STOPP: Screening Tool of Older Person's Prescriptions.

Table 2. Updated Beers (2002) criteria for potentially inappropriate medication use in older adults: independent of diagnosis or condition

Drug	Concern	Severity rating (high or low)
Propoxyphene (Darvon) and combination products (Darvon with ASA, Darvon-N and Darvocet-N)	Offers few analgesic advantages over paracetamol (acetaminophen), yet is associated with the adverse effects of other narcotic drugs	Low
Indomethacin (Indocin and Indocin SR)	Of all available NSAIDs, this drug produces the most CNS adverse effects	High
Pentazocine (Talwin)	Narcotic analgesic that causes more CNS adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs. Additionally, it is a mixed agonist and antagonist	High
Trimethobenzamide (Tigan)	One of the least effective antiemetic drugs, yet it can cause extrapyramidal adverse effects	High
Muscle relaxants and antispasmodics: methocarbamol (Robaxin), carisoprodol (Soma), chlorzoxazone (Paraflex), metaxalone (Skelaxin), cyclobenzaprine (Flexeril) and oxybutynin (Ditropan). Do not consider the extended-release formulation of Ditropan XL	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients because they cause anticholinergic adverse effects, sedation and weakness. Additionally, their effectiveness at doses tolerated by elderly patients is questionable	High
Flurazepam (Dalmane)	This benzodiazepine hypnotic has an extremely long half-life in elderly patients (often days), producing prolonged sedation and increasing the incidence of falls and fracture. Medium- or short-acting benzodiazepines are preferable	High
Amitriptyline (Elavil), chlordiazepoxide-amitriptyline (Limbitrol) and perphenazine-amitriptyline (Triavil)	Because of its strong anticholinergic and sedation properties, amitriptyline is rarely the antidepressant of choice for elderly patients	High
Doxepin (Sinequan)	Because of its strong anticholinergic and sedating properties, doxepin is rarely the antidepressant of choice for elderly patients	High

Table 2. Updated Beers (2002) criteria for potentially inappropriate medication use in older adults: independent of diagnosis or condition (*Continued*)

Meprobamate (Miltown and Equanil)	This is a highly addictive and sedating anxiolytic. Those using meprobamate for prolonged periods may become addicted and may need to be withdrawn slowly	High
Doses of short-acting benzodiazepines: doses greater than lorazepam (Ativan) 3 mg; oxazepam (Serax) 60 mg; iprazolam (Xanax) 2 mg; temazepam (Restoril) 15 mg and triazolam (Halcion) 0.25 mg	Because of increased sensitivity to benzodiazepines in elderly patients, smaller doses may be effective and safer. Total daily doses should rarely exceed the suggested maximum	High
Long-acting benzodiazepines: chlordiazepoxide (Librium), chlordiazepoxide-amitriptyline (Limbitrol), clidinium-chlordiazepoxide (Librax), diazepam (Valium) , quazepam (Doral), halazepam (Paxipam) and chlorazepate (Tranxene)	These drugs have a long half-life in elderly patients (often several days), producing prolonged sedation and increasing the risk of falls and fractures. Short- and intermediate-acting benzodiazepines are preferred if a benzodiazepine is required	High
Disopyramide (Norpace and Norpace CR)	Of all antiarrhythmic drugs, this is the most potent negative inotrope and therefore may induce heart failure in elderly patients. It also has strong anticholinergic effects. Other antiarrhythmic drugs should be used as well	High
Digoxin (Lanoxin) (should not exceed 0.125 mg/d except when treating atrial arrhythmias)	Decreased renal clearance may lead to increased risk of toxic effects	Low
Short-acting dipyridamole (Persantine). Do not consider the long-acting dipyridamole (which has better properties than the short-acting formulation in older adults) except with patients with artificial heart valves	May cause orthostatic hypotension	Low
Methyldopa (Aldomet) and methyldopa-hydrochlorothiazide (Aldoril)	May cause bradycardia and exacerbate depression in elderly patients	High
Reserpine at doses > 0.25 mg	May induce depression, impotence, sedation and orthostatic hypotension	Low
Chlorpropamide (Diabinese)	It has a prolonged half-life in elderly patients and could cause prolonged hypoglycaemia. Additionally, it is the only oral hypoglycaemic agent that causes SIADH	High

Table 2. Updated Beers (2002) criteria for potentially inappropriate medication use in older adults: independent of diagnosis or condition (*Continued*)

GI antispasmodic drugs: dicyclomine (Bentyl), hyoscyamine (Levsin and Levsinex), propantheline (Pro-Banthine), belladonna alkaloids (Donnatal and others) and clidinium-chlordiazepoxide (Librax)	GI antispasmodic drugs have potent anticholinergic effects and have uncertain effectiveness. These drugs should be avoided (especially for long-term use)	High
Anticholinergics and antihistamines: chlorpheniramine (Chlor-Trimeton), diphenhydramine (Benadryl), hydroxyzine (Vistaril and Atarax), cyproheptadine (Periactin), promethazine (Phenergan), tripelennamine, dexchlorpheniramine (Polaramine)	All non-prescription and many prescription antihistamines may have potent anticholinergic properties. Non-anticholinergic antihistamines are preferred in elderly patients for the treatment of allergic reactions	High
Diphenhydramine (Benadryl)	May cause confusion and sedation. Should not be used as a hypnotic, and when used to treat emergency allergic reactions, it should be used in the smallest possible dose	High
Ergot mesyloids (Hydergine) and cyclandelate (Cyclospasmol)	Have not been shown to be effective in the doses studied	Low
Ferrous sulphate > 325 mg/d	Doses > 325 mg/d do not dramatically increase the amount absorbed but greatly increase the incidence of constipation	Low
All barbiturates (except phenobarbital) except when used to control seizures	Are highly addictive and cause more adverse effects than most sedative or hypnotic drugs in elderly patients	High
Meperidine (Demerol)	Not an effective oral analgesic in doses commonly used. May cause confusion and has many disadvantages compared with other narcotic drugs	High
Ticlopidine (Ticlid)	Has been shown to be no better than aspirin in preventing clotting and may be considerably more toxic Safer, more effective alternatives exist	High
Ketorolac (Toradol)	Immediate and long-term use should be avoided in older people, as a significant number have asymptomatic GI pathological conditions	High
Amphetamines and anorexic agents	These drugs have potential for causing dependence, hypertension, angina and my-	High

Table 2. Updated Beers (2002) criteria for potentially inappropriate medication use in older adults: independent of diagnosis or condition (*Continued*)

	ocardial infarction	
Long-term use of full-dosage, longer half-life, non-COX-selective NSAIDs: naproxen (Naprosyn, Avaprox and Aleve), oxaprozin (Daypro) and piroxicam (Feldene)	Have the potential to produce GI bleeding, renal failure, hypertension and heart failure	High
Daily fluoxetine (Prozac)	Long half-life of drug and risk of producing excessive CNS stimulation, sleep disturbances and increasing agitation. Safer alternatives are available	High
Long-term use of stimulant laxatives: bisacodyl (Dulcolax), cascara sagrada and Neoloid except in the presence of opiate analgesic use	May exacerbate bowel dysfunction	High
Amiodarone (Cordarone)	Associated with QT interval problems and risk of provoking torsades de pointes. Lack of efficacy in older adults	High
Orphenadrine (Norflex)	Causes greater sedation and anticholinergic adverse effects than safer alternatives	High
Guanethidine (Ismelin)	May cause orthostatic hypotension. Safer alternatives are available	High
Guanadrel (Hylorel)	May cause orthostatic hypotension	High
Cyclandelate (Cyclospasmol)	Lack of efficacy	Low
Isoxsurpine (Vasodilan)	Lack of efficacy	Low
Nitrofurantoin (Macrodantin)	Potential for renal impairment. Safer alternatives are available	High
Doxazosin (Cardura)	Potential for hypotension, dry mouth and urinary problems	Low
Methyltestosterone (Android, Virilon and Testrad)	Potential for prostatic hyperplasia and cardiac problems	High
Thioridazine (Mellaril)	Greater potential for CNS and extrapyramidal adverse effects	High
Mesoridazine (Serentil)	CNS and extrapyramidal adverse effects	High

Table 2. Updated Beers (2002) criteria for potentially inappropriate medication use in older adults: independent of diagnosis or condition (*Continued*)

Short-acting nifedipine (Procardia and Adalat)	Potential for hypotension and constipation	High
Clonidine (Catapres)	Potential for orthostatic hypotension and CNS adverse effects	Low
Mineral oil	Potential for aspiration and adverse effects. Safer alternatives are available	High
Cimetidine (Tagamet)	CNS adverse effects including confusion	Low
Ethacrynic acid (Edecrin)	Potential for hypertension and fluid imbalances. Safer alternatives are available	Low
Desiccated thyroid	Concerns about cardiac effects. Safer alternatives are available	High
Amphetamines (excluding methylphenidate hydrochloride and anorexic agents)	CNS stimulant adverse effects	High
Oestrogens only (oral)	Evidence of the carcinogenic (breast and endometrial cancer) potential of these agents and lack of cardioprotective effects in older women	Low

Source: Fick 2003.

