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

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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 there is growing interest in appropriate polypharmacy, where many medicines may be used to achieve better clinical outcomes for patients.

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

A range of literature databases including MEDLINE and EMBASE were searched in addition to handsearching reference lists. Search terms included polypharmacy, Beers criteria, 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 aged 65 years and older where a validated measure of appropriateness was used (e.g. Beers criteria or Medication Appropriateness Index - MAI).

Data collection and analysis

Three authors independently reviewed abstracts of eligible studies, extracted data and assessed risk of bias of included studies. Study specific estimates were pooled, using a random-effects model to yield summary estimates of effect and 95% confidence intervals.

Main results

Electronic searches identified 2200 potentially relevant citations, of which 139 were examined in detail. Following assessment, 10 studies were included. One intervention was computerised decision support and nine were complex, multifaceted pharmaceutical care provided in a variety of settings. Appropriateness of prescribing was measured using the MAI score postintervention (seven studies) and/or Beers criteria (four studies). The interventions included in this review demonstrated a reduction in inappropriate medication use. A mean difference of -6.78 (95% CI -12.34 to -1.22) in the change in MAI score in favour of the intervention group (four studies). Postintervention pooled data (five studies) showed a mean reduction of -3.88 (95% CI -5.40 to -2.35) in the summated MAI score and a mean reduction of -0.06 (95% CI -0.16 to 0.04) in the number of Beers drugs per patient (three studies). Evidence of the effect of the interventions on hospital admissions (four studies) was conflicting. Medication-related problems, reported as the number of adverse drug events (three studies), reduced significantly (35%) postintervention.

Authors' conclusions

It is unclear if interventions to improve appropriate polypharmacy, such as pharmaceutical care, resulted in a clinically significant improvement; however, they appear beneficial in terms of reducing inappropriate prescribing and medication-related problems.

PLAIN LANGUAGE SUMMARY

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

Taking medicines for chronic illnesses both to treat symptoms and to prevent diseases getting worse 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 safe medication for their illness. The actions taken included pharmaceutical care, a service provided by pharmacists, which 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, a programme on the doctor's computer that helps him/her to decide on the right 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 and reducing medication-related problems in this group, but it is not clear if this always results in clinical improvements.

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

Patient or population: older people
Settings: all
Intervention: pharmaceutical care
Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk (95% CI)				
	Usual care	Pharmaceutical care				
Summated MAI score MAI Follow-up: 0 to 12 months	The mean summated MAI score in the control groups was 1.44	The mean summated MAI score in the intervention groups was **3.88 lower** (5.4 to 2.35 lower)		965 (5 studies)	⊕◯◯◯ **very low**[1,2,3]	
Change in MAI score The change in the MAI Follow-up: 0 to 3 months	The mean change in MAI score in the control groups was 1.43	The mean change in MAI score in the intervention groups was **3.81 higher** (1.17 lower to 8.78 higher)		424 (4 studies)	⊕◯◯◯ **very low**[1,2,3]	
Number of Beers drugs per patient The Beers criteria Follow-up: 0 to 12 months	The mean number of beers drugs per patient in the control groups was 0.23	The mean number of Beers drugs per patient in the intervention groups was **0.06 lower** (0.16 lower to 0.04 higher)		1440 (3 studies)	⊕◯◯◯ **very low**[1,2,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

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.

[1] Limitations in the design of studies included in the analysis such as lack of protection against contamination, lack of allocation concealment and the absence of a power calculation resulted in the evidence being downgraded

[2] Statistically significant heterogeneity, variation in effect sizes and overlap in CIs reported in some studies resulted in downgrading the quality of evidence

[3] Relating to precision studies tended to have wide CIs as a result of large standard deviations and this was independent of sample size

BACKGROUND

Prescribing for older people is complex due to 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).

Polypharmacy has a range of definitions that refer to the use of multiple medication regimens, but no standard definition is used consistently (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 aged 65 years or over, as this age group often suffers from multiple comorbidities such as heart disease and diabetes that require multiple medications for treatment and prophylaxis. In the USA, the prevalence of polypharmacy, defined by Kaufman as five or more medicines, in older people was approximately 7% (Kaufman 2002) and individuals over 65 years of age, who constituted less than 15% of the American population, purchased 33% of prescription medicines and 40% of over-the-counter (OTC) medicines (Werder 2003). In 2007, people of 65 years and over constituted 16% of the UK population, yet consumed 43% of all National Health Service (NHS) resources in 2003 to 2004 (Philp 2007). The average number of medicines prescribed for people aged 60 years and over in England has almost doubled from 21.2 to 40.8 items per person per year over the past decade (Information Centre 2007).

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, for example 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 white race and education (Fillenbaum 1996), health status factors such as poorer 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, supplemental insurance and multiple providers of health care (Espino 1998; Hajar 2007).

Recent promotion of the use of clinical guidelines has influenced prescribing patterns and these 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 frequently recommend adding medications for secondary prevention. For example, within the UK, current guidelines such as the Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice (JBS 2005) advocate this approach. Diseases such as tuberculosis and congestive heart failure, with well-understood causes and pathophysiologies, are often treated with multiple therapeutic drug combinations. However, it has been reported that some clinical guidelines do not modify or discuss the applicability of their recommendations, for older patients, with multiple comorbidities, take account of patient preferences or comment on the quality of the evidence underpinning 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.

Polypharmacy is, however, associated with negative health outcomes including adverse drug reactions, poor adherence and geriatric syndromes, for example, urinary incontinence, cognitive impairment and impaired balance leading to falls (Hajar 2007). The chance of medication-related problems occurring is increased in older age because the ageing process reduces the efficiency of the body's organs to eliminate drugs (Mangoni 2003). The risk of an ADE is 13% with the use of two medications, but with five medications, 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).The poor understanding of causes of certain disorders makes prescribing drug combinations more difficult. Treating poorly understood diseases may be a risk factor for inappropriate polypharmacy (Werder 2003).

Appropriate or therapeutic polypharmacy also occurs when the results of clinical trials recommend using multiple medications to treat specific diseases (Gurwitz 2004). There is increasing acceptance that such appropriate polypharmacy may be beneficial and there are many conditions in which the combined use of three or more drugs is beneficial and appropriate especially in older people with multiple comorbidities. 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 the 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 also the addition of useful ones.

Under-prescribing is defined as a lack of drug treatment for a present disease for which drug therapy is indicated according to clinical practice guidelines (Lipton 1992). Under-prescribing can

be equally as challenging as polypharmacy, in older people, and it has only recently gained recognition as a concern. Under-prescribing has also been shown to be associated with polypharmacy (Kuijpers 2007); the probability of under-prescription increases with the number of medicines used. In one study, the treatment of current medical problems, in geriatric patients, was compared with general practitioners (GPs) and national guidelines (Kuijpers 2007). Polypharmacy was present in 61% of 150 patients and under-prescription in 31%. Of patients with polypharmacy, 42.9% were under-treated, in contrast to 13.5% of patients using four medicines or less (odds ratio (OR) 4.8, 95% confidence interval (CI) 2.0 to 11.2) showing that the estimated probability of under-prescription increased significantly with the number of drugs. These findings may be explained by the unwillingness of GPs to prescribe additional drugs to patients with polypharmacy (e.g. complexity of drug regimens, fear of ADEs, drug-drug interactions and poor adherence) (Kuijpers 2007). This so-called treatment-risk paradox or risk-treatment mismatch exists and may be observed in patients who are at highest risk for complications, having 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 physician's dilemma, and choosing the best interventions aimed at ensuring appropriate polypharmacy is 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 in older people, we included interventions addressing this problem, that is the promotion of appropriate polypharmacy.

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

Description of the intervention

An improvement in appropriate polypharmacy can be achieved through a wide range of interventions. These can be classified as professional, for example education programmes for prescribers or consumers; organisational, for example medication review clinics, specific audits on benzodiazepine use; or financial, for example prescribing incentive schemes and regulatory interventions. Interventions that reduce the risk of medication-related problems are important to consider (Fick 2008). These may be undertaken 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 the risk factors for polypharmacy, it is possible to decrease its associated morbidity, mortality and cost (Werder 2003).

Methods recommended in many intervention studies include adopting 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 about which types of interventions can improve appropriate polypharmacy.

How the intervention might work

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

1. Improvement of appropriate polypharmacy through the removal of inappropriately prescribed medication.
2. Increase in appropriate medications by promoting adherence to evidence-based therapy.

Computerised decision support (CDS), aimed at prescribers, where electronic alerts are produced to guide the prescriber to the right treatment, has been successful in reducing inappropriate prescribing in older people. Pharmacist-led interventions such as medication review, coordinated transition from hospital to long-term care facilities and pharmacist consultation to patients and physician have been shown to effectively reduce inappropriate prescribing and ADEs (Hanlon 1996; Kaur 2009). Multidisciplinary case conferences involving GPs, geriatricians, pharmacists and residential care staff where individual patients cases are discussed 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 is frequently associated with polypharmacy (Cowan 2002). The prevalence of inappropriate prescribing (and hence polypharmacy) is high (Simon 2005). Therefore, 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

The aim of this review was to determine the effectiveness of interventions designed to improve the appropriate use of polypharmacy (assessed by validated measures) in older people and reduce the risk of medication-related problems. The specific objectives were:

- to determine what interventions that alone, or in combination, are effective in improving the appropriate use of polypharmacy for older people and
- to determine whether these interventions are effective in 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 the comparison groups in the trial. If the author(s) stated explicitly that the groups compared in the trial were established by random allocation, then we classified the trial as an RCT. If the 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 or more, who had more than one long-term medical condition, including those where polypharmacy (classified as four or more medicines) was common practice, for example, Parkinson's disease or diabetes. We considered trials for inclusion if they included a majority (80% or more) of subjects aged 65 years or more or if the mean age 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 the authors to check the availability of the relevant data. We excluded studies where the intervention focussed on people with a single long-term medical condition or who were receiving short-term polypharmacy, for example those who were terminally ill or 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 solely targeted at drug prescription, and multifaceted interventions, for example specialist clinics involving comprehensive geriatric assessment, where the majority of the outcomes related to polypharmacy. We included studies of interventions where the target was polypharmacy across all ages, provided the 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 government policy or legislative changes affecting prescribing

Types of outcome measures

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

Primary outcomes

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

1. Appropriateness of medications prescribed, measured by a validated instrument, for example Beers criteria (Fick 2003) or MAI (Knight 2001).
2. 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 Tool "(START")" criteria (Barry 2007).
3. Hospital admissions.

Secondary outcomes

Secondary outcomes included the following.

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

Search methods for identification of studies

Related systematic reviews were identified by searching the Database of Abstracts of Reviews of Effectiveness (DARE), MEDLINE and EMBASE. Primary studies were identified using the databases, sources, and approaches detailed below. All sources were searched from database start date to April 2009; an update search was run in MEDLINE, EMBASE and *The Cochrane Library* in May 2010.

Databases

MEDLINE, OVID <1948-, In-Process, Daily Update>
EMBASE, OVID <1947->
PsycINFO, OVID <1806->
AARP AgeLine, OVID <1978 ->
OVID Evidence Based Medicine (EBM) Collection, including: Cochrane Central Register of Controlled Trials (CENTRAL), ACP Journal Club, DARE, NHS-EED <all dates>
Cochrane Central Register of Controlled Trials (CENTRAL), Wiley [OVID search translated and rerun in Wiley interface for 2010 update search]
CINAHL (Cumulative Index to Nursing and Allied Health Literature), EbscoHost <1980 ->
The EPOC Specialised Register, Reference Manager
Science Citation Index, Social Sciences Citation Index [1975 -] (ISI Web of Science)
Clinical Trials Registry: www.clinicaltrials.gov

Strategy development process

The search strategy published in the protocol (Appendix 2) was assessed by M. Fiander, EPOC Trials Search Co-ordinator (TSC) and was broadened to improve retrieval of relevant material. Strategies for MEDLINE, EMBASE, CINAHL, AgeLine, PsycINFO, *The Cochrane Library* and DARE were written by the TSC in consultation with the authors. Strategies for all databases reflect an iterative development process whereby the TSC sought feedback from the authors on the relevance of citations identified by various search terms and edited search strategies accordingly. The Medical Subject Heading (MeSH) polypharmacy was searched as were synonyms and phrases related to polypharmacy such as: Beer's Criteria, over-prescribing, under-prescribing, optimal/suboptimal prescribing, and ACOVE (Assessing Care of Vulnerable Elders). The broader concept of medication errors was also searched. These concepts were combined using the Boolean operator 'AND' with terms describing the population of interest, for examplee.g. aged, geriatrics, etc. Future search strategies for this topic should, however, search the term polypharmacy alone (e.g. not ANDed with "age" terms since the majority of literature on polypharmacy focusses on elderly populations.