CNS: central nervous system; COX: cyclo-oxygenase; CR: controlled release; GI: gastrointestinal; NSAID: non-steroidal anti-inflammatory drug; SIADH: syndrome of inappropriate antidiuretic hormone hypersecretion; SR: slow release.

Table 3. Updated Beers (2002) criteria for potentially inappropriate medication use in older adults: considering diagnoses or conditions

Disease or condition	Drug	Concern	Severity rating (high or low)
Heart failure	Disopyramide (Norpace) and high-sodium-content drugs (sodium and sodium salts (alginate bicarbonate, biphosphate, citrate, phosphate, salicylate, and sulphate))	Negative inotropic effect. Potential to promote fluid retention and exacerbation of heart failure	High
Hypertension	Phenylpropanolamine hydrochloride (removed from the market in 2001), pseudoephedrine; diet pills and am-	May produce elevation of blood pressure secondary to sympathomimetic activity	High

Table 3. Updated Beers (2002) criteria for potentially inappropriate medication use in older adults: considering diagnoses or conditions (*Continued*)

	phetamines		
Gastric or duodenal ulcers	NSAIDs and aspirin (> 325 mg) (COXIBs excluded)	May exacerbate existing ulcers or produce new/additional ulcers	High
Seizures or epilepsy	Clozapine (Clozaril), chlorpromazine (Thorazine), thioridazine (Mellaril) and thiothixene (Navane)	May lower seizure thresholds	High
Blood clotting disorders or receiving anticoagulant therapy	Aspirin, NSAIDs, dipyridamole (Persantin), ticlopidine (Ticlid) and clopidogrel (Plavix)	May prolong clotting time and elevate INR values or inhibit platelet aggregation, resulting in increased potential for bleeding	High
Bladder outflow obstruction	Anticholinergics and antihistamines, gastrointestinal antispasmodics, muscle relaxants, oxybutynin (Ditropan), flavoxate (Urispas), anticholinergics, antidepressants, decongestants and tolterodine (Detrol)	May decrease urinary flow, leading to urinary retention	High
Stress incontinence	α-Blockers (doxazosin, prazosin and terazosin), anticholinergics, tricyclic antidepressants (imipramine hydrochloride, doxepin hydrochloride and amitriptyline hydrochloride) and long-acting benzodiazepines	May produce polyuria and worsening of incontinence	High
Arrhythmias	Tricyclic antidepressants (imipramine hydrochloride, doxepin hydrochloride and amitriptyline hydrochloride)	Concern due to proarrhythmic effects and ability to produce QT interval changes	High
Insomnia	Decongestants, theophylline (Theodur), methylphenidate (Ritalin), MAOIs and amphetamines	Concern due to CNS stimulant effects	High
Parkinson's disease	Metoclopramide (Reglan), conventional antipsychotics and tacrine (Cognex)	Concern due to their antidopaminergic/ cholinergic effects	High

Table 3. Updated Beers (2002) criteria for potentially inappropriate medication use in older adults: considering diagnoses or conditions (*Continued*)

Cognitive impairment	Barbiturates, anticholinergics, antispasmodics and muscle relaxants. CNS stimulants: dextroamphetamine (Adderall), methylphenidate (Ritalin), methamphetamine (Desoxyn) and pemolin	Concern due to CNS-altering effects	High
Depression	Long-term benzodiazepine use. Sympatholytic agents: methyldopa (Aldomet), reserpine and guanethidine (Ismelin)	May produce or exacerbate depression	High
Anorexia and malnutrition	CNS stimulants: dextroamphetamine (Adderall), methylphenidate (Ritalin), methamphetamine (Desoxyn), pemolin and fluoxetine (Prozac)	Concern due to appetite-suppressing effects	High
Syncope or falls	Short- to intermediate-acting benzodiazepine and tricyclic antidepressants (imipramine hydrochloride, doxepin hydrochloride and amitriptyline hydrochloride)	May produce ataxia, impaired psychomotor function, syncope and additional falls	High
SIADH/hyponatraemia	SSRIs: fluoxetine (Prozac), citalopram (Celexa), fluvoxamine (Luvox), paroxetine (Paxil) and sertraline (Zoloft)	May exacerbate or cause SIADH	Low
Seizure disorder	Bupropion (Wellbutrin)	May lower seizure threshold	High
Obesity	Olanzapine (Zyprexa)	May stimulate appetite and increase weight gain	Low
COPD	Long-acting benzodiazepines: chlordiazepoxide (Librium), chlordiazepoxide-amitriptyline (Limbitrol), clidinium-chlordiazepoxide (Librax), diazepam (Valium), quazepam (Doral), halazepam (Paxipam) and chlorazepate (Tranxene). β-Block-	CNS adverse effects. May induce respiratory depression. May exacerbate or cause respiratory depression	High

Table 3. Updated Beers (2002) criteria for potentially inappropriate medication use in older adults: considering diagnoses or conditions (*Continued*)

	ers: propranolol		
Chronic constipation	Calcium channel blockers, anticholinergics and tricyclic antidepressant (imipramine hydrochloride, doxepin hydrochloride and amitriptyline hydrochloride)	May exacerbate constipation	Low

Source: Fick 2003.

COPD: chronic obstructive pulmonary disease; COXIB: cyclo-oxygenase inhibitor; INR: international normalized ratio; MAOI: monoamine oxidase inhibitor; NSAID: non-steroidal anti-inflammatory drug; SIADH: syndrome of inappropriate antidiuretic hormone secretion; SSRIs: selective serotonin reuptake inhibitors.

Table 4. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults: independent of diagnosis or condition

Organ System or Therapeutic Category or Drug	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Anticholinergics (excludes TCAs)				
First-generation antihistamines (as single agent or as part of combination products) Brompheniramine Carbinoxamine Chlorpheniramine Clemastine Cyproheptadine Dexbrompheniramine Dexchlorpheniramine Diphenhydramine (oral) Doxylamine Hydroxyzine Promethazine Triprolidine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; greater risk of confusion, dry mouth, constipation and other anticholinergic effects and toxicity Use of diphenhydramine in special situations such as short-term treatment of severe allergic reaction may be appropriate	Avoid	Hydroxyzine and promethazine: high; all others: moderate	Strong
Antiparkinson agents Benztropine (oral) Trihexyphenidyl	Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson's disease	Avoid	Moderate	Strong

Table 4. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults: independent of diagnosis or condition (*Continued*)

Antispasmodics Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine Hyoscyamine Propantheline Scopolamine	Highly anticholinergic, uncertain effectiveness	Avoid except in short-term palliative care to decrease oral secretions	Moderate	Strong
Antithrombotics				
Dipyridamole, oral short-acting* (does not apply to extended-release combination with aspirin)	May cause orthostatic hypotension; more effective alternatives available; intravenous form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
Ticlopidine*	Safer effective alternatives available	Avoid	Moderate	Strong
Anti-infective				
Nitrofurantoin	Potential for pulmonary toxicity; safer alternatives available; lack of efficacy in patients with CrCl < 60 mL/min due to inadequate drug concentration in the urine	Avoid for long-term suppression; avoid in patients with CrCl < 60 mL/min	Moderate	Strong
Cardiovascular				
Alpha$_1$-blockers Doxazosin Prazosin Terazosin	High risk of orthostatic hypotension; not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile	Avoid use as an antihypertensive	Moderate	Strong
Alpha-agonists, central Clonidine Guanabenz* Guanfacine* Methyldopa* Reserpine (> 0.1 mg/d)*	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension	Avoid clonidine as a first-line antihypertensive Avoid others as listed	Low	Strong

Table 4. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults: independent of diagnosis or condition (*Continued*)

Antiarrhythmic drugs (Class Ia, Ic, III) Amiodarone Dofetilide Dronedarone Flecainide Ibutilide Procainamide Propafenone Quinidine Sotalol	Data suggest that rate control yields better balance of benefits and harms than rhythm control for most older adults Amiodarone is associated with multiple toxicities, including thyroid disease, pulmonary disorders and QT interval prolongation	Avoid antiarrhythmic drugs as first-line treatment of atrial fibrillation	High	Strong
Disopyramide*	Disopyramide is a potent negative inotrope and therefore may induce heart failure in older adults; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong
Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or heart failure. In general, rate control is preferred over rhythm control for atrial fibrillation	Avoid in patients with permanent atrial fibrillation or heart failure	Moderate	Strong
Digoxin > 0.125 mg/d	In heart failure, higher dosages are associated with no additional benefit and may increase risk of toxicity; slow renal clearance may lead to risk of toxic effects	Avoid	Moderate	Strong
Nifedipine, immediate release*	Potential for hypotension; risk of precipitating myocardial ischaemia	Avoid	High	Strong
Spironolactone > 25 mg/d	In heart failure, the risk of hyperkalaemia is higher in older adults, especially if taking > 25 mg/d or taking concomitant NSAID, an-	Avoid in patients with heart failure or with a CrCl < 30 mL/min	Moderate	Strong

Table 4. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults: independent of diagnosis or condition (*Continued*)

	giotensin-converting enzyme inhibitor, angiotensin receptor blocker or potassium supplement			
Central nervous system				
Tertiary TCAs, alone or in combination: Amitriptyline Chlordiazepoxide-amitriptyline Clomipramine Doxepin > 6 mg/d Imipramine Perphenazine-amitriptyline Trimipramine	Highly anticholinergic, sedating and causing orthostatic hypotension; safety profile of low-dose doxepin (≤ 6 mg/d) is comparable with that of placebo	Avoid	High	Strong
Antipsychotics, first (conventional) and second (atypical) generation (see AGS 2012 for full list)	Increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia	Avoid use for behavioural problems of dementia unless non-pharmacological options have failed and patient is threat to self or others	Moderate	Strong
Thioridazine Mesoridazine	Highly anticholinergic and risk of QT interval prolongation	Avoid	Moderate	Strong
Barbiturates Amobarbital* Butabarbital* Butalbital Mephobarbital* Pentobarbital* Phenobarbital Secobarbital*	High rate of physical dependence; tolerance to sleep benefits; risk of overdose at low dosages	Avoid	High	Strong
Benzodiazepines *Short- and intermediate-acting:* Alprazolam Estazolam Lorazepam Oxazepam Temazepam	Older adults have increased sensitivity to benzodiazepines and slower metabolism of long-acting agents. In general, all benzodiazepines increase risk of cognitive impairment,	Avoid benzodiazepines (any type) for treatment of insomnia, agitation or delirium	High	Strong

Table 4. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults: independent of diagnosis or condition (*Continued*)

Triazolam *Long-acting:* Clorazepate Chlordiazepoxide Chlordiazepoxide-amitriptyline Clidinium-chlordiazepoxide Clonazepam Diazepam Flurazepam Quazepam	delirium, falls, fractures and motor vehicle accidents in older adults May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, periprocedural anaesthesia and end-of-life care			
Chloral hydrate*	Tolerance occurs within 10 days, and risks outweigh benefits in light of overdose with doses only 3 times the recommended dose	Avoid	Low	Strong
Meprobamate	High rate of physical dependence; very sedating	Avoid	Moderate	Strong
Non-benzodiazepine hypnotics Eszopiclone Zolpidem Zaleplon	Benzodiazepine-receptor agonists that have adverse events similar to those of benzodiazepines in older adults (e.g. delirium, falls, fractures) ; minimal improvement in sleep latency and duration	Avoid long-term use (> 90 days)	Moderate	Strong
Ergot mesylates* Isoxsuprine*	Lack of efficacy	Avoid	High	Strong
Endocrine				
Androgens Methyltestosterone* Testosterone	Potential for cardiac problems and contraindicated in men with prostate cancer	Avoid unless indicated for moderate to severe hypogonadism	Moderate	Weak
Desiccated thyroid	Concerns about cardiac effects; safer alternatives available	Avoid	Low	Strong

Table 4. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults: independent of diagnosis or condition (*Continued*)

Oestrogens with or without progestins	Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women Evidence that vaginal oestrogens for treatment of vaginal dryness are safe and effective in women with breast cancer, especially at dosages of estradiol < 25 μg twice weekly	Avoid oral and topical patch Topical vaginal cream: acceptable to use low-dose intravaginal oestrogen for the management of dyspareunia, lower urinary tract infection and other vaginal symptoms	Oral and patch: high Topical: moderate	Oral and patch: strong Topical: weak
Growth hormone	Effect on body composition is small and is associated with oedema, arthralgia, carpal tunnel syndrome, gynaecomastia, impaired fasting glucose	Avoid, except as hormone replacement after pituitary gland removal	High	Strong
Insulin, sliding scale	Higher risk of hypoglycaemia without improvement in hyperglycaemia management regardless of care setting	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulphonylureas, long duration Chlorpropamide Glyburide	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycaemia; causes syndrome of inappropriate antidiuretic hormone secretion Glyburide: greater risk of severe prolonged hypoglycaemia in older adults	Avoid	High	Strong
Gastrointestinal				

Table 4. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults: independent of diagnosis or condition (*Continued*)

Metoclopramide	Can cause extrapyramidal effects including tardive dyskinesia; risk may be even greater in frail older adults	Avoid, unless for gastroparesis	Moderate	Strong
Mineral oil, oral	Potential for aspiration and adverse effects; safer alternatives available	Avoid	Moderate	Strong
Trimethobenzamide	One of the least effective antiemetic drugs; can cause extrapyramidal adverse effects	Avoid	Moderate	Strong
Pain				
Meperidine	Not an effective oral analgesic in dosages commonly used; may cause neurotoxicity; safer alternatives available	Avoid	High	Strong
Non-COX-selective NSAIDs, oral Aspirin > 325 mg/d Diclofenac Diflunisal Etodolac Fenoprofen Ibuprofen Ketoprofen Meclofenamate Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin	Increase risk of GI bleeding and peptic ulcer disease in high-risk groups, including those aged > 75 or taking oral or parenteral corticosteroids, anticoagulants or antiplatelet agents. Use of proton pump inhibitor or misoprostol reduces but does not eliminate risk. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occurs in approximately 1% of patients treated for 3 to 6 months and in approximately 2% to 4% of patients treated for 1 year. These trends continue with longer duration of use	Avoid long-term use unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol)	Moderate	Strong

Table 4. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults: independent of diagnosis or condition (*Continued*)

Indomethacin Ketorolac, includes parenteral	Increase risk of GI bleeding and peptic ulcer disease in high-risk groups (see above Non-COX-selective NSAIDs) Of all the NSAIDs, indomethacin has the most adverse effects	Avoid	Indomethacin: moderate Ketorolac: high	Strong
Pentazocine*	Opioid analgesic that causes CNS adverse effects, including confusion and hallucinations, more commonly than other narcotic drugs; also a mixed agonist and antagonist; safer alternatives available	Avoid	Low	Strong
Skeletal muscle relaxants Carisoprodol Chlorzoxazone Cyclobenzaprine Metaxalone Methocarbamol Orphenadrine	Most muscle relaxants are poorly tolerated by older adults because of anticholinergic adverse effects, sedation, risk of fracture; effectiveness at dosages tolerated by older adults is questionable	Avoid	Moderate	Strong

Source: AGS 2012.
CNS = central nervous system; COX = cyclo-oxygenase; CrCl = creatinine clearance; GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug; TCA = tricyclic antidepressant
*Infrequently used drugs.

Table 5. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome

Disease or syndrome	Drug	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Cardiovascular					
Heart failure	NSAIDs and COX-2 inhibitors Non-dihydropyridine CCBs (avoid only for systolic heart failure)	Potential to promote fluid retention and exacerbate heart failure	Avoid	NSAIDs: moderate CCBs: moderate Thiazolidinediones (glitazones): high Cilostazol: low Dronedarone: mod-	Strong

Table 5. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome (*Continued*)

	Diltiazem Verapamil Pioglitazone, rosiglitazone Cilostazol Dronedarone			erate	
Syncope	AChEIs Peripheral alpha-blockers Doxazosin Prazosin Terazosin Tertiary TCAs Chlorpromazine, thioridazine and olanzapine	Increase risk of orthostatic hypotension or bradycardia	Avoid	Alpha-blockers: high TCAs, AChEIs and antipsychotics: moderate	AChEIs and TCAs: strong Alpha-blockers and antipsychotics: weak
Central nervous system					
Chronic seizures or epilepsy	Bupropion Chlorpromazine Clozapine Maprotiline Olanzapine Thioridazine Thiothixene Tramadol	Lower seizure threshold; may be acceptable in patients with well-controlled seizures in whom alternative agents have not been effective	Avoid	Moderate	Strong
Delirium	All TCAs Anticholinergics (see AGS 2012 for full list) Benzodiazepines Chlorpromazine Corticosteroids H_2-receptor antagonist Meperidine Sedative-hypnotics Thioridazine	Avoid in older adults with or at high risk of delirium because of inducing or worsening delirium in older adults; if discontinued drugs used long-term, taper to avoid withdrawal symptoms	Avoid	Moderate	Strong
Dementia and cognitive impairment	Anticholinergics (see AGS 2012 for full list) Benzodiazepines H_2-receptor antagonists	Avoid because of adverse CNS effects Avoid antipsychotics for behavioural problems of dementia un-	Avoid	High	Strong