The first search of MEDLINE and EMBASE in April 2009 used a single search strategy combining both MEDLINE and EMBASE controlled vocabulary, MeSH and EMTREE, respectively,under the assumption that MeSH would identify only MEDLINE citations and that EMTREE terms would identify only EMBASE citations but this was not the case. Thus, strategies in 2010 were run in each database independently. The 2009 MEDLINE/EMBASE strategy is in Appendix 3, AARP Appendix 4, CENTRAL Appendix 5, PsycINFO Appendix 6, and CINAHL Appendix 7. The 2010 update search was run in MEDLINE, EMBASE (Appendix 8), and CENTRAL (Appendix 9. Changes between the 2009 and 2010 strategies were made based on an analysis of keywords and controlled vocabulary of relevant studies and a validated Cochrane RCT filter (cf. the *Cochrane Handbook for Systematic Reviews of Interventions*, Section 6.4d) and revised EPOC filter were applied.

Searching other resources

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

Data collection and analysis

Selection of studies

Two review authors (SP and CH) screened titles and abstracts identified in searches independently to assess which studies met the inclusion criteria. We excluded any papers that did not meet the inclusion criteria at this stage. If there was uncertainty or disagreement, we reached consensus by discussion with the co-review authors (MB, CC and NK). Two review authors (SP and CH) obtained full-text articles and assessed them independently to ensure they met the previously defined inclusion criteria.

Data extraction and management

Three review authors independently extracted details of articles included in the review including the 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 authors 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 (RevMan 2008).
We have 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

At least two review authors independently assessed the internal validity of each included study, and resolved discrepancies by discussion or with the involvement of another review author.
We used The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008) 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 risk 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 have reported all included studies in the Cochrane 'Risk of bias' tables.

Measures of treatment effect

We measured the effect of the intervention by reference to published tools for measuring inappropriate prescribing and tools to assess appropriateness of prescribing as outlined above, for example MAI, Beers criteria. We have reported outcomes for each study in natural units. Where baseline results were available from studies, pre- and postintervention means and proportions for both study and control groups have been reported. We analysed data using RevMan 5. Wherever possible, results have been presented with 95% CIs and estimates for dichotomous outcomes (e.g. number of patients receiving appropriate polypharmacy) as risk ratios.

Unit of analysis issues

We examined the methods of analysis of all study types critically. Where studies with a unit of analysis error were identified, the data were re-analysed excluding such studies (sensitivity analysis).

Dealing with missing data

No studies were excluded from a meta-analysis due to a differential loss to follow-up between groups greater than 20%.

Assessment of reporting biases

We assessed reporting bias by scrutinising the study results using the 'Risk of bias' tables in RevMan 5. We examined funnel plots corresponding to meta-analysis of the primary outcome in order 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 the participants, interventions and outcomes. We grouped studies and described them according to type of intervention, setting and study design, together with an assessment of the evidence of 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. We considered only groups of studies of the same design for pooling (RCTs and CCTs).
Where it was not possible to combine outcome data due to differences in the reporting or substantive heterogeneity, we have reported a narrative summary.

Sensitivity analysis

We performed a sensitivity analysis for pooled results based on methodological quality to assess the overall effect. We excluded one study, which had a unit of analysis error, and another study which was an outlier and had a much larger effect size than other studies in the review as well as high risk of bias in respect of contamination, selective outcome reporting and allocation concealment.

Ongoing studies

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

Summary of findings

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

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The electronic searches identified 2657 potentially relevant citations, of which 139 appeared to meet the inclusion criteria following review of the titles and abstracts. We retrieved the full publications for a more detailed assessment.

Fifty five studies were excluded primarily because of an unsuitable design, for example observational study, no control group. In five studies, the participants were too young as the mean age was less than 65 years and no data were available separately for those aged 65 years and over. There were 18 studies on a single long-term medical condition that were not polypharmacy-focussed.

We excluded a further 51 studies primarily because of the outcome measure used (the primary outcome being the change in the prevalence of appropriate use of polypharmacy, measured by a validated instrument).

Validated measures of appropriateness were used in 22 studies. These measures were: ACOVE (two studies; Spinewine 2007; Wenger 2007), Beers criteria (12 studies; Bergkvist 2009; Burnett 2009; Christensen 2004; Crotty 2004b; Fick 2004; Laroche 2006; Monane 1998; Roughead 2007; Schmader 2004; Spinewine 2007; Trygstad 2005; Trygstad 2009; Willcox 1994; Zuckerman 2005), McLeod criteria (1 study; Tamblyn 2003) and the MAI (nine studies; Bucci 2003; Crotty 2004a; Davis 2007; Hanlon 1996; Kassam 2003; Spinewine 2007; Taylor 2003). Of these, 10 studies met all other inclusion criteria (including study design, study population, types of intervention examined) and remained in the review.

Included studies

Ten studies were included in the review: 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. Details are provided in the Characteristics of included studies table and are briefly summarised below.

Study design

The included studies consisted of six RCTs (Bucci 2003; Crotty 2004b; Hanlon 1996; Schmader 2004; Spinewine 2007; Taylor 2003) and two cluster RCTs (Crotty 2004a; Tamblyn 2003). Two studies were controlled before and after studies (Trygstad 2005; Trygstad 2009).

Settings

Of the five studies (962 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 was at the hospital/care home interface (Crotty 2004b) and one was performed in an inpatient setting (Spinewine 2007). Two studies (12,629 participants) were conducted in the primary care setting in community-based family-medicine clinics (Taylor 2003) and in GPs' 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 four countries: Australia (two studies), Belgium (one study), Canada (two studies) and the USA (five studies).

Participants

A total of 21,911 participants were included in this review. The mean age of intervention group participants was 74.2 years and of the control group participants was 74.9 years. Just fewer than 50% (48.8%) of the intervention group participants were female while 50.2% of the control group were female. Ethnicity was not reported in the majority of studies; of the four studies (8685 participants) that did report this, 68.7% of participants were white.

All of the participants had more than one long-term medical condition and were receiving four or more medicines at baseline. In nine of the 10 studies where data were available (9351 participants), the participants were prescribed a mean of 7.72 (intervention) and 7.71 (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, the interventions were classified as organisational according to EPOC definitions; none of the included studies was classified as professional, financial or regulatory.

Nine studies examined complex, multifaceted interventions of pharmaceutical care in a variety of settings. Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite 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 the physician, patient and carer (Hepler 1990). One unifaceted study (Tamblyn 2003) examined CDS provided to GPs in their own practices.

Pharmaceutical care was 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) and inpatient services on hospital wards as a clinical pharmacy service (Spinewine 2007) or took part in the hospital discharge process (Crotty 2004b). In community settings, pharmaceutical care services, including medication reviews, patient interviews and counselling, were undertaken by pharmacists in community-based family medicine clinics (Taylor 2003). In nursing homes, multidisciplinary case conferences combined with staff education were provided by pharmacists (Crotty 2004a) and a drug therapy management service was also provided (Trygstad 2005;

Trygstad 2009).

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

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

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

Education was also provided to prescribers and multidisciplinary team healthcare professionals specifically as part of the intervention in five studies (Bucci 2003; Crotty 2004a; Crotty 2004b; Hanlon 1996; Spinewine 2007) at case conferences and during ward rounds or by providing evidence-based information and answering specific medication-related queries. In two studies where the pharmacist was part of a multidisciplinary team, no educational intervention was specified in the methodology (Schmader 2004; Taylor 2003).

The timing of intervention provision was variable. Interventions were delivered over a period of time, for example during the length of hospital inpatient stay and at discharge (Schmader 2004; Spinewine 2007) or over several clinic visits and several months on an ongoing basis (Tamblyn 2003). Interventions were also delivered at the time of an event, for example 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). All study interventions except three (Crotty 2004b; Schmader 2004; Spinewine 2007) were administered during a single episode of care. The interventions were provided over varying durations, ranging from 5 to 6 months (Bucci 2003; Trygstad 2005) to 3 years and 3 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 the prevalence of appropriate use of polypharmacy, measured by a validated instrument. Validated measures of appropriateness reported in all of the included studies were measured independently by pharmacists or the research team who had access to patients' charts and medication records except in Trygstad 2005 and Trygstad 2009 where the Medicaid dispensed prescription claims database was used. The length of time between delivery of the intervention and the follow-up outcome measurement varied from immediately postintervention (e.g. posthospital discharge or clinic visit (Schmader 2004; Spinewine 2007; Tamblyn 2003) to at least 1 month (Bucci 2003), 8 weeks (Crotty 2004b), 0 to 3 months (Crotty 2004a; Trygstad 2005; Trygstad 2009) and up to 1 year (Hanlon 1996; Taylor 2003).

Seven studies measured appropriateness using the summated MAI score postintervention (Bucci 2003; Crotty 2004a; Crotty 2004b; Hanlon 1996; Schmader 2004; Spinewine 2007; Taylor 2003). If it was not possible to calculate the change in MAI from the results presented, the study authors were contacted to obtain the change in the summated MAI score. One study reported the MAI score in terms of 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 reported the number of patients with one or more Beers criteria drugs postintervention (Spinewine 2007). Data for the change in the number of Beers drugs were not reported by the Spinewine 2007 study authors.

One study measured appropriateness using the McLeod criteria and reported the rate of inappropriate medications prescribed per physician visit postintervention (Tamblyn 2003). No other validated criteria (e.g. Zhan, Screening Tool of Older Person's Prescriptions (STOPP) or START) were reported.

Under-use of medication was reported in two studies (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 Underutilisation of Medication (AUM) instrument (Jeffery 1999) by Schmader 2004 whereas Spinewine 2007 used seven process measures, from the full range of ACOVE criteria (Wenger 2001), which relate to the inappropriate under-use of medication.

Hospital admissions were measured by examination of hospital records at 8 weeks postintervention (Crotty 2004b; Spinewine 2007), after 3 months (Trygstad 2005) and after 1 year (Taylor 2003). Six studies did not measure this outcome.