Table 5. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome (*Continued*)

	Zolpidem Antipsychotics, long-term and as-needed use	less non-pharmacological options have failed and patient is a threat to himself or others. Antipsychotics are associated with increased risk of cerebrovascular accident (stroke) and mortality in persons with dementia			
History of falls or fractures	Anticonvulsants Antipsychotics Benzodiazepines Non-benzodiazepine hypnotics Eszopiclone Zaleplon Zolpidem TCAs and selective serotonin reuptake inhibitors	Ability to produce ataxia, impaired psychomotor function, syncope and additional falls; shorter-acting benzodiazepines are not safer than long-acting ones	Avoid unless safer alternatives are not available; avoid anticonvulsants except for seizure disorders	High	Strong
Insomnia	Oral decongestants Pseudoephedrine Phenylephrine Stimulants Amphetamine Methylphenidate Pemoline Theobromines Theophylline Caffeine	CNS stimulant effects	Avoid	Moderate	Strong
Parkinson's disease	All antipsychotics (see AGS 2012 for full list, except for quetiapine and clozapine) Antiemetics Metoclopramide Prochlorperazine Promethazine	Dopamine receptor antagonists with potential to worsen parkinsonian symptoms Quetiapine and clozapine appear to be less likely to precipitate worsening of Parkinson's disease	Avoid	Moderate	Strong
Gastrointestinal					

Table 5. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome (*Continued*)

Chronic constipation	Oral antimuscarinics for urinary incontinence Darifenacin Fesoterodine Oxybutynin (oral) Solifenacin Tolterodine Trospium Non-dihydropyridine CCB Diltiazem Verapamil First-generation antihistamines as single agent or part of combination products Brompheniramine (various) Carbinoxamine Chlorpheniramine Clemastine (various) Cyproheptadine Dexbrompheniramine Dexchlorpheniramine (various) Diphenhydramine Doxylamine Hydroxyzine Promethazine Triprolidine Anticholinergics and antispasmodics (see AGS 2012 for full list of drugs with strong anticholinergic properties) Antipsychotics Belladonna alkaloids Clidinium-chlordiazepoxide Dicyclomine	Can worsen constipation; agents for urinary incontinence: Antimuscarinics overall differ in incidence of constipation; response variable; consider alternative agent if constipation develops	Avoid unless no other alternatives	For urinary incontinence: high All others: moderate to low	Weak

Table 5. Updated Beers (2012) criteria for potentially inappropriate medication usage in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome (*Continued*)

	Hyoscyamine Propantheline Scopolamine Tertiary TCAs (amitriptyline, clomipramine, doxepin, imipramine and trimipramine)				
History of gastric or duodenal ulcers	Aspirin (> 325 mg/d) Non-COX-2-selective NSAIDs	May exacerbate existing ulcers or cause new or additional ulcers	Avoid unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol)	Moderate	Strong
Kidney and urinary tract					
Chronic kidney disease Stages IV and V	NSAIDs Triamterene (alone or in combination)	May increase risk of kidney injury	Avoid	NSAIDs: moderate Triamterene: low	NSAIDs: strong Triamterene: weak
Urinary incontinence (all types) in women	Oestrogen oral and transdermal (excludes intravaginal oestrogen)	Aggravate incontinence	Avoid in women	High	Strong
Lower urinary tract symptoms, benign prostatic hyperplasia	Inhaled anticholinergic agents Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (see AGS 2012 for complete list)	May decrease urinary flow and cause urinary retention	Avoid in men	Moderate	Inhaled agents: strong All others: weak
Stress or mixed urinary incontinence	Alpha-blockers Doxazosin Prazosin Terazosin	Aggravate incontinence	Avoid in women	Moderate	Strong

Source: AGS 2012.
CCB = calcium channel blocker; AChEI = acetylcholinesterase inhibitor; CNS = central nervous system; COX = cyclo-oxygenase; NSAID = non-steroidal anti-inflammatory drug; TCA = tricyclic antidepressant

Table 6. Updated Beers (2012) criteria for potentially inappropriate medications to be used with caution in older adults

Drug	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Aspirin for primary prevention of cardiac events	Lack of evidence of benefit versus risk in individuals aged ≥ 80	Use with caution in adults aged ≥ 80	Low	Weak
Dabigatran	Greater risk of bleeding than with warfarin in adults aged ≥ 75; lack of evidence of efficacy and safety in individuals with CrCl < 30 mL/min	Use with caution in adults aged ≥ 75 or if CrCl < 30 mL/min	Moderate	Weak
Prasugrel	Greater risk of bleeding in older adults; risk may be offset by benefit in highest-risk older adults (e.g. with prior myocardial infarction or diabetes mellitus)	Use with caution in adults aged ≥ 75	Moderate	Weak
Antipsychotics Carbamazepine Carboplatin Cisplatin Mirtazapine Serotonin-norepinephrine reuptake inhibitor Selective serotonin reuptake inhibitor Tricyclic antidepressants Vincristine	May exacerbate or cause syndrome of inappropriate antidiuretic hormone secretion or hyponatraemia; need to monitor sodium level closely when starting or changing dosages in older adults because of increased risk	Use with caution	Moderate	Strong
Vasodilators	May exacerbate episodes of syncope in individuals with history of syncope			

Source: AGS 2012.
CrCl = creatinine clearance.

APPENDICES

Appendix 1. The Medication Appropriateness Index (MAI) and the Beers criteria

The MAI was designed to assist physicians and pharmacists in assessing the appropriateness of a medication for a given patient. The MAI requires clinicians to rate 10 explicit criteria to determine whether a given medication is appropriate for an individual. For each criterion, the index has operational definitions, explicit instructions and examples, and the evaluator rates whether the particular medication is "appropriate," "marginally appropriate" or "inappropriate" (Table 1).

The 10 explicit criteria are:

1. Indication: the sign, symptom, disease or condition for which the medication is prescribed.
2. Effectiveness: producing a beneficial result.
3. Dosage: total amount of medication taken per 24-hour period.
4. Directions: instructions to the patient for proper use of a medication.
5. Practicality: capability of being used or being put into practice.
6. Drug-drug interaction: the effect that administration of one medication has on another drug; clinical significance connotes a harmful interaction.
7. Drug-disease interaction: the effect that the drug has on a pre-existing disease or condition; clinical significance connotes a harmful interaction.
8. Unnecessary duplication: non-beneficial or risky prescribing of two or more drugs from the same chemical or pharmacological class.
9. Duration: length of therapy.
10. Expensiveness: cost of drug in comparison with other agents of equal efficacy and safety.

These are measured on a 3-point scale (Table 1).

To assess the effects of the interventions on prescribing appropriateness, patient MAI scores may be determined by summing MAI medication scores across all evaluated medications. Thus, this patient MAI score depends on the number of medications taken by the patient and the MAI score per medication.

Furthermore, to determine a single summated score for each drug, in addition to an overall score for the patient, a weighting scheme was developed. A weight of three was given for indication and effectiveness. A weight of two was assigned to dosage, correct directions, drug-drug interactions and drug-disease interactions. A weight of one was assigned to practical directions, expense, duplication and duration.

The Beers criteria are consensus explicit criteria used to enhance safe medication use in older adults when precise clinical information is lacking (see Table 2; Table 3; Table 4; Table 5; Table 6). The Beers criteria are based on expert consensus developed through an extensive literature review with a bibliography and a questionnaire evaluated by nationally recognised experts in geriatric care, clinical pharmacology and psychopharmacology using a modified Delphi technique to reach consensus. These criteria have been used to survey clinical medication usage, to analyse computerised administrative data sets and to evaluate intervention studies to decrease medication problems in older adults.

The most recent version of Beers criteria (AGS 2012) comprises three lists. The first list comprises 34 individual medications or classes of medications that should be avoided in older adults and their concerns (Table 4). The second list includes diseases or conditions and drugs that should be avoided in older adults with these conditions (Table 5). The third list provides medications to be used with caution in older adults (Table 6). The statements in each list are rated on the basis of quality of evidence and the strength of recommendations using the American College of Physicians' Guideline Grading System.

Appendix 2. Search strategies 2013

MEDLINE (Ovid)

Search date: November 13, 2013

1 polypharmacy/ or polypharma$.ti,ab. (4819)

2 ((beer$ or shan? or mcleod?) adj3 criter$).ti,ab. (276)

3 ((concomitant$ or concurrent$ or inappropriat$ or suboptim$ or sub-optim$ or unnecessary or incorrect$ or excess$ or multip$ or inadvert$) adj2 (medicine? or medicat$ or prescrib$ or prescription$ or drug$)).ti,ab. (18680)

4 ((over adj1 (prescrib$ or prescript$)) or (over-prescrib$ or overprescrib$) or ("or more" adj (medication$ or prescrib$ or prescript$))).ti,ab. (1507)

5 ((under adj1 prescrib$) or underprescrib$ or under-prescrib$).ti,ab. (375)
6 "medication appropriateness index$".ti,ab. (70)
7 (quality adj2 (prescribing or prescription$ or medication$)).ti,ab. (874)
8 (improv$ adj2 (prescrib$ or pharmaco$ or prescription$)).ti,ab. (4361)
9 (Prescrib$ adj cascade$).ti,ab. (17)
10 ("assessing care of vulnerable elders" or ACOVE).ti,ab. (68)
11 ((multi-drug$ or multidrug$) adj2 (prescrib$ or prescription$ or regimen? or therap$ or treatment?)).ti,ab. (3293)
12 Medication errors/ [ML] (10421)
13 medication error/ [EM] (10421)
14 or/1-12 [ML Med Errors] (41930)
15 or/1-11,13 [EM Med Errors] (41930)
16 aged/ or frail elderly/ or very elderly/ or aged hospital patient/ [EM] (2342983)
17 exp Aged/ or Geriatrics/ [ML] (2382459)
18 (elder$ or geriatric$).ti,ab. (204045)
19 ((old$ or aged) adj (person$ or adult$ or people or patient$ or inpatient$ or outpatient$)).ti,ab. (116222)
20 Veteran/ [EM] (9541)
21 Veterans/ [ML] (9541)
22 veteran$.ti,ab. (21940)
23 or/16,18-20,22 [EM Aged] (2445456)
24 or/17-19,21-22 [ML Aged] (2477728)
25 ((pre adj10 post) or pretest$ or posttest$).ti,ab. (68752)
26 ((before adj2 after) or (before adj7 during)).ti,ab. (250366)
27 ("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab. (104880)
28 ("time series" adj2 interrupt$).ti,ab. (1192)
29 (time point? or (period? adj4 (interrupted or multiple or time or various or varying or week? or month? or year?))).ti,ab. (450052)
30 (cluster$ adj (analys$ or design$ or study or studies)).ti,ab. (17149)
31 Cluster analysis/ or quasi experimental study/ or pretest posttest control group design/ [EM] (46125)
32 (intervention? or multiintervention? or multi-intervention? or postintervention? or post-intervention? or preintervention? or pre-intervention?).ti,ab. (536544)
33 (effectiveness or implement$).ti. (87659)
34 Guideline adherence/ or Practice Guidelines as Topic/ or "Consensus Development Conferences as Topic"/ [ML] (93761)
35 (collaborat$ or teambased or team-based or interdisciplinar$ or inter-disciplinar$ or cross-disciplin$).ti,ab. or team?.ti. or (multi-facet$ or multifacet$).ti,ab. (130680)
36 ((guideline? or pathway? or protocol?) adj3 (adhere$ or concord$ or uptake or up-take)).ti,ab. (6964)
37 ((consensus adj develop$) or ((position or consensus) adj (statement? or development))).ti,ab. (6957)
38 or/25-30,32-37 [ML EPOC Filter] (1585629)
39 or/25-33,35-37 [EM EPOC Filter] (1545378)
40 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. (934359)
41 exp animals/ not humans.sh. (4060475)
42 40 not 41 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing] (863723)
43 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw. (1132812)
44 randomized controlled trial/ or crossover-procedure/ or double-blind procedure/ or single-blind procedure/ [EM] (390283)
45 or/43-44 [EM RCT per Cochrane 6.3.2.2] (1205490)
46 (random$ or placebo$ or double-blind$).tw. [EM RCT Wong J Med Libr Assoc 94(1) January 2006] (818391)
47 15 and 23 and 45 (1708)
48 from 47 keep 1-941 (941)
49 48 not (42 or 38) (166)
50 [from 49 keep 1-226] (0)
51 [from 50 keep 1-226] (0)
52 15 and 23 and 39 (2512)

53 from 52 keep 1-1374 (1374)
54 53 not (45 or 42 or 38) (15)
55 from 54 keep 1-2 (2)
56 14 and 24 and 42 (1499)
57 (14 and 24 and 38) not 56 [EPOC FIlter results] (2195)
58 adolescent/ or child/ or child, preschool/ or exp infant/ (2884036)
59 (adolescent? or child? or children? or teen? or teenager?).ti. (559259)
60 1 not 59 [Polypharm MeSH and KW NOT child/adolescent] (4736)
61 (60 and (or/42,56)) not (or/56-57) [Polypharm not child rct & epoc --excluding results from original search strategy] (196)
62 (201005$ or 201006$ or 201007$ or 201008$ or 201009$ or 201010$ or 201011$ or 201012$ or 2011$ or 2012$ or 2013$).ed,ep,dp. (4386331)
63 56 and 62 [RCT results May 2010-Nov 13, 2013] (434)
64 57 and 62 [EPOC Filter results May 2010-Nov 13-2013] (806)

EMBASE (Ovid)
Search date: November 13, 2013

1 polypharmacy/ or polypharma$.ti,ab. (8557)
2 ((beer$ or shan? or mcleod?) adj3 criter$).ti,ab. (441)
3 ((concomitant$ or concurrent$ or inappropriat$ or suboptim$ or sub-optim$ or unnecessary or incorrect$ or excess$ or multip$ or inadvert$) adj2 (medicine? or medicat$ or prescrib$ or prescription$ or drug$)).ti,ab. (25870)
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5 ((under adj1 prescrib$) or underprescrib$ or under-prescrib$).ti,ab. (508)
6 "medication appropriateness index$".ti,ab. (90)
7 (quality adj2 (prescribing or prescription$ or medication$)).ti,ab. (1262)
8 (improv$ adj2 (prescrib$ or pharmaco$ or prescription$)).ti,ab. (5621)
9 (Prescrib$ adj cascade$).ti,ab. (28)
10 ("assessing care of vulnerable elders" or ACOVE).ti,ab. (98)
11 ((multi-drug$ or multidrug$) adj2 (prescrib$ or prescription$ or regimen? or therap$ or treatment?)).ti,ab. (3912)
12 Medication errors/ [ML] (12281)
13 medication error/ [EM] (12281)
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15 or/1-11,13 [EM Med Errors] (56789)
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24 or/17-19,21-22 [ML Aged] (2454970)
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26 ((before adj2 after) or (before adj7 during)).ti,ab. (326158)
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28 ("time series" adj2 interrupt$).ti,ab. (1143)
29 (time point? or (period? adj4 (interrupted or multiple or time or various or varying or week? or month? or year?))).ti,ab. (595096)
30 (cluster$ adj (analys$ or design$ or study or studies)).ti,ab. (19855)
31 Cluster analysis/ or quasi experimental study/ or pretest posttest control group design/ [EM] (38566)
32 (intervention? or multiintervention? or multi-intervention? or postintervention? or post-intervention? or preintervention? or pre-intervention?).ti,ab. (661390)

33 (effectiveness or implement$).ti. (108425)
34 Guideline adherence/ or Practice Guidelines as Topic/ or "Consensus Development Conferences as Topic"/ [ML] (237870)
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36 ((guideline? or pathway? or protocol?) adj3 (adhere$ or concord$ or uptake or up-take)).ti,ab. (8991)
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39 or/25-33,35-37 [EM EPOC Filter] (1952266)
40 (random$ or placebo$ or double-blind$).tw. [EM RCT Wong J Med Libr Assoc 94(1) January 2006] (987462)
41 adolescent/ or child/ or child, preschool/ or exp infant/ (2540746)
42 (adolescent? or child? or children? or teen? or teenager?).ti. (715355)
43 (201018$ or 201019$ or 20102$ or 20103$ or 20104$ or 20105$ or 2011$ or 2012$ or 2013$).em,dp. (3739873)
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46 44 and 43 [RCT results May 2010 to Nov 2013] (464)
47 45 and 43 [EPOC Filter results May 2010-Nov 2013] (797)
48 1 not (or/41-42,44-45) [Polyph EMTREE not adolscent] (7011)
49 48 and (or/39-40) [Polyph not adolescent & RCT/EPOC Filters all years] (910)
50 48 and 40 [RCT polyphnot adolescent all years] (317)
51 (48 and 39) not 50 [EPOC results polyph not adolescent] (593)
52 51 not placebo?.ti,ab,hw. (567)
53 46 not placebo?.ti,ab,hw. [RCT results May 2010 to Nov 2013] (373)
54 (45 and 43) not placebo?.ti,ab,hw. [EPOC Filter results May 2010-Nov 2013] (792)
55 (48 and 40) not placebo?.ti,ab,hw. [RCT polyphnot adolescent all years] (231)
56 (48 and 39) not (50 or placebo?.ti,ab,hw.) [EPOC results polyph not adolescent] (567)