Medication-related problems, a secondary outcome measure, was measured in six studies and reported as medication misadventure (defined as an iatrogenic incident that occurs as a result of error, immunological response or idiosyncratic response and is always unexpected or undesirable to the patient) (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 patient 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

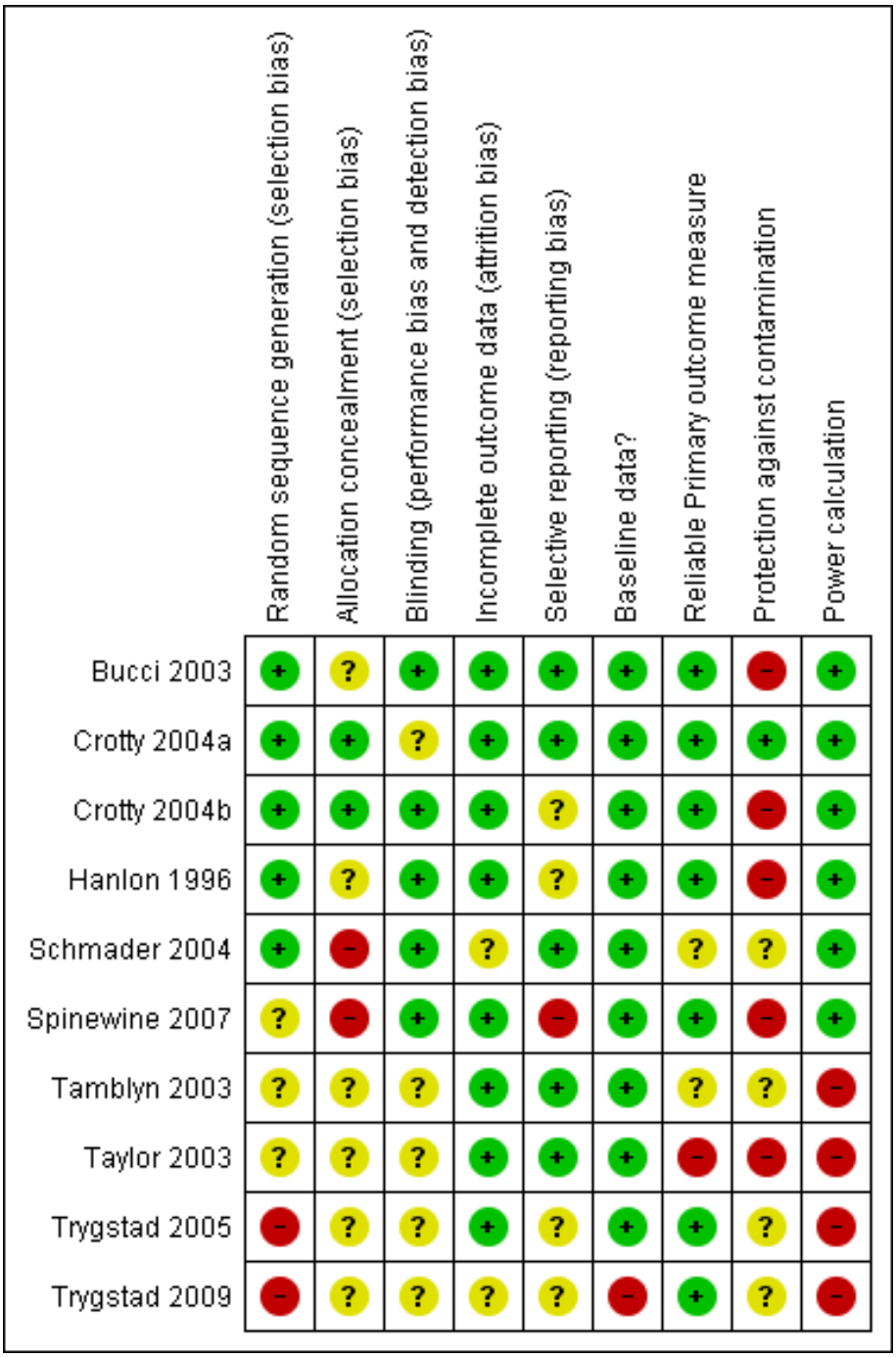
The excluded studies that were read in full (129 studies) are summarised with the reasons for exclusions in the Characteristics of excluded studies table.

Studies of unsuitable design (55 studies) were excluded from the review. The most common reason for exclusion of other studies was they did not measure appropriateness (91 studies;e.g. they only considered the number of drugs prescribed (12 studies) or used a non-validated measure of appropriateness; e.g. algorithms or guideline adherence (26 studies). Where non-validated measures of appropriateness were reported, the use of expert opinion to decide the appropriateness of prescribing was most common (10 studies; Allard 2001; Avorn 1992; Claesson 1998; Coleman 1999; Ledwidge 2004; Lipton 1992; Meredith 2002; Raebel 2007; Sellors 2003; Simon 2006). Non-validated variations of the MAI score was used in two studies (Mador 2004 (psychoactive drugs only), RESPECT 2010 (UK-version of MAI)). Other reasons for exclusion were that the participants were too young (five studies) or the study was not polypharmacy-focussed (18 studies).

Risk of bias in included studies

Details of the risk of bias are presented in Figure 1 and in the Characteristics of included studies tables

Figure 1. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



There were no major differences in the risk of bias of studies included in the review.

Allocation

Five trials reported adequate sequence generation (Bucci 2003; Crotty 2004a; Crotty 2004b; Hanlon 1996; Schmader 2004) and two reported concealment of allocation (Crotty 2004a; Crotty 2004b).

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 was adequately addressed in eight of the studies. In one study (Schmader 2004) 864 participants were randomised but only 834 were included in the analysis and no intention-to-treat analysis was reported. Therefore it was unclear if all outcome data were included.

Selective reporting

One study (Trygstad 2009) did not report baseline data and all but one study (Spinewine 2007) reported on the primary and secondary outcomes that have been described in the methods. In this 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 four studies it was unclear if there had been protection against contamination (Schmader 2004; Tamblyn 2003; Trygstad 2005; Trygstad 2009) and the remaining studies had a 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 the difference in outcomes between the two groups (Higgins 2008). 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 knowledge of the intervention. The possible influence of contamination bias should be considered when interpreting the results of this review.

Five studies (Bucci 2003; Crotty 2004a; Crotty 2004b; 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 indicated little evidence of publication bias (Figure 2; Figure 3).

Figure 2. Funnel plot of comparison: 1 Postintervention analysis, outcome: 1.1 Change in MAI score.

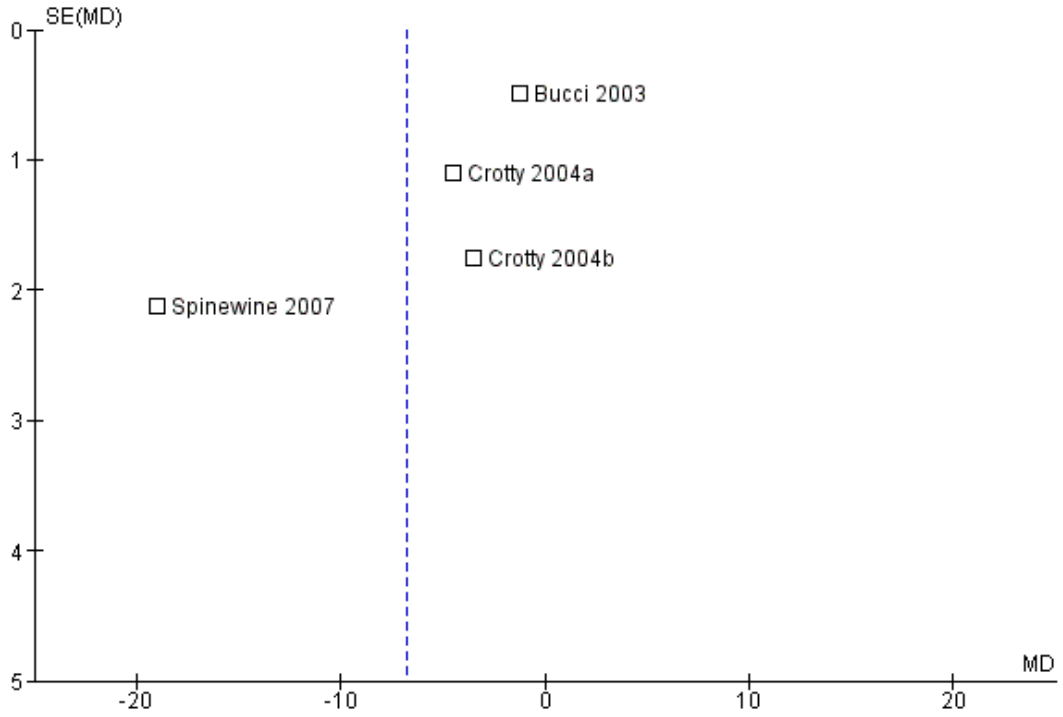
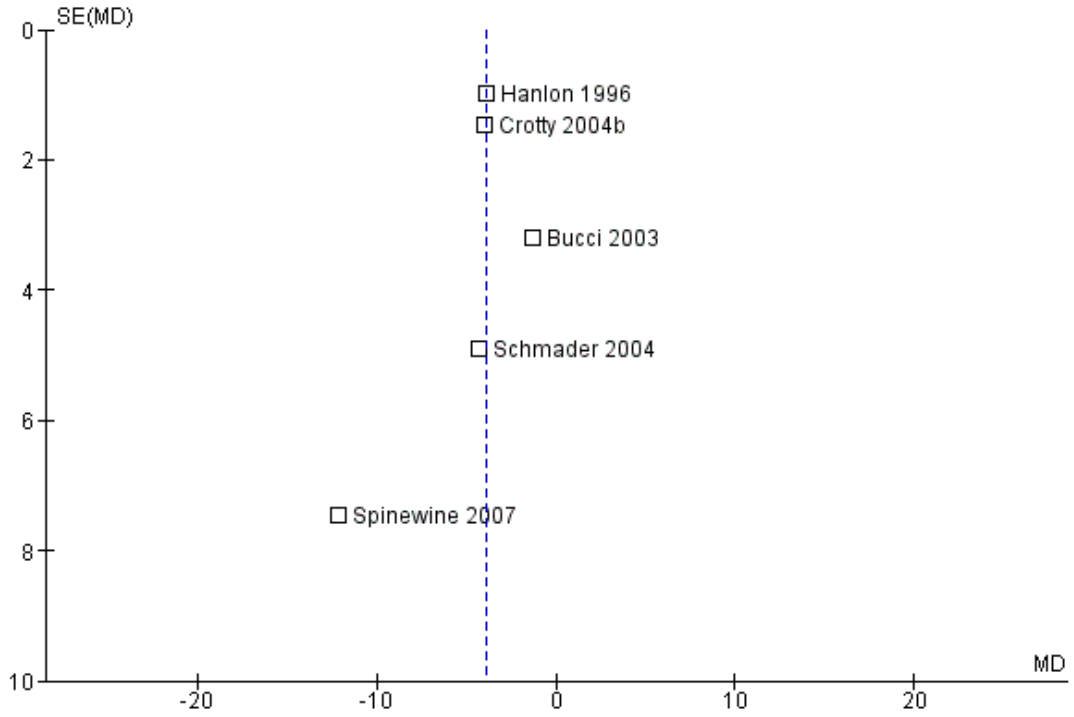


Figure 3. Funnel plot of comparison: 1 Postintervention analysis, outcome: 1.4 Summated MAI score.



Effects of interventions

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

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

Medication-related problems, reported in six studies as ADEs (Crotty 2004b; Hanlon 1996; Schmader 2004), medication misadventures (Taylor 2003) or potential drug therapy problems (Trygstad 2005; Trygstad 2009), reduced as a result of the interventions, although not all the results were statistically significant. An improvement in adherence to medication was demonstrated (Taylor 2003) but no changes in HRQoL (Hanlon 1996; Taylor 2003) were detected.

Primary outcome results

As there was only one unifaceted study included (Tamblyn 2003), a subgroup analysis was not possible. Tamblyn 2003 was also not included in the meta-analysis as a different outcome measure was used (McLeod criteria, McLeod 1997) and this was not considered similar enough to the other outcomes to combine.

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

Change in summated MAI score postintervention

Two studies reported the appropriateness of polypharmacy as the change in the summated MAI scores (Bucci 2003; Crotty 2004a) and further unpublished data were received from the authors of two studies (Crotty 2004b; Spinewine 2007). The combined number of participants was 210 intervention and 214 controls. The comparison of the change in MAI score over time in the intervention group compared with the control group is shown in Analysis 1.1. Overall there was a larger reduction in mean MAI in the intervention compared with the control group by on average -6.78 (95% CI -12.34 to -1.22). There was marked and significant heterogeneity between the studies (I^2 = 96%, P < 0.0001). Crotty 2004a had a unit of analysis error; nursing homes were the unit of randomisation but the analysis was conducted at the patient level. Sensitivity analysis, excluding Crotty 2004a from the above

model, included 178 intervention participants and 175 controls with a mean difference in the change of MAI score of -7.75 (95% CI -17.06 to 1.56, I^2 = 97%) in favour of the intervention group (Analysis 1.2). Sensitivity analyses removing both Crotty 2004a and Spinewine 2007 (an outlying study with a large effect size that had a high risk of bias in respect of contamination, allocation concealment and selective outcome reporting) resulted in a mean difference of -1.79 (95% CI -3.73 to 0.16; I^2 = 39%) (Analysis 1.3).