Cochrane Central Register of Controlled Trials (Ovid)
Search date: November 14, 2013

1 polypharm$.ti,ab,kf,hw,kw,sh. (146)
2 (overprescrib$ or underprescrib$).ti,ab. (11)
3 ((inappropriat$ or suboptim$ or sub-optim$ or unnecessary or incorrect$ or excess$ or multip$ or concurrent$ or inadvert$) adj2 (medici$ or medicat$ or prescrib$ or prescription$ or drug$)).ti,ab. (872)
4 ((old$ or aged) adj (person$ or adult$ or people or patient$ or inpatient$ or outpatient$)).ti,ab. (5706)
5 geriatric?.ti,ab,hw,kw,sh. (2968)
6 aged.sh. (137372)
7 elderly.ti,ab,sh. (11802)
8 elderly.hw. (671)
9 elderly.kw. (171)
10 or/7-9 (12078)
11 4 or 5 or 6 or 10 (144456)
12 (or/2-3) and 11 [overprescribing terms & aged] (257)
13 (or/2-3) not (child or children or infant? or teen$ or adolescent?).ti,sh,kw. (719)
14 or/1,12-13 [Results]

The Cochrane Library **; ACP Journal Club, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database, Health Technology Assessment, Cochrane Methodology Register (Ovid)**
Search date: November 14, 2013
1 polypharm$.ti,ab,kf,hw,kw,sh. (31)
2 (overprescrib$ or underprescrib$).ti,ab. (1)
3 ((inappropriat$ or suboptim$ or sub-optim$ or unnecessary or incorrect$ or excess$ or multip$ or concurrent$ or inadvert$) adj2 (medici$ or medicat$ or prescrib$ or prescription$ or drug$)).ti,ab. (58)
4 ((old$ or aged) adj (person$ or adult$ or people or patient$ or inpatient$ or outpatient$)).ti,ab. (762)

5 geriatric?.ti,ab,hw,kw,sh. (299)
6 aged.sh. (4897)
7 elderly.ti,ab,sh. (776)
8 elderly.hw. (32)
9 elderly.kw. (59)
10 or/7-9 (834)
11 4 or 5 or 6 or 10 (6161)
12 (or/2-3) and 11 [overprescribing terms & aged] (11)
13 (or/2-3) not (child or children or infant? or teen$ or adolescent?).ti,sh,kw. (54)
14 or/1,12-13 [Results] (81)
15 from 14 keep 1-20 [ACP] (20)
16 from 14 keep 21-36 [CDSR] (16)
17 from 14 keep 37-42 [methodology register] (6)
18 from 14 keep 43-68 [DARE] (26)
19 from 14 keep 69-74 [HTA] (6)
20 from 14 keep 75-81 [EED] (7)

PsycINFO (Ovid)
Search date: November 17, 2013

1 polypharmacy/ or polypharma$.ti,ab. (1405)
2 (beer$ adj1 criter$).ti,ab. (60)
3 ((inappropriat$ or suboptim$ or sub-optim$ or unnecessary or incorrect$ or excess$ or multip$ or concurrent$ or inadvert$) adj2 (medici$ or medicat$ or prescrib$ or prescription$ or drug$)).ti,ab. (2332)
4 ((over adj1 (prescrib$ or prescript$)) or (over-prescrib$ or overprescrib$) or ("or more" adj (medication$ or prescrib$ or prescript$))).ti,ab. (327)
5 ((under adj1 prescrib$) or underprescrib$ or under-prescrib$).ti,ab. (55)
6 "medication appropriateness index$".ti,ab. (15)
7 (quality adj1 (prescribing or prescription$ or medication$)).ti,ab. (62)
8 (improv$ adj1 (prescrib$ or pharmaco$ or prescription$)).ti,ab. (158)
9 (Prescrib$ adj1 cascade$).ti,ab. (5)
10 ("assessing care of vulnerable elders" or ACOVE).ti,ab. (40)
11 ((multi-drug$ or multidrug$) adj2 (prescrib$ or prescription$ or regimen? or therap$ or treatment?)).ti,ab. (66)
12 or/1-11 (4170)
13 geriatric patients/ (10518)
14 (elder$ or geriatric$).ti,ab. (56687)
15 geriatric$.sh. (18325)
16 ((old$ or aged) adj (person$ or adult$ or people or patient$ or inpatient$ or outpatient$)).ti,ab. (46697)
17 Military veterans/ (7276)
18 veteran$.ti,ab. (12479)
19 or/13-18 (107921)
20 random$.ti,ab. (124078)
21 (control$ adj2 (group$ or study or studies or trial?)).ti,ab. (95509)
22 "interrupted time series".ti,ab. (418)
23 (cluster$ adj (analys$ or design$ or study or studies)).ti,ab. (7054)
24 ("quasi-experiment$" or "quasi-random$").ti,ab. (6341)
25 ((pretest or posttest) adj2 (control or group or design? or study or studies)).ti,ab. (2927)
26 (before adj1 after adj2 (study or studies or trial? or design?)).ti,ab. (175)
27 (intervention? or evaluat$).ti. (99509)
28 or/20-27 (283787)
29 (STOPP or ACOVE or BEER? CRITERIA).ti,ab. (97)
30 12 and 19 and 28 (128)
31 ((or/1,29) and 28) not 30 (215)

32 or/30-31 (343)
33 remove duplicates from 32 (343)
34 (child or children or teen? or teenager? or adolescent? or infant? or p?ediatric$).ti. or placebo.ti,ab,hw. (314293)
35 33 not 34 (271)

CINAHL (EBSCO)
Search date: November 19, 2013

#	Query	Results	Action
S52	S50 OR S51	514	
S51	(((S1 or S2) AND S9)) AND (S46 OR S25) NOT (S47 OR S45)	29	
S50	S48 OR S49	514	
S49	(S16 AND S46) NOT S48	356	
S48	S16 AND S25	158	
S47	TI animal or animals or mouse or mice or bovine or cow or equine or monkey or cat or dog or cats or dogs	11,113	
S46	S44 NOT S45	275,475	
S45	TI ("case control*" OR placebo*) OR AB placebo* OR MW placebo*	26,577	
S44	S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43	286,529	
S43	TI ((control w3 area) or (control w3 cohort*) or (control w3 compar*) or (control w3 condition) or (control w3 group*) or (control w3 intervention*) or (control w3 participant*) or (control w3 study)) or AB ((control w3 area) or (control w3 cohort*) or (control w3 compar*) or (control w3 condition) or (control w3 group*) or (control w3 intervention*) or (control w3 participant*) or (control w3 study))	44,901	
S42	AB ((study n3 aim) or "our study")	52,756	

(*Continued*)

S41	TI (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop)) or AB (pre-workshop or preworkshop or post-workshop or postworkshop or (before n3 workshop) or (after n3 workshop))	306	
S40	TI (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*) or AB (demonstration project OR demonstration projects OR preimplement* or pre-implement* or post-implement* or postimplement*)	1,288	
S39	(intervention n6 clinician*) or (intervention n6 community) or (intervention n6 complex) or (intervention n6 design*) or (intervention n6 doctor*) or (intervention n6 educational) or (intervention n6 family doctor*) or (intervention n6 family physician*) or (intervention n6 family practitioner*) or (intervention n6 financial) or (intervention n6 GP) or (intervention n6 general practice*) Or (intervention n6 hospital*) or (intervention n6 impact*) Or (intervention n6 improv*) or (intervention n6 individualize*) Or (intervention n6 individualise*) or (intervention n6 individualizing) or (intervention n6 individualising) or (intervention n6 interdisciplin*) or (intervention n6 multicomponent) or (intervention n6 multi-component) or (intervention n6 multidisciplin*) or (intervention n6 multi-disciplin*) or (intervention n6 multifacet*) or (intervention n6 multi-facet*) or (intervention n6 multimodal*) or (intervention n6 multi-modal*) or (intervention n6 personalize*) or(intervention n6 personalise*) or (intervention n6 personalizing) or (intervention n6 personalising) or (intervention n6 pharmacies) or (intervention n6 pharmacist*) or (intervention n6 pharmacy) or (intervention n6 physician*) or	40,352	

(*Continued*)

	(intervention n6 practitioner*) Or (intervention n6 prescrib*) or (intervention n6 prescription*) or (intervention n6 primary care) or (intervention n6 professional*) or (intervention* n6 provider*) or (intervention* n6 regulatory) or (intervention n6 tailor*) or (intervention n6 target*) or (intervention n6 team*) or (intervention n6 usual care)		
S38	TI (collaborativ* or collaboration* or tailored or personalised or personalized) or AB (collaborativ* or collaboration* or tailored)	35,591	
S37	TI (pilot or piloting or piloted)	11,605	
S36	AB ((quasi* W3 method*) or (quasi* W3 study) or (quasi* W3 studies) or (quasi* W3 trial) or (quasi* W3 design*) or (experimental W3 design*)) OR AB ((quasi-experiment* or quasiexperiment* or quasi-random* or quasirandom* or quasi control* or quasicontrol*))	7,264	
S35	AB time series	1,746	
S34	TI time series	237	
S33	AB (before* n10 during or before n10 after) or TI (before* n10 during or before n10 after) or TI (during N5 period) OR AB (during N5 period)	56,091	
S32	TI ((time point) OR (time points)) OR AB ((time points n3 over) or (time points n3 multiple) or (time points n3 three) or (time points n3 four) or (time points n3 five) or (time points n3 six) or (time points n3 seven) or (time points n3 eight) or (time points n3 nine) or (time points n3 ten) or (time points n3 eleven) or (time points n3 twelve) or (time points n3 month*) or (time points n3 hour*) or (time points n3 day*) or (time points n3 "more than")) or AB ((time points n3 over) or (time points n3 multiple) or (time points n3 three) or (time points n3 four) or (time points n3 five) or (time	4,771	

	points n3 six) or (time points n3 seven) or (time points n3 eight) or (time points n3 nine) or (time points n3 ten) or (time points n3 eleven) or (time points n3 twelve) or (time points n3 month*) or (time points n3 hour*) or (time points n3 day*) or (time points n3 "more than")) OR AB ((time periods n3 over) or (time periods n3 multiple) or (time periods n3 three) or (time periods n3 four) or (time periods n3 five) or (time periods n3 six) or (time periods n3 seven) or (time periods n3 eight) or (time periods n3 nine) or (time periods n3 ten) or (time periods n3 eleven) or (time periods n3 twelve) or (time periods n3 month*) or (time periods n3 hour*) or (time periods n3 day*) or (time periods n3 "more than")) or AB ((time periods n3 over) or (time periods n3 multiple) or (time periods n3 three) or (time periods n3 four) or (time periods n3 five) or (time periods n3 six) or (time periods n3 seven) or (time periods n3 eight) or (time periods n3 nine) or (time periods n3 ten) or (time periods n3 eleven) or (time periods n3 twelve) or (time periods n3 month*) or (time periods n3 hour*) or (time periods n3 day*) or (time periods n3 "more than")) OR AB ((time period n3 over) or (time period n3 multiple) or (time period n3 three) or (time period n3 four) or (time period n3 five) or (time period n3 six) or (time period n3 seven) or (time period n3 eight) or (time period n3 nine) or (time period n3 ten) or (time period n3 eleven) or (time period n3 twelve) or (time period n3 month*) or (time period n3 hour*) or (time period n3 day*) or (time period n3 "more than")) or AB ((time period n3 over) or (time period n3 multiple) or (time period n3 three) or (time period n3 four) or (time period n3 five) or (time period n3 six) or (time period n3 seven) or (time period n3 eight) or (time period n3 nine) or (time period n3 ten) or (time period n3 eleven) or (time period n3 twelve) or (time period n3 month*)		

(*Continued*)

	or (time period n3 hour*) or (time period n3 day*) or (time period n3 "more than"))		
S31	TI (pre w7 post) or AB (pre w7 post)	8,908	
S30	MH "Multiple Time Series" or MH "Time Series"	1,315	
S29	TI ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies) or AB ((comparative N2 study) or (comparative N2 studies) or evaluation study or evaluation studies)	10,240	
S28	MH "Experimental Studies" or MH "Community Trials" or MH "Community Trials" or MH "Pretest-Posttest Design+" or MH "Quasi-Experimental Studies+" OR MH "Pilot Studies" or MH "Policy Studies+" OR MH "Multicenter Studies"	71,177	
S27	TI (pre-test* or pretest* or posttest* or post-test*) or AB (pre-test* or pretest* or posttest* or "post test*) OR TI (preimplement*" or pre-implement*) or AB (pre-implement* or preimplement*)	6,678	
S26	TI (intervention* or multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*) or AB (multiintervention* or multi-intervention* or postintervention* or post-intervention* or preintervention* or pre-intervention*)	35,022	
S25	(S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24) NOT (TI placebo* or AB placebo* or MW placebo*)	109,218	
S24	TI controlled AND TI (trial or trials or study or experiment* or intervention or assessment or evaluation or pilot or cluster or group or groups)	17,668	

(*Continued*)

S23	AB ((multicent* n2 design*) or (multicent* n2 study) or (multicent* n2 studies) or (multicent* n2 trial*)) or AB ((multi-cent* n2 design*) or (multi-cent* n2 study) or (multi-cent* n2 studies) or (multi-cent* n2 trial*))	6,485	
S22	TI multicentre or multicenter or multi-centre or multi-center	16,243	
S21	TI (cluster AND (trial* or study or group or groups or cohort or design or experiment*)) OR AB ((cluster N4 trial*) or (cluster N4 study) or (cluster N4 group) or (cluster N4 groups) or (cluster N4 cohort) or (cluster N4 design))	2,125	
S20	TI (control group or control groups OR control* experiment* or control* design or controlled study) OR AB (control group OR control groups or control* cohort* or controlled experiment* controlled design or controlled study)	48,381	
S19	TI random* or AB ((random* N2 alloc*) or (Random* n3 cluster*) or ("unit of randomi*") or (random* n3 method) or (random* n3 group) or (random* n3 patient*) or (random* n3 subject*) or (random* n3 participant*)) or AB (randomly)	64,213	
S18	TI ("clinical study" or "clinical studies") or AB ("clinical study" or "clinical studies")	6,727	
S17	(MM "Clinical Trials+")	8,066	
S16	S14 OR S15	2,574	
S15	(((S6 AND S9) or (S6 NOT S13)) not S14) OR ((S1 or S2) AND S9)	603	
S14	((S3 AND S9) OR (S3 not S13)) OR TI polypharmacy	1,988	
S13	S10 OR S11 OR S12	178,812	

(*Continued*)

S12	TI (child or children or infant or infants or adolescent*)	126,450	
S11	TI (pediatric* or paediatric*) OR AB (pediatric* or paediatric*) OR MW (pediatric* or paediatric*)	62,627	
S10	(MM "Infant+") OR (MM "Child+") OR (MM "Adolescence+")	17,781	
S9	S7 OR S8	339,802	
S8	TI (elderly or elder or "aged adult*" or geriatric* or Older adult* OR "OLD AGE" OR VETERAN*) or AB (elderly or elder or "aged adult*" or geriatric* or Older adult* old age OR veteran*)	69,372	
S7	(MH "Aged+") or MW (veteran*)	327,259	
S6	S4 or S5	714	
S5	TI (underprescrib* or "over prescrib*" or "prescrib* quality") or TI ("quality prescrib*") or AB ("quality prescrib*") or AB (underprescrib* or "over prescrib*" or "prescrib* quality")	133	
S4	(TI ("inappropriat* medicat*" or "medication appropriateness") or AB ("inappropriat* medicat*" or "medication appropriateness") or MW ("inappropriat* medicat*" or "medication appropriateness")) OR (TI ("suboptim* medicat*" or "sub-optim* medicat*" or "unnecessar* medicat*" or "concurrent* prescri*" or "inadvert* prescri*" or "incorrect* prescri*" or "excess* prescri*" or "multip* prescri*" or "inappropriat* prescri*" or "unnecessar* prescri*" or "suboptim* prescri") or AB ("inappropriat* prescri*" or "suboptim* prescri" or "unnecessar* prescri*" or "incorrect* prescri*" or "excess* prescri*" or "multip* prescri*" or "concurrent* prescri*" or "inadvert* prescri*" or "suboptim* medicat*" or "sub-optim* medicat*" or "unnecessar* medicat*"))	593	

(*Continued*)

S3	(TI polypharm* or AB polypharm* or MW polypharm*) OR (TI "beer* criter*" or AB "beer* criter*" or MW "beer* criter*") OR TI "Assessing Care of Vulnerable Elders" or AB "Assessing Care of Vulnerable Elders" OR TI (acove) or AB (acove)	2,016	
S2	TI ((Prevent* OR reduc*) AND (medication* error*)) OR AB ((Prevent* N3 medication error*) OR (REDUC* N3 medication error*))	726	
S1	TI (Prevent* or reduc*) and MH ("medication errors")	915	