Prevalence of appropriate use of polypharmacy postintervention

a. Summated MAI score postintervention

Postintervention pooled data from five studies (Bucci 2003; Crotty 2004b; Hanlon 1996; Schmader 2004; Spinewine 2007) with 488 (intervention) and 477 (control) participants showed a mean improvement of -3.88 (95% CI -5.40 to -2.35) in the summated MAI score postintervention in favour of the intervention group (see Data and analyses section, Postintervention Analysis 1.4). There was little evidence of heterogeneity between these estimates (I^2 = 0%)

b. 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.

c. Beers criteria

a. Number of Beers drugs postintervention

Pooled data from two studies (Schmader 2004; Spinewine 2007) with 298 intervention and 288 controls showed a mean reduction of -0.10 (95% CI -0.28 to 0.09) in the number of Beers list drugs per patient postintervention (I^2 = 89%) (post-intervention 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 the study design, analysis and reporting (e.g. using propensity matching, results reported as difference in difference) differed from others resulting in estimates that were not sufficiently similar to include. We were unable to ascertain the standard deviation of the results for Trygstad 2005 and it was also not included in the meta-analysis.

b. Number of patients with one or more Beers drugs

As well as the total number of Beers list drugs postintervention, Spinewine 2007 also reported the proportion of patients taking one or more Beers list drugs pre- and postintervention. The OR of receiving one or more Beers list drugs postintervention (at hospital discharge) was 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.

d. McLeod criteria

The McLeod criteria were used in one study (Tamblyn 2003) to identify the initiation and discontinuation rates of 159 prescription-related problems. During the 13-month study period the number of inappropriate medications started by the 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.

e. Under-use of medication

The intervention group ACOVE scores (Spinewine 2007) were significantly reduced from 50.0 at baseline to 14.6 postintervention (P < 0.001) compared to the control group (58.9 at baseline to 44.4 postintervention, P = 0.02) indicating that intervention patients were six times as likely as control patients to have at least one improvement in appropriate prescribing (OR 6.1, 95% CI 2.2 to 17.0) postintervention. In the Schmader 2004 study, a significant reduction in the number of conditions with omitted drugs was observed postintervention; the difference in change AUM score was -0.3 (P < 0.0001). No meta-analysis was possible as these measures were measured differently and under-use was not reported in other studies.

Hospital Admissions

There were four studies measuring hospital admissions postintervention (Crotty 2004b; Spinewine 2007; Taylor 2003, Trygstad 2009). Spinewine 2007 reported no significant reduction in hospitalisations and the remaining studies reported some overall reductions in hospital admissions using a variety of measurements as detailed below.

Taylor 2003 reported a significant reduction in hospital admissions (P = 0.003) but not the number of emergency department visits (P = 0.44) during the intervention year compared to preintervention. Crotty 2004b reported a reduction in hospital usage among patients still alive at 8 weeks postintervention (OR 0.38; 95% CI 0.15 to 0.99). However, analysis of all patients including deaths and loss to follow-up showed similar hospital usage in both the intervention and control groups (-9 (16.7%) with intervention

versus -15 (26.8%) with control; risk reduction (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 = 0.04) but the remaining eight cohorts had an RR below 1.0, which was not statistically significant at the P < 0.05 level.

Because of the 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 statistically significant reductions were observed in the cohorts receiving retrospective medication review. In the remaining three studies appropriateness of prescribing improved as shown by reductions in the 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 as ADEs in three studies (Crotty 2004b; Hanlon 1996; Schmader 2004). A significant reduction was found in the number of ADEs postintervention. For example, the risk of a serious ADE was significantly reduced (P = 0.05) by 35% in a GEM clinic compared with usual outpatient care (Schmader 2004).

No significant reductions in medication misadventures postintervention (Taylor 2003) were reported. In the intervention group 2.8% of patients and 3.0% of control group patients had at least one medication misadventure at 12 months (P = 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). No statistical significance was reported in either paper. At 3 months, duration alert rates reduced by 6.3% in the intervention group (n = 5160) and 16.7% in the control group (n = 2202); clinical initiatives reduced by 10.8% in the intervention group and 0.7% in the control group and therapeutic duplication 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 3 months, duration of therapy alerts reduced by 27.8% (difference in the difference (DID) =-0.023); there was a mean DID in clinical initiative alerts of -0.24 (P < 0.05), a reduction of 13.9% and therapeutic duplication alerts reduced by 5.6% (DID = -0.87) (Trygstad 2009).

Adherence to medication

One study (Taylor 2003) reported adherence to medication in terms of compliance scores, calculated from assessment of patients' reports of missed doses. Patients 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) while the control group (n = 36) did not change; from 88.9% ± 5.8% at baseline to 88.9% ± 6.3% at 12 months (P = 0.115).

Quality of life (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 the endpoint.

Quality assessment - the GRADE APPROACH

Using the GRADE Pro assessment tool the studies included in this review were deemed to be of very low quality.

Factors that were considered in the GRADE assessment include:

1. Limitations in the design and implementation: major limitations that are likely to result in a biased assessment of the intervention effect include lack of allocation concealment, lack of blinding (particularly with subjective outcomes highly susceptible to biased assessment), a large loss to follow-up, randomised trials stopped early for benefit or selective reporting of outcomes. The 'Risk of bias' assessment carried out for a Cochrane review should feed directly into this GRADE factor. In particular, 'low risk of bias' would indicate 'no limitation'; 'unclear risk of bias' would indicate either 'no limitation' or 'serious limitation'; and 'high risk of bias' would indicate either 'serious limitation' or 'very serious limitation'. We found serious limitations in the design and implementation in a number of studies included in this review: for example, allocation concealment was not conducted in the studies by Schmader 2004 and Spinewine 2007 and the presence of allocation concealment was unclear in all other studies included in the review except Crotty 2004a and Crotty 2004b. The method of randomisation was not reported in the studies by Trygstad 2005 and Trygstad 2009 and was unclear in the studies by Spinewine 2007, Taylor 2003 and Tamblyn 2003. Protection against contamination was absent in the studies by Bucci 2003, Crotty 2004b, Hanlon 1996, Spinewine 2007 and Taylor 2003. Only one study in the review provided firm evidence of protection against contamination (Crotty 2004a).
2. Indirectness of evidence. Two types of indirectness are relevant. First, a review comparing the effectiveness of alternative interventions (say A and B) may find that randomised trials are available, but they have compared A with placebo and B with placebo. Thus, the evidence is restricted to indirect comparisons between A and B. Second, a review may find randomised trials

that meet eligibility criteria but that address a restricted version of the main review question in terms of population, intervention, comparator or outcomes. We found no serious problems relating to indirectness of evidence among the studies included in this review.

3. Unexplained heterogeneity or inconsistency of results: when studies yield widely differing estimates of effect (heterogeneity or variability in results), investigators should look for robust explanations for that heterogeneity. For instance, the study by Spinewine 2007 had a much larger effect size than the others in Analysis 1.1.

4. Imprecision of results: when studies include few participants and few events and thus have wide CIs, authors can lower their rating of the quality of the evidence. The studies by Crotty 2004b and Spinewine 2007 had larger CIs than the other studies included in the review Analysis 1.1, which were deemed to represent a degree of imprecision in the results.

5. High probability of publication bias: the quality of evidence level may be downgraded if investigators fail to report studies (typically those that show no effect: publication bias) or outcomes (typically those that may be harmful or for which no effect was observed: selective outcome reporting bias) on the basis of results. There was no evidence of publication bias detected among studies included in this review.

DISCUSSION

Summary of main results

Of 138 studies originally identified, many were excluded due to poor design, the choice of outcome measures used, or both. 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 the 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, which showed a small effect on the appropriateness of polypharmacy (Analysis 1.1). The postintervention summated MAI results of five studies were pooled in a meta-analysis (Analysis 1.4), which appeared to indicate that pharmaceutical care interventions had a positive impact on the improvement of appropriate polypharmacy. There was little evidence of heterogeneity in the effect of the interventions on the summated MAI score (I^2 = 0).

The change in summated MAI score results were normally distributed and more suitable for meta-analysis, but there was greater heterogeneity among the included studies (I^2 = 96%), largely due to the influence of the results of one study (Spinewine 2007). Overall a significant reduction in the summated MAI score post intervention was observed. A sensitivity analysis removing Crotty 2004a, which had a unit of analysis error, from the meta-analysis further improved the effect estimate. Furthermore the removal of an outlying study with a large effect size (Spinewine 2007) reduced the heterogeneity but also reduced the effect estimate. This may have been related to the small sample size for this meta-analysis (82 intervention patients and 85 control patients). Combination of the two studies using the number of Beers list drugs per patient as a measure of appropriateness (Schmader 2004; Spinewine 2007) showed a non-significant reduction in the number of Beers list drugs per patient. This reduction is unlikely to have any clinical significance. Only one study reported in terms of the ACOVE criteria, which measure the under-use of medication (Spinewine 2007).

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

Overall completeness and applicability of evidence

The types of interventions included in the review were limited. Few trials aimed to improve the skills of the prescriber. The majority of interventions were pharmaceutical care interventions including outreach by pharmacists, screening of automated drug alerts by consultant pharmacists visiting nursing homes and clinical pharmacist interventions in various settings. Only one trial was identified that involved CDS. The interventions were complex and mostly multifaceted. The variation in heterogeneity observed in the pooled estimates should be treated cautiously as the interventions did not seem to work consistently across all studies. This is perhaps because of differences in how the interventions were provided, background practice and culture and variable processes in delivery of care. In addition, there may be study-specific factors such as the variation in the quality of studies. The method sections of the studies provided little detail about how complex interventions were developed, the design of the trials and how staff were trained in the delivery of the intervention. Other information pertinent to the success of pharmaceutical care interventions including documentation, communication and sharing of information and the extent of access of intervention pharmacists to clinical records was not clear 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 has operational definitions, explicit instructions, and examples and the evaluator rates whether the particular medication is 'appropriate', 'marginally appropriate' or 'inappropriate'. Each patient can score between 0 and 18, repre-

senting 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 of the magnitude -3.88 represents in the clinical significance of reduction of risk of harm. However, improvement in these scores is important as quality of prescribing is assuming increasing importance as a means of preventing avoidable medication-related harm.

There was evidence of potential bias in some studies, for example only two 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.