The Joanna Briggs Institute (Ovid)
Search date: November 6, 2013
---
1 polypharmacy.mp. [mp=text, heading word, subject area node, title] (61)
2 polypharmacy.ti,hw. (7)
3 (polypharmacy adj4 (prevent$ or reducing or reduce? or reduction or improvement or intervention or collaborat$)).mp. (7)
4 (medication error? and (elder$ or aged or older or geriatric? or nursing home?)).ti. (6)
5 (medication reconciliation and (elder$ or aged or older or geriatric? or nursing home?)).ti. (2)
6 or/1-5 (62)
7 limit 6 to ("systematic review protocols" or systematic reviews or technical reports)
ClinicalTrials.gov, US National Institutes of Health (NIH) http://clinicaltrials.gov/
Search date: November 14, 2013
1 polypharmacy (39)
2 hyperpharmacotherapy (0)
3 "Assessing Care of Vulnerable Elders" (1)
4 ACOVE (3)
5 "beers criteria" (5)
6 "beer's criteria" (5)
7 "medication appropriateness index" (5)
8 "STOPP-START" OR "STOPP START" (0)
9 (STOPP AND START) (5)
10 "Screening Tool of Older Persons' Potentially Inappropriate Prescriptions" (3)
11 "Screening Tool of Older Persons Potentially Inappropriate Prescriptions" (3)
12 "Screening Tool to Alert Doctors to Right Treatment" (3)
13 (STOPP AND START) OR "Screening Tool of Older Persons' Potentially Inappropriate Prescriptions" (6)
14 "Screening Tool of Older Persons' Potentially Inappropriate Prescriptions" OR "Screening Tool to Alert Doctors to Right Treatment" (4)
15 "McLeod criteria" OR "McLeods criteria" OR "McLeods criteria" (0)
16 "zhan criteria" OR "zhan's criteria" OR "zhans criteria" (0)
17 overprescribing OR overprescribe OR overprescription (5)
18 underprescribing OR underprescribe OR underprescription (3)

19 1 OR 4 OR 5 OR 7 OR 12 OR 13 (47)
20 17 AND 18 (21)
21 19 AND 20 (61*)
*Imported results from #19 and #20 into Microsoft Excel, identified and removed duplicates using NCT number.

Appendix 3. Reviews screened for included studies

(1) Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. Journal of the American Academy of Nurse Practitioners 2005 Apr;17(4):123-32.

(2) Garcia RM. Five ways you can reduce inappropriate prescribing in the elderly: a systematic review. Journal of Family Practice 2006 Apr;55(4):305-12.

(3) George J, Elliott RA, Stewart DC. A systematic review of interventions to improve medication taking in elderly patients prescribed multiple medications. Drugs & Aging 2008;25(4):307-24.

(4) Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. American Journal of Geriatric Pharmacotherapy 2007;5(4): 345-51.

(5) Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database of Systematic Reviews 2008;2(CD000011).

(6) Holland R, Desborough J, Goodyer L, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. British Journal of Clinical Pharmacology 2008 Mar; 65(3):303-16.

(7) Huss A, Stuck AE, Rubenstein LZ, Egger M, Clough-Gorr KM. Multidimensional preventive home visit programs for community-dwelling older adults: a systematic review and meta-analysis of randomized controlled trials. The Journals of Gerontology Series A, Biological Sciences and Medical Sciences 2008;63(3):298-307.

(8) Jano E, Aparasu RR. Healthcare outcomes associated with Beers' criteria: a systematic review. The Annals of Pharmacotherapy 2007 Mar;41(3):438-47.

(9) Kaur S, Mitchell G, Vitetta L, Roberts MS. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. Drugs & Aging 2009;26(12):1013-28.

(10) Maeda K. Systematic review of the effects of improvement of prescription to reduce the number of medications in the elderly with polypharmacy. Yakugaku Zasshi 2009 May;129(5):631-45.

(11) Milton JC, Hill-Smith I, Jackson SH. Prescribing for older people. BMJ 2008 Mar 15;336(7644):606-9.

(12) Rollason V, Vogt N. Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. Drugs & Aging 2003;20(11):817-32.

(13) Royal S, Smeaton L, Avery AJ, Hurwitz B, Sheikh A. Interventions in primary care to reduce medication related adverse events and hospital admissions: systematic review and meta-analysis. Quality & Safety in Health Care 2006 Feb;15(1):23-31.

(14) Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C, et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? Lancet 2007;370(9582):173-84.

(15) Wenger NS, Roth CP, Shekelle P, ACOVE I. Introduction to the assessing care of vulnerable elders-3 quality indicator measurement set. Journal of the American Geriatrics Society 2007 Oct;55(Suppl 2):S247-s52.

(16) Yourman L, Concato J, Agostini JV. Use of computer decision support interventions to improve medication prescribing in older adults: a systematic review. American Journal of Geriatric Pharmacotherapy 2008 Jun;6(2):119-29.
(17) Alldred DP, Raynor DK, Hughes C, Barber N, Chen TF, Spoor P. Interventions to optimise prescribing for older people in care homes. Cochrane Database of Systematic Reviews 2013; 2:CD009095.
(18) Christensen M, Lundh A. Medication review in hospitalised patients to reduce morbidity and mortality. Cochrane Database of Systematic Reviews 2013;2:CD008986.
(19) Clyne B, Bradley MC, Hughes C, Fahey T, Lapane KL. Electronic prescribing and other forms of technology to reduce inappropriate medication use and polypharmacy in older people: a review of current evidence. Clinics in Geriatric Medicine 2012;28(2):301-22.
(20) Fleming A, Browne J, Byrne S. The effect of interventions to reduce potentially inappropriate antibiotic prescribing in long-term care facilities: a systematic review of randomised controlled trials. Drugs & Aging 2013;30(6):401-8.
(20) Forsetlund L, Eike MC, Gjerberg E, Vist GE. Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials. BMC Geriatrics 2011;11:16.
(21) Frazier SC. Health outcomes and polypharmacy in elderly individuals: an integrated literature review. Journal of Gerontological Nursing 2005;31(9):4-11.
(22) George J, Elliott RA, Stewart DC. A systematic review of interventions to improve medication taking in elderly patients prescribed multiple medications. Drugs & Aging 2008;25(4):307-24.
(23) Loganathan M, Singh S, Franklin BD, Bottle A, Majeed A. Interventions to optimise prescribing in care homes: systematic review. Age and Ageing 2011;40(2):150-62.
(24) Maeda K. Systematic review of the effects of improvement of prescription to reduce the number of medications in the elderly with polypharmacy. Yakugaku Zasshi : Journal of the Pharmaceutical Society of Japan 2009;129(5):631-45.
(25) Tani H, Uchida H, Suzuki T, Fujii Y, Mimura M. Interventions to reduce antipsychotic polypharmacy: a systematic review. Schizophrenia Research 2013;143(1):215-20.
(26) Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. Drugs & Aging 2013;30(5):285-307.

WHAT'S NEW

Last assessed as up-to-date: 21 August 2014.

Date	Event	Description
24 September 2014	New search has been performed	Updated searches completed. Two studies added to review
24 September 2014	New citation required but conclusions have not changed	No change to conclusions. First update

CONTRIBUTIONS OF AUTHORS

S Patterson (SP) prepared the protocol under the direction of C Hughes (CH), N Kerse (NK) and CR Cardwell (CRC). C Cadogan (CC) and C Ryan (CR) were involved in updating the review. SP, M Bradley (MB), CH, CC and CR are pharmacists, NK is a GP and an experienced researcher with an interest in geriatric medicine and CRC is a biomedical statistician. MB, CH, NK, CR and CRC have been involved in systematic reviews in other areas. SP undertook the database searches and reviewed the literature identified in the original review. CH and CC undertook the second review update including data extraction, risk of bias assessment and writing of the review update. MB, NK and CR acted as independent co-review authors.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Queen's University Belfast, School of Pharmacy, UK.

External sources

- Research and Development Office, Northern Ireland, UK.

Fellowship awarded to Dr. Susan Patterson to undertake the original review for 2 years, 2 days per week

- The Dunhill Medical Trust, London, UK.

This work was supported by The Dunhill Medical Trust [grant number: R298/0513]

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As only two studies (Bucci 2003; Crotty 2004a) reported the primary outcome measure of change in the appropriate use of polypharmacy, we used postintervention results of summated MAI scores and the number of Beers drugs per participant in the meta-analyses to compare the effect sizes of the interventions.

The search strategy was modified slightly from that used in the original review to avoid limiting the search unnecessarily. Based on a recommendation made following the search development process for the previous review, the term 'polypharmacy' was searched alone (e.g. not combined with the concept of "age" using the Boolean operator "AND") because most of the literature on polypharmacy focuses on older populations.

Science Citation Index, Social Sciences Citation Index (via the Institute on Scientific Information (ISI) Web of Science) and AARP AgeLine were not searched for this update after a review of previously included studies revealed that they were not a reliable source of studies for this topic.

INDEX TERMS

Medical Subject Headings (MeSH)

*Medication Therapy Management; *Polypharmacy; *Quality Improvement; Drug Prescriptions [standards]; Drug-Related Side Effects and Adverse Reactions; Randomized Controlled Trials as Topic

MeSH check words

Aged; Humans