There have been few rigorously conducted studies testing interventions that examined clinically relevant outcomes such as hospital admissions or ADEs. Four studies in this review reported hospital admissions postintervention (Crotty 2004b; Spinewine 2007; Taylor 2003; Trygstad 2009) and in three studies (Crotty 2004b; Spinewine 2007; Taylor 2003) the appropriateness of prescribing improved as shown by reductions in the MAI but the association with hospital admissions was inconsistent. In the fourth study (Trygstad 2009), no difference was found in the number of Beers list alerts postintervention but there was a reduction in the relative risk of hospitalisation. The differences between studies in the use of different appropriateness scales make it difficult to assess the extent of the improvement in medication appropriateness on hospital admissions. Similarly, associations between measures of appropriateness and ADEs appeared to exist but were difficult to assess due to the variations in scales used to measure the outcomes and 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 ensure that older people are prescribed appropriate medication that enhances their quality of life. However, the focus of a number of studies identified was a reduction of the number of medications, rather than improving overall appropriateness of prescribing including under-prescribing, that is recommending medications that are clinically indicated yet currently missing. Such undertreatment 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

The variation in heterogeneity between studies included in this review, should be treated cautiously as the interventions did not seem to work consistently across all studies. Factors contributing to this heterogeneity included variation in types, intensity and duration of interventions, or differences in timing of follow-up measurements. This is perhaps because of differences in how the interventions were provided, background practice and culture and variable processes in delivery of care. In addition, there may be study-specific factors such as the variation in the quality of studies. The method sections of the studies provided little detail about how complex interventions were developed, the design of the trials and how staff were trained in the delivery of the intervention. Other information pertinent to the success of pharmaceutical care interventions including documentation, communication and sharing of information and the extent of access of intervention pharmacists to clinical records was not clear in the papers. It was often unclear exactly what processes constituted successful interventions and this may have contributed to the heterogeneity of the results. A limited number of studies were included in this review as there was a paucity of studies in this area that used validated instruments to measure 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 patient included just two studies. The quality of evidence presented in this review was described by the GRADE assessment system as very low. The main limitations of studies that contributed to the assignment of this grade were issues with the design of studies (e.g. It was unclear if allocation was concealed in six studies, protection from contamination was confirmed in only one study), imprecision and heterogeneity. Only six studies reported power calculations (Bucci 2003; Crotty 2004a; Crotty 2004b; Hanlon 1996; Schmader 2004; Taylor 2003) and so in the remaining four it is unknown if they had adequate power (80%) to detect changes in the summated MAI score of 0.9 or more (See Characteristics of included studies tables).

No language restrictions were placed on the search strategy but the trials included were all in English and were conducted in developed countries. We were able to pool data on a limited number of studies. Despite the limited number of studies included, funnel plots of studies reporting the MAI detected no apparent publication bias (Figure 2; Figure 3).

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 written recommendations (Rollason 2003). In addition, another narrative review reported that the timely provision of the intervention, that is prospective advice at the time of prescription rather than dispensing of medication is also more effective (Spinewine 2007a). In general, other studies were unable to detect the effects of pharmaceutical care on reduction of hospital admissions (Holland 2007) or ADEs

(Holland 2007; Spinewine 2007a). One systematic review (Kaur 2009) identified that the most successful types of intervention to reduce inappropriate prescribing in older people were those that had multidisciplinary involvement including a geriatrician, utilised CDS, and those that had mandatory pharmaceutical services or drug restriction policies in place. The results from this current review largely support the above findings as the majority of the pharmaceutical care interventions involved a multidisciplinary component and the CDS intervention study (Tamblyn 2003) had a positive result.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence obtained from the combination of the studies is rather weak, and is unclear if interventions to improve appropriate polypharmacy, such as pharmaceutical care, resulted in a clinically significant improvement. There is uncertainty about the effect of such interventions on hospital admissions and ADEs, and it could be argued that these are the critical outcomes for patients. However, the interventions appear beneficial in terms of reducing inappropriate prescribing and reducing some medication-related problems, as well as encouraging proper use of medications and general health promotion and education.

From the results of this review we can recommend that pharmaceutical care appears to improve appropriate polypharmacy especially when there is a multidisciplinary element to the provision of care (Bucci 2003; Crotty 2004a; Crotty 2004b; 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 to improve appropriate polypharmacy (Tamblyn 2003).

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

We are uncertain about which elements of the intervention processes constitute success in improving appropriate polypharmacy and a number of unanswered questions remain. 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- 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 the prescribers, the patients and the staff in various settings will 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. The term "'polypharmacy'" can be both negative and positive and this duality of meaning makes objective research difficult (Bushardt 2008). Future studies should utilise clearer definitions of appropriate polypharmacy, for example, hyperpharmacotherapy (too many drugs) (Bushardt 2005) and there should be an acceptance that appropriate polypharmacy is not just about the reduction in the numbers of drugs but rather the prescription of medication appropriate to the needs of patients. Older patients frequently have complex needs therefore it is also important to focus on undertreatment to guide best practice. Older patients are frequently under-represented in clinical trials, are more vulnerable to treatment-induced harm and often are unable to participate in treatment decisions fully (Scott 2010).

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. Careful documentation of the development of the intervention and the training and background of the providers that may be critical to the effectiveness of the intervention is essential to facilitate replication of successful interventions in practice. Relevant risk factors for polypharmacy should also be included in intervention development. Demographic factors, such as white race and education (Fillenbaum 1996), health status, poorer health and access to health care (Hajar 2007), multiple providers of health care (Espino 1998), and number of healthcare visits (Jörgensen 2001), could be considered more pragmatically in designing future interventions. Documentation and analysis of intervention processes utilised would enable identification of the critical elements for successful interventions. Detailed information of how these processes were conducted were absent from the studies included in this review; this information may be gleaned by conducting qualitative research, for example interviewing recipients of the interventions.

A two-stage process of simple screening at drug level only (this could be automatically generated by computer, e.g. Christensen 2004) then application of a more comprehensive tool such as the MAI by clinically trained personnel, for example consultant allowing detection of clinical problems through clinical knowledge and access to patients, medical records or both, may be beneficial.

It is likely that increasingly, policy makers will also be interested in the costs of these types of interventions.

Perhaps most critically, the selection of clinical and humanis-

tic 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 comorbid 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 there are many (appropriate polypharmacy) or too many (inappropriate polypharmacy) medications is difficult. The complexity of the clinical situation, the patients' 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 the measure should be globally applicable across various healthcare and cultural settings; for example "'STOPP"' and "'START"' are new, recently validated, instruments that may go some way to fulfilling this need (Gallagher 2008). In addition, regional drug availability, economic considerations and clinical practice patterns can impact on criteria selection. Research to validate the several newer criteria in various practice settings and to explore the effect of adhering to the guidelines on patient outcomes is warranted. Data from such research will aid practitioners in identifying preferred criteria (Levy 2010).

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, for example a population of quite healthy 70-year-old people may respond differently to an intervention compared to very frail 92 year olds.

Establishing the reasons why not all interventions are accepted may be enlightening and support research into the development of universally successful interventions. There appears to be a ceiling (75% approximately) effect where inappropriate prescribing continues despite the evidence-base of interventions (Furniss 2000; Zermansky 2006). Use of qualitative methodology by interviewing prescribers may uncover reasons why they did not accept interventions (e.g. timing or appropriateness of the intervention provision or expertise of providers). There is additionally a need to explore and understand poor prescribing practice in order to know how to improve it and enhance patient safety through reducing the need for intervention.

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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: patient Follow-up: 1 month after intervention Duration: unclear Providers: pharmacists
Participants	Setting/patients: 80 participants (39 intervention and 41 control) patients 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 (control) Male sex: 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 patient's drug-related needs and ensuring continuity of care. Specifically, this involved the pharmacist reviewing the appropriateness of drug therapy and making recommendations for change, providing information about medications, their administration and their adverse effects Those randomised to the non-intervention group received usual care from other clinic staff
Outcomes	Patient outcomes were assessed by the research assistant pharmacist at baseline and follow-up using the MAI and the directive guidance scale Appropriateness of prescribing determined by pre- 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 patient chart was reviewed by a research assistant pharmacist blinded to the intervention and information required to assess the appropriateness of medications was abstracted. A summated MAI score was determined for each patient 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
Allocation concealment (selection bias)	Unclear risk	Insufficient information to judge yes/no

Bucci 2003 (*Continued*)

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 patient in intervention group had died at follow-up
Selective reporting (reporting bias)	Low risk	All outcomes reported
Baseline data?	Low risk	Baseline patient 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 the 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 10% dropout rate requires a sample size of 76 subjects

Crotty 2004a

Methods	Study design: RCT (cluster) Unit of allocation: 10 residential facilities Unit of analysis: patient Follow-up: 3 months Duration: 2 case conferences 6 to 12 weeks apart Providers: resident's GP, geriatrician, pharmacist, care home staff and Alzheimer's Society representative
Participants	Setting/patients: 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 (95% CI 81.3 to 85.9) (external control) Male sex: 44% (intervention), 43% (external control) Ethnicity: no information given
Interventions	A medication review was conducted prior to a multidisciplinary 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 conjunction with the care staff A half day training workshop examining the use of a toolkit in the management of challenging behaviours was provided to all facilities in the study including the control facilities
Outcomes	Medication appropriateness was assessed using the MAI. The change in MAI was reported. All residents had their medication charts reviewed pre- and postintervention 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 each resident 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 the 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 patient behaviours were stated as the objectives
Baseline data?	Low risk	Characteristics of residents at baseline were reported
Reliable Primary outcome measure	Low risk	The MAI has good to excellent reproducibility (kappa value = 0.59 to 0.83)

Crotty 2004a (*Continued*)

Protection against contamination	Low risk	No evidence of a carryover effect to other residents within the facilities
Power calculation	Low risk	An effect size of 0.9 in the MAI between the 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: patients Follow-up: at 8 weeks Duration: unclear Providers: transition coordinator pharmacist, nurses
Participants	Setting/patients: 110 (56 intervention and 54 control) eligible patients making first-time transition from a hospital to 1 of 85 long-term residential care facility in Southern Adelaide South Australia. Patients were eligible if they or their career gave consent and they had a life expectancy of > 1 month Focus on polypharmacy: the number of pre-admission 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 sex: 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 both the patients' family physicians and community pharmacists were faxed a medication transfer summary compiled by the transition pharmacist. After transfer, the transition pharmacist coordinated 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, community pharmacist and 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	

Risk of bias

Crotty 2004b (*Continued*)

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 patient medication charts and case notes
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 patients 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 there was no significant difference in the mean MAI
Reliable Primary outcome measure	Low risk	The validity of the MAI has been reported previously
Protection against contamination	High risk	The transition pharmacist also coordinated a case-conference involving him 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 use 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

Hanlon 1996

Methods	Study design: RCT Unit of allocation/analysis: patients Follow-up: 3 and 12 months after randomisation Duration: unclear Providers: geriatrician, clinical pharmacist, nurse
Participants	Setting/patients: 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 patients 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 (intervention), 69.9 ± 4.1 (control) Male sex: 98.1% (intervention), 100% (control) Ethnicity:% white 79 (intervention), 74.8 (control)
Interventions	The clinical pharmacist: monitored drug therapy outcomes by reviewing each patient's medical record and medication list, ascertained current medication use, identified drug-related problems by meeting with patients and carers and evaluated patients' 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 patient regarding drug-related problems and encouraged compliance In the control group the clinic nurse reviewed patients' current medications before the visit
Outcomes	Patient MAI scores were determined by summing MAI medication scores across evaluated medications HRQoL Patient medication compliance and knowledge were assessed by patient self-report Potential ADEs Patient satisfaction
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised to either the control or 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. The HRQoL was assessed by blinded interviewers

Hanlon 1996 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	36 patients were not interviewed. 5 in both 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 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	Previously MAI assessments made by a clinical pharmacist and a physician demonstrated excellent inter-rater (kappa value = 0.83) and intra-rater reliability (kappa value = 0.92)
Protection against contamination	High risk	There was potential for contamination since physicians had patients in both intervention and control groups
Power calculation	Low risk	100 subjects per group were required to obtain 80% power to detect an effect size of 0.4. 84 patients per group to obtain 80% power to detect an effect size of 0.5

Schmader 2004

Methods	Study design: RCT (2 x 2 factorial design) Unit of allocation/analysis: patient Follow-up: closeout telephone interviews 12 months after randomisation Duration: patients were followed for 12 months Provider: pharmacists/nurses/geriatrician/social worker
Participants	834 (430 intervention (inpatient), 404 control (inpatient)) patients who were 65 years old or more, 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 patient in the geriatric inpatient unit was 7.7 and 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 more (234 people in intervention group, 213 people in control group) % Male: 97% intervention, 98% control 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

Schmader 2004 (*Continued*)

	6 outpatient teams. For patients assigned to the GEM unit or clinic, team members implemented evaluation and management protocols Usual inpatient care was the customary medical or surgical treatment 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 Beers list at baseline and 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 patient'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	Patient characteristics at baseline were reported
Reliable Primary outcome measure	Unclear risk	The primary outcomes were related to adverse drug reactions which were assumed when the relation between an event and a drug was determined to be causally related. Disagreements on the item level were resolved by clinical consensus conference
Protection against contamination	Unclear risk	Insufficient information to permit judgement of yes/no

Schmader 2004 (*Continued*)

Power calculation	Low risk	376 subjects per group (total of 752 subjects) were required to obtain 80% power and a 95% confidence interval

Spinewine 2007

Methods	Study design: RCT Unit of allocation/analysis: patient Follow-up: 1 month, 3 months and 1 year Duration: from admission to discharge Provider: pharmacists
Participants	Setting/patients: 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 the mean (± SD) number of prescribed drugs was 7.9 (± 3.5) for patients in the intervention group and 7.3 (± 3.3) for those in the control group Age (MEAN ± SD): 82.4 ± 6.9 intervention, 81.9 ± 6.2 control Female sex: 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 multidisciplinary rounds, had direct contact with patients and carers and had access to patient medical records. For every patient the pharmacist performed a medication history on admission and prepared a patient 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 from healthcare professionals about medications. At discharge the pharmacist provided written and oral information on treatment changes to the patient 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 discharge
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was alternate and stratified for age, number of prescribed medicines and identity of the resident in charge of the

Spinewine 2007 (*Continued*)

		patient. 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	Due to the nature of the project physicians were not blinded to group assignment however MAI, Beers, ACOVE and hospital admissions all carried out in a blinded manner
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 patients were transferred to another unit in both the control and intervention groups 5 patients died in each of the groups (10 people in total)
Selective reporting (reporting bias)	High risk	A secondary outcome "'medications taken"' was not reported
Baseline data?	Low risk	Baseline patient characteristics 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 patients
Power calculation	Low risk	90 patients per group were required to have 80% power to detect a 20% absolute improvement in ACOVE and Beers criteria. 28 patients 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: patients Follow-up: Follow-up was terminated after an inappropriate prescription had been initiated or discontinued Duration: 13 months Provider: physician

Tamblyn 2003 (*Continued*)

Participants	Setting/patients: 107 primary care physicians with at least 100 patients, 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 randomised. Patients were 66 years of age or older and 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 (intervention), 75.3 ± 6.2 (control) Female sex: 61.2% (intervention), 64.2% (control) Ethnicity: no information given
Interventions	Each physician was given a computer, printer, health record software and dial-up access to the internet. The software documented health problems and medication supplied. For each patient, trained personnel developed a health problem list, documented 26 health problems related to the 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)).The data were integrated into the patient's health record and categorised as having been prescribed by the study physician or by another physician. Alerts were instituted to identify the 159 clinically relevant prescribing problems in 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 by the physician in the chart. 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
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

Tamblyn 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of inappropriate scripts started per 1000 visits and the number of inappropriate scripts discontinued per 1000 visits were reported
Selective reporting (reporting bias)	Low risk	Results of outcomes specified in the methodology were all 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 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 given

Taylor 2003

Methods	Study design: RCT Unit of allocation/analysis: patient Follow-up: 12 months Duration: baseline until 12 months Provider: pharmacists
Participants	Setting/patients: 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 sex: 36.4% (intervention), 27.8% (control) Ethnicity: % white = 60.6% (intervention), 61.1% (control)
Interventions	Patients received usual medical care along with pharmacotherapeutic interventions by a pharmacist during regularly scheduled clinic visits, based on the principles of pharmaceutical care. A patient 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. The 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 the 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 patient education that included a brief review of the disease, important lifestyle modifications and basic drug information. Pharmacists monitored patients' responses to drugs and attempted to improve compliance by consolidating medication regimens, reducing dosage frequency, devising medication reminders and teaching patients techniques for using devices such as inhalers. In addition to this, a system was developed in which the patient, physician or nurse reported suspected problems with drug therapy. Patients, nurses and physicians were educated about the signs and symptoms of medication misadventures The control group received standard medical care.
Outcomes	The number of inappropriate prescriptions at baseline and at 12 months using the MAI The change in the 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 patients 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
Protection against contamination	High risk	Although patients were randomised, physicians were not because of the small number of physicians practising in the rural community

Taylor 2003 (*Continued*)

Power calculation	High risk	No power calculation given

Trygstad 2005

Methods	Study design: controlled before and after study Unit of allocation/analysis: patient Follow-up: 3 months March to June 2003 Duration: 6 months Providers: pharmacists
Participants	Setting/patients: 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 prior to the start of the study Age (mean ± SD): 77.57 ± 12.72 years Male sex: 24.98%
Interventions	An on-site drug profile review by pharmacists was completed. 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 the drugs for which a claim was paid in the 90 days prior to the 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 in 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 patients, 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	The comparison group consisted of patients in nursing homes not responding to the invitation for inclusion in phase 1 of the intervention

Trygstad 2005 (*Continued*)

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 sent to consultant pharmacists. However, it does not state if the patient 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 the 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	This is unclear as the authors stated that comparison group homes participated after 6 months
Power calculation	High risk	No power calculation given

Trygstad 2009

Methods	Study design: controlled before and after Unit of allocation/analysis: patient Follow-up: 3 months Duration: 3 months Providers: pharmacists
Participants	Setting/patients: 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 sex: 24.9%
Interventions	Prescription drug records of all North Carolina nursing facilities were retrieved from Medicaid claims databases for the period of 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. These were Beers drug alerts, Prescription Advantage List (PAL) alerts, Clinical Initiatives alerts, duration alerts for specific drugs and therapeutic duplication alerts. The alerts were generated retrospectively from claims data and provided to the consultant pharmacist for their retrospective reviews together with the residents' most recent drug claims profile. These profiles were comprehensive in nature and considered all drugs on a residents 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 patients, 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 if the consultant pharmacists worked in both the 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
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.

Trygstad 2009 (*Continued*)

Reliable Primary outcome measure	Low risk	Beers criteria
Protection against contamination	Unclear risk	It is not clear if the consultant pharmacists worked in both the 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
Atkin 1996	Outcome measure. No measure of appropriateness
Avorn 1992	Outcome measure. Appropriateness criteria not validated (expert opinion)
Bartlett 2008	Unsuitable study design. No measure of appropriateness
Bergkvist 2009	Unsuitable study design
Bloomfield 2005	Not polypharmacy focus. No measure of appropriateness
Bosma 2008	Unsuitable study design. Appropriateness criteria not validated (WinAP HighRisk Drugs)
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)

(*Continued*)

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
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
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
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 measure of appropriateness
Gislason 2007	Unsuitable study design. No measure of appropriateness
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

(*Continued*)

Hamilton 2007	Not polypharmacy focus. Participants too young. No measure of appropriateness
Hobbs 2006	Unsuitable study design. No measure of appropriateness
Humphries 2007	Unsuitable study design. 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
Kjekshus 2005	Unsuitable study design. No measure of appropriateness
Kroenke 1990	Outcome measure. No measure of appropriateness
Kwan 2007	Outcome measure. No measure of appropriateness
Lalonde 2008	Outcome measure. No measure of appropriateness
Lapane 2007	Unsuitable study design. No measure of appropriateness
Laroche 2006	Unsuitable study design
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
Lipton 1992	Outcome measure. Appropriateness criteria not validated (expert opinion)
Lipton 1994	Outcome measure. No measure of appropriateness
Lourens 1994	Outcome measure. No measure of appropriateness

(*Continued*)

Mador 2004	Not polypharmacy focus. Appropriateness of psychoactive drugs only 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
Masoudi 2005	Unsuitable study design. No measure of appropriateness
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
Mistler 2009	Unsuitable study design. Appropriateness criteria not validated (medication-reduction algorithm)
Monane 1998	Unsuitable study design
Muir 2001	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
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
Pepine 1998	Unsuitable study design. No measure of appropriateness

(*Continued*)

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
Pool 2007	Not polypharmacy focus. No measure of appropriateness
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)
Roughead 2007	Unsuitable study design
Roughead 2007	Unsuitable study design. No measure of appropriateness
Saltvedt 2002	Outcome measure. No measure of appropriateness
Schmidt 2008	Not polypharmacy focus. No measure of appropriateness
Schrader 1996	Unsuitable study design. No measure of appropriateness
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

(*Continued*)

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
Terceros 2007	Unsuitable study design. No measure of appropriateness
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 ongoing studies *[ordered by study ID]*

Gladman

Trial name or title	Acute medical unit comprehensive geriatric assessment intervention study: a multicentre randomised interventional process of care trial (AMIGOS)
Methods	Multicentre randomised interventional process of care trial
Participants	Patient participants: attending and being discharged from the Acute Medical Unit (AMU) at Queen's Medical Centre, Nottingham or Leicester Royal Infirmary, Leicester; aged 70 years or over, either sex; identified as being at high risk of adverse outcomes using the Identification of Seniors At Risk (ISAR) score Carer participants: identified as carer of a patient participant; any carer present with the patient participant will be invited to be a carer participant for the study
Interventions	Comprehensive Geriatric Assessment: the participants will be allocated to the intervention or the control arm (usual care), using an internet-based randomisation procedure. Those allocated to usual care will go home as planned. Those allocated to the interface geriatrician will be reviewed by a geriatrician prior to being discharged. The geriatrician will reassess their clinical care, focussing on geriatric syndromes, such as polypharmacy (multiple medications)
Outcomes	Primary: number of days spent at home over 90 days of follow-up Secondary (at 90 days): death; institutionalisation; hospital use (emergency department, AMU admissions, clinics); personal activities of daily living (Barthel ADL Index); self reported falls over previous 90 days; medication audit against STOPP/START criteria at 90 days; psychological well-being (General Health Questionnaire [GHQ12]); Quality of life (EuroQoL EQ5D) and ICECAP; resource use; carer strain: Caregiver Strain Index; carer generic quality of life: EuroQol EQ5D; carer specific quality of life: CQLIR
Starting date	15 June 2010
Contact information	John Gladman Division of Rehabilitation and Ageing, Medical School, Queens Medical Centre, Derby Road, Nottingham. NG7 2UH, UK john.gladman@nottingham.ac.uk
Notes	

Rosenthal

Trial name or title	Randomized Controlled Trial of Enhanced Pharmacy Care in Older Veteran Outpatients
Methods	RCT. Patients were randomised to usual care or to the intervention
Participants	Older outpatients. Patients enrolled in Veterans Affairs primary care clinics who are 65 years and older and who are receiving prescriptions for 5 or more scheduled medications
Interventions	Behavioural intervention - enhanced pharmacy care The intervention included a structured medication history and medical records review. For intervention patients, therapeutic recommendations were developed and presented to primary care providers

Rosenthal (*Continued*)

Outcomes	Medication appropriateness No. of medications Cost of prescribed medicines between baseline and follow-up in both intervention and controls Baseline and 3-month measures obtained
Starting date	Unknown
Contact information	Gary E. Rosenthal, MD, Principal Investigator, VA Medical Center, Iowa City, Iowa, 52246-2208 USA
Notes	Clinical Trials.gov identifier: NCT00122122

Wei

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 Patients in the intervention group will receive pharmaceutical care delivered by clinical pharmacist, which including medication review, medication reconciliation, patient 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 medication (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)

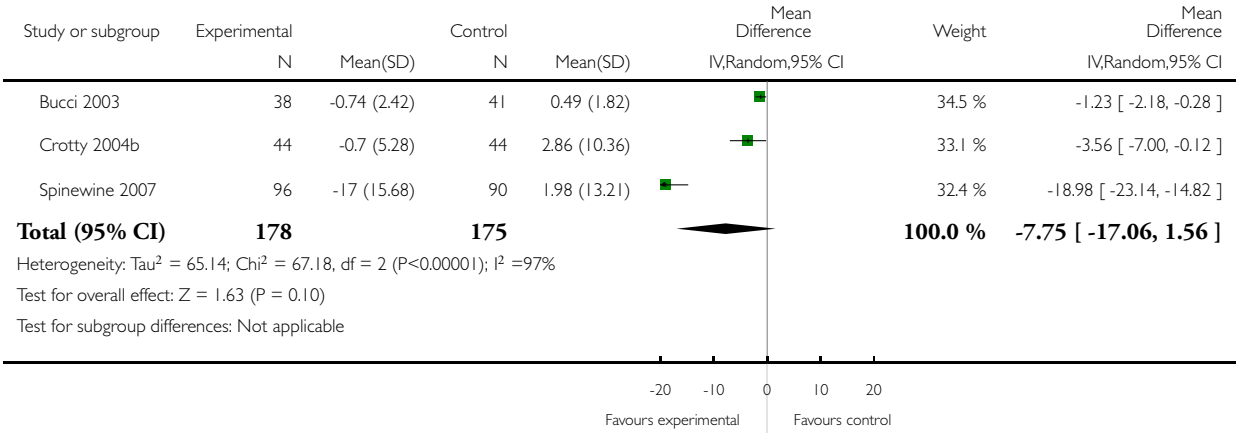
Test for subgroup differences: Not applicable

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)

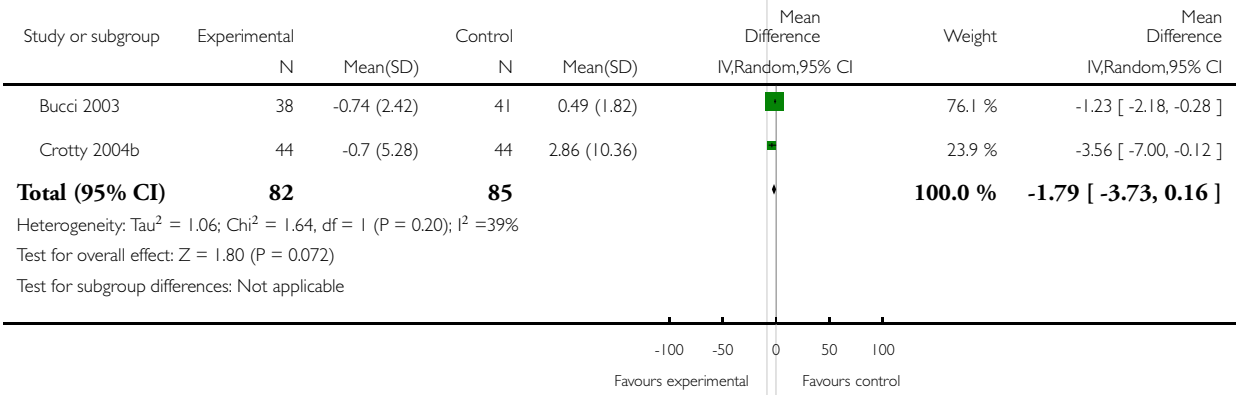


Analysis 1.3. Comparison 1 Postintervention analysis, Outcome 3 Change in MAI (excl Crotty 2004a and Spinewine 2007).

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

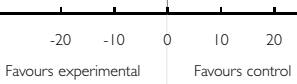
Outcome: 4 Summated MAI score

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

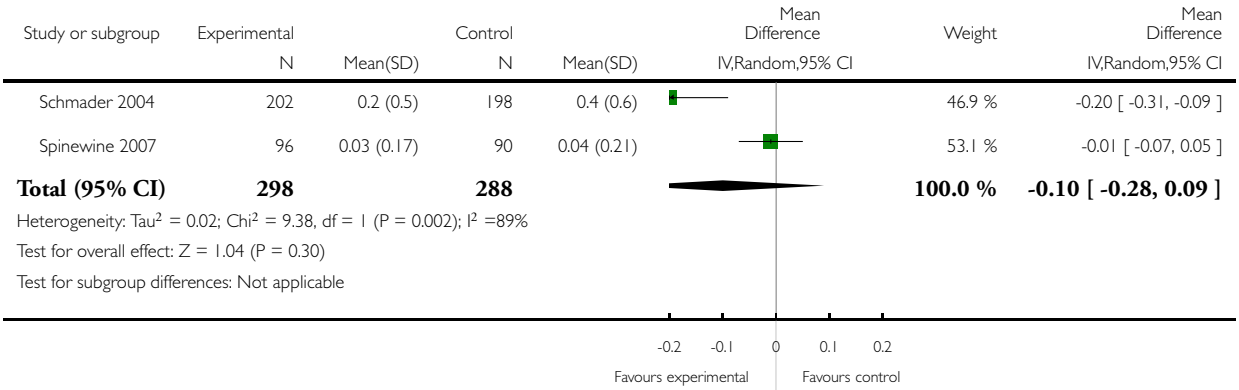


Analysis 1.5. Comparison 1 Postintervention analysis, Outcome 5 Number of Beers drugs per patient.

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

DK: Don't know

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

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 has 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	High

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

	narcotic drugs. Additionally, it is a mixed agonist and antagonist	
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 Ditropan XL	Most muscle relaxants and antispasmodic drugs are poorly tolerated by elderly patients, since these 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
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 as well as safer. Total daily doses should rarely exceed the suggested maximums	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

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

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	High
Digoxin (Lanoxin) (should not exceed 0. 125 mg/day 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 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
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 when treating 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

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

Ergot mesyloids (Hydergine) and cyclandelate (Cyclospasmol)	Have not been shown to be effective in the doses studied	Low
Ferrous sulphate > 325 mg/day	Doses > 325 mg/day 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 to 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, since a significant number have asymptomatic GI pathological conditions	High
Amphetamines and anorexic agents	These drugs have potential for causing dependence, hypertension, angina and myocardial infarction	High
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 exist	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

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

Orphenadrine (Norflex)	Causes more sedation and anticholinergic adverse effects than safer alternatives	High
Guanethidine (Ismelin)	May cause orthostatic hypotension. Safer alternatives exist	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 available	High
Doxazosin (Cardura)	Potential for hypotension, dry mouth and urinary problems	Low
Methyltestosterone (Android, Virilon and Testrad)	Potential for prostatic hypertrophy and cardiac problems.	High
Thioridazine (Mellaril)	Greater potential for CNS and extrapyramidal adverse effects	High
Mesoridazine (Serentil)	CNS and extrapyramidal adverse effects	High
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 available	High
Cimetidine (Tagamet)	CNS adverse effects including confusion	Low
Ethacrynic acid (Edecrin)	Potential for hypertension and fluid imbalances. Safer alternatives available	Low
Desiccated thyroid	Concerns about cardiac effects. Safer alternatives available	High
Amphetamines (excluding methylphenidate hydrochloride and anorexics)	CNS stimulant adverse effects	High

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

Oestrogens only (oral)	Evidence of the carcinogenic (breast and endometrial cancer) potential of these agents and lack of cardioprotective effect 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 amphetamines	May produce elevation of blood pressure secondary to sympathomimetic activity	High
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 an increased potential for bleeding.	High
Bladder outflow obstruction	Anticholinergics and antihistamines, gastrointestinal antispasmodics, muscle relaxants,	May decrease urinary flow, leading to urinary retention	High

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

	oxybutynin (Ditropan), flavoxate (Urispas), anticholinergics, antidepressants, decongestants and tolterodine (Detrol)		
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
Parkinsons disease	Metoclopramide (Reglan), conventional antipsychotics, and tacrine (Cognex)	Concern due to their antidopaminergic/ cholinergic effects	High
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

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

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-Blockers: propranolol	CNS adverse effects. May induce respiratory depression. May exacerbate or cause respiratory depression	High
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.

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 the proper use of a medication.
5. Practicality: capability of being used or being put into practice.
6. Drug-drug interaction: the effect that the 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 to other agents of equal efficacy and safety.

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

To assess the effect 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, in order 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. The Beers criteria are based on expert consensus developed through an extensive literature review with a bibliography and questionnaire evaluated by nationally recognised experts in geriatric care, clinical pharmacology and psychopharmacology using a modified Delphi technique to reach consensus. The criteria have been used to survey clinical medication use, analyse computerised administrative data sets and evaluate intervention studies to decrease medication problems in older adults.

The Beers criteria comprise two lists. The first list comprises 48 individual medications or classes of medications that should be avoided in older adults and their potential concerns (Table 2). The second list comprises 20 diseases or conditions and drugs that should be avoided in older adults with these conditions (Table 3). Sixty-six of these of these potentially inappropriate drugs were considered by the panel to have adverse outcomes of high severity.

Appendix 2. MEDLINE Strategy per Protocol

1. polypharmacy/ or polypharm$.ti,ab.
2. (beer$ adj1 criter$).ti,ab.
3. ((inappropriat$ or suboptim$ or sub-optim$ or unnecessary or incorrect$ or excess$ or multip$ or concurrent$) adj2 (medici$ or medicat$ or prescrib$ or prescription$ or drug$)).ti,ab.
4. ((over adj1 (prescrib$ or prescript$)) or (over-prescrib$ or overprescrib$)).ti,ab.
5. ((under adj1 prescrib$) or underprescrib$ or under-prescrib$).ti,ab.
6. "medication appropriateness index$".ti,ab.
7. (quality adj1 (prescribing or prescription$ or medication$)).ti,ab.
8. (improv$ adj1 (prescrib$ or pharmaco$ or prescription$)).ti,ab.
9. (Prescrib$ adj1 cascade$).ti,ab.
10. ("assessing care of vulnerable elders" or ACOVE).ti,ab.

11. (multi-drug$ or multidrug$).ti,ab.
12. medication errors/
13. or/1-12
14. exp Aged/ or Geriatrics/
15. (aged or elder$ or geriatric$).ti,ab.
16. (old$ adj (person$ or adult$ or people or patient$ or inpatient$ or outpatient$)).ti,ab.
17. Veterans/
18. veteran$.ti,ab.
19. or/14-18
20. randomized controlled trial.pt.
21. random$.ti,ab.
22. control$.ti,ab.
23. or/20-23
13 and 19 and 23 = 690 citations with no language or date restrictions [searched MEDLINE 1950 to 2008]

Appendix 3. MEDLINE & EMBASE 2009

Database: EMBASE, Ovid MEDLINE(R), Ovid MEDLINE(R) Daily Update [6 January, 2009]
Search Strategy: PolyPharm ML-EM v1.1

1 polypharmacy/ [ML] or polypharma$.ti,ab. (6018) [ML]
2 (beer$ adj1 criter$).ti,ab. (217)
3 ((inappropriat$ 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$)).ti,ab. (20167)
4 ((over adj1 (prescrib$ or prescript$)) or (over-prescrib$ or overprescrib$) or ("or more" adj (medication$ or prescrib$ or prescript$))).ti,ab. (1802)
5 ((under adj1 prescrib$) or underprescrib$ or under-prescrib$).ti,ab. (492)
6 "medication appropriateness index$".ti,ab. (74)
7 (quality adj1 (prescribing or prescription$ or medication$)).ti,ab. (379)
8 (improv$ adj1 (prescrib$ or pharmaco$ or prescription$)).ti,ab. (2435)
9 (Prescrib$ adj1 cascade$).ti,ab. (19)
10 ("assessing care of vulnerable elders" or ACOVE).ti,ab. (61)
11 ((multi-drug$ or multidrug$) adj2 (prescrib$ or prescription$ or regimen? or therap$ or treatment?)).ti,ab. (4318)
12 medication errors/ [ML] or Medication Error/ [EM] (10087)
13 or/1-12 (43833)
14 exp Aged/ [ML] or Geriatrics/ [ML] or aged/ [EM]or aged hospital patient/ [EM] or frail elderly/[EM] or very elderly/ [EM](2890948)
15 (elder$ or geriatric$).ti,ab. (299418)
16 ((old$ or aged) adj (person$ or adult$ or people or patient$ or inpatient$ or outpatient$)).ti,ab. (154581)
17 Veterans/ [ML] or Veteran/ [EM] (7691)
18 veteran$.ti,ab. (27912)
19 or/14-18 (3045064)
20 randomized controlled trial.pt. [ML] or "Randomized Controlled Trial"/ [EM Heading; maps to publication type in ML](437056)
21 random$.ti,ab. (898609)
22 controlled clinical trial.pt. [ML] or Controlled Study/ [EM heading] or "Controlled Clinical Trial"/ [ype in ML] (2900297)
23 or/20-22 (3633910)
24 humans/ (17361757)
25 animals/ (4440686)
26 24 not (24 and 25) (16257400)
27 13 and 19 and 23 and 26 **(2042) [ML/EM RCT RESULTS]**
28 systematic review$.ti,ab. or "systematic review"/ (52479)
29 meta-analysis.pt. [ML] or meta analysis/ [EM Heading; maps to publication type in ML] (54767)

30 (meta-analyls?s or metanalys?s or metaanalys?s).ti,ab. (2266)
31 or/28-30 (90063) [Systematic Review Filter]
32 13 and 19 and 26 and 31 (116) [Systematic Reviews]
33 "interrupted time series".ti,ab. or Cluster analysis/ [ML] or (cluster$ adj (analys$ or design$ or study or studies)).ti,ab. (41448)
34 ("quasi-experiment$" or "quasi-random$").ti,ab. or quasi experimental study/ [EM heading; does not map in Medline] or pretest posttest control group design/ [EM](7533)
35 (before adj1 after adj2 (study or studies or trial? or design?)).ti,ab. (1369)
36 (intervention? or evaluat$).ti. (618897)
37 or/33-36 (666241) [Non-RCT Study Terms used as Filter]
38 13 and 19 and 37 and 26 **(365) [ML/EM Non-RCT RESULTS]**
39 Practice guideline.pt. [ML](13214)
40 guideline?.ti. (60199)
41 (consensus develop$ or ((position or consensus) adj1 (statement? or development))).ti. (4878)
42 practice guideline/ or clinical pathway/ or clinical protocol/ or consensus development/ or evidence based medicine/ (234533)
43 or/39-42 (273384) [Guidelines etc. used as filter]
44 13 and 19 and 26 and 43 (516) [Guideline Results]
45 27 or 38 (2262) [RCT & Non-RCT Results]
46 remove duplicates from 45 (1848) [Net Trial Results]
47 remove duplicates from 44 (470) [Net Guideline/Consensus/EBM Results]
48 remove duplicates from 32 (98) [Net SR Results]

Appendix 4. AARP AgeLine 2009

Database: AARP AgeLine, OVID <1978 to December 2008> [6 January, 2009]

1 polypharm$.ti,ab,de,id. (275)
2 "beer$ criteria".ti,ab,de,id. (20)
3 ((inappropriat$ or suboptim$ or sub-optim$ or unnecessary or incorrect$ or excess$ or multip$ or concurrent$ or inadvert$) adj (medici$ or medicat$ or prescrib$ or prescription$ or drug$)).ti,ab. (251)
4 overprescrib$.ti,ab. (17)
5 underprescrib$.ti,ab. (3)
6 "medication appropriateness index$".ti,ab. (6)
7 (quality adj (prescribing or prescription$ or medication$)).ti,ab. (11)
8 (improv$ adj (prescrib$ or pharmaco$ or prescription$)).ti,ab. (18)
9 Prescrib$ cascade$.ti,ab. (1)
10 ("assessing care of vulnerable elders" or ACOVE).ti,ab. (10)
11 (multidrug$ adj (prescrib$ or prescription$ or regimen? or therap$ or treatment?)).ti,ab. (1)
12 Medication error$.de. (206)
13 or/1-12 (624)
14 "Randomized-Controlled-Trials".de. (793)
15 random$.ti,ab. (4396)
16 ("cluster$ analys$" or "cluster$ design$" or "cluster$ studies" or "cluster study").ti,ab. (132)
17 (before adj2 after).ti,ab. (0)
18 (intervention? or evaluat$).ti. (2506)
19 interrupted time series.ti,ab. (17)
20 ((pretest or posttest) adj1 control$).ti,ab. (22)
21 ("quasi-experiment$" or "quasi-random$" or quasiexperiment$ or quasirandom$).ti,ab. (119)
22 or/14-21 (6751)
23 journal$.pt. (68517)
24 13 and 22 and 23 (54)

Appendix 5. Cochrane Central Register of Controlled Trials via EBM 2009 Reviews Collection, OVID 2009

Database: All EBM Reviews - Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED (January 2009)
15 polypharm$.ti,ab,kf,hw,kw,sh. (135)
16 (overprescrib$ or underprescrib$).ti,ab. (9)
17 ((inappropriat$ 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$)).ti,ab. (751)
18 or/15-17 (884) [Polypharmacy]
19 aged$.sh. (113270)
20 "middle aged".sh. (174665)
21 19 not 20 (12907)
22 ((old$ or aged) adj (person$ or adult$ or people or patient$ or inpatient$ or outpatient$)).ti,ab. (4226)
23 "frail elderly".sh. (339)
24 elderly.ti,ab. (9991)
25 or/21-24 (21895) [Aged]
26 18 and 25 (102) [Polypharmacy and Aged]

Appendix 6. PsycINFO 2009

PsycINFO, OVID run 1 June 2009
1 polypharmacy/ or polypharma$.ti,ab.
2 (beer$ adj1 criter$).ti,ab.
3 ((inappropriat$ 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$)).ti,ab.
4 ((over adj1 (prescrib$ or prescript$)) or (over-prescrib$ or overprescrib$) or ("or more" adj (medication$ or prescrib$ or prescript$))).ti,ab.
5 ((under adj1 prescrib$) or underprescrib$ or under-prescrib$).ti,ab.
6 "medication appropriateness index$".ti,ab.
7 (quality adj1 (prescribing or prescription$ or medication$)).ti,ab.
8 (improv$ adj1 (prescrib$ or pharmaco$ or prescription$)).ti,ab.
9 (Prescrib$ adj1 cascade$).ti,ab.
10 ("assessing care of vulnerable elders" or ACOVE).ti,ab.
11 ((multi-drug$ or multidrug$) adj2 (prescrib$ or prescription$ or regimen? or therap$ or treatment?)).ti,ab.
12 or/1-11
13 geriatric patients/
14 (elder$ or geriatric$).ti,ab.
15 geriatric$.sh.
16 ((old$ or aged) adj (person$ or adult$ or people or patient$ or inpatient$ or outpatient$)).ti,ab.
17 Military veterans/
18 veteran$.ti,ab.
19 or/13-14,16-18
20 or/13-18
21 random$.ti,ab.
22 (control$ adj2 (group$ or study or studies or trial?)).ti,ab.
23 "interrupted time series".ti,ab.
24 (cluster$ adj (analys$ or design$ or study or studies)).ti,ab.
25 ("quasi-experiment$" or "quasi-random$").ti,ab.
26 ((pretest or posttest) adj2 (control or group or design? or study or studies)).ti,ab.
27 (before adj1 after adj2 (study or studies or trial? or design?)).ti,ab.
28 (intervention? or evaluat$).ti.
29 or/21-28 [52 unique citations were identified after deduping in OVID against MEDLINE, EMBASE, and AARP results]

Appendix 7. CINAHL 2009

	Search Date: [Monday, 4 May 2009 1:11:04 PM]	
#	Query	Results
1	TI polypharm* or AB polypharm* or MW polypharm*	1088
2	TI "beer* criter*" or AB "beer* criter*" or MW "beer* criter*"	51
3	TI ("inappropriat* medicat*" or "medication appropriateness") or AB ("inappropriat* medicat*" or "medication appropriateness") or MW ("inappropriat* medicat*" or "medication appropriateness")	133
4	TI "inappropriat* prescri*" or "suboptim* prescri"	46
5	TI ("inappropriat* prescri*" or "suboptim* prescri") or AB ("inappropriat* prescri*" or "suboptim* prescri")	144
6	TI ("sub-optim* prescri*" or "unnecessar* prescri*") or AB ("sub-optim* prescri*" or "unnecessar* prescri*")	20
7	TI ("incorrect* prescri*" or "excess* prescri*" or "multip* prescri*") or AB ("incorrect* prescri*" or "excess* prescri*" or "multip* prescri*")	39
8	TI ("concurrent* prescri*" or "inadvert* prescri*" or "inappropriat* medicat*") or AB ("concurrent* prescri*" or "inadvert* prescri*" or "inappropriat* medicat*")	122
9	TI ("suboptim* medicat*" or "sub-optim* medicat*" or "unnecessar* medicat*") or AB ("suboptim* medicat*" or "sub-optim* medicat*" or "unnecessar* medicat*")	29
10	TI ("incorrect* prescri*" or "incorrect* medicat*" or "suboptim* medicat*") or AB ("incorrect* prescri*" or "incorrect* medicat*" or "suboptim* medicat*")	30
11	TI ("inappropriat* drug*" or "suboptim* drug*" or "sub-optim* drug*") or AB ("inappropriat* drug*" or "suboptim* drug*" or "sub-optim* drug*")	83
12	TI ("unnecessar* drug*" or "incorrect* drug*" or "multip* drug*" or "concurrent* drug*" or "inadvert* drug*") or AB ("unnecessar* drug*" or "incorrect* drug*" or "multip* drug*" or "concurrent* drug*" or "inadvert* drug*")	283

(*Continued*)

13	TI (underprescrib* or "over prescrib*") or AB (underprescrib* or "over prescrib*")	73
14	TI "quality prescrib*" or AB "quality prescrib*"	2
15	TI "prescrib* quality" or AB "prescrib* quality"	14
16	TI ("improv* prescrib*" or "prescri* improv*") or AB ("improv* prescrib*" or "prescri* improv*")	67
17	TI acove or AB acove	6
18	TI "Assessing Care of Vulnerable Elders" or AB "Assessing Care of Vulnerable Elders"	14
19	TI ("multidrug* prescri*" or "multidrug* regime*" or "multidrug* therap*" or "multidrug* treatment*") or AB ("multidrug* prescri*" or "multidrug* regime*" or "multidrug* therap*" or "multidrug* treatment*")	73
20	TI ("multi-drug* prescri*" or "multi-drug* regime*" or "multi-drug* therap*" or "multi-drug* treatment*") or AB ("multi-drug* prescri*" or "multi-drug* regime*" or "multi-drug* therap*" or "multi-drug* treatment*")	11
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	1926
22	(MH "Aged+") or (MH "Aged, 80 and Over")	203625
23	(MH "Aged, Hospitalized")	1343
24	MH frail elderly	1829
25	TI (elderly or elder or "aged adult*" or geriatric*) or AB (elderly or elder or "aged adult*" or geriatric*) or MW (elderly or elder or "aged adult*" or geriatric*)	45329
26	TI ("old* adult*" or "old* person*" or "old* inpatient*" or "old* patient*" or "old* outpatient*" or "old* people") or AB ("old* adult*" or "old* person*" or "old* inpatient*" or "old* patient*" or "old* outpatient*" or "old* people") or TI ("elder* adult*" or "elder* person*" or "elder* inpatient*" or "elder* patient*" or "elder* outpatient*" or "elder* people") or AB ("elder* adult*" or "elder* person*" or "elder* inpatient*" or "elder* patient*" or "elder* outpatient*" or "elder* people")	31692
27	TI veteran* or AB veteran* or MW veteran*	7090

(*Continued*)

28	TI "medication error*" or AB "medication error*"	1809
29	(MH "Medication Errors")	5768
30	28 or 29	6011
31	22 or 23 or 24 or 25 or 26 or 27	220382
32	21 and 31	1022
33	21 and 31	394
34	21 or 30	7758
35	31 and 34	614
36	(31 and 34) and (33 or 35)	513

Appendix 8. MEDLINE and EMBASE (revised) 2010

EMBASE, Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) (Friday, 21 May 2010 00:17:01 GMT)

1 polypharmacy/ or polypharma$.ti,ab. (6692)
2 ((beer$ or shan? or mcleod?) adj3 criter$).ti,ab. (293)
3 ((concomitant$ 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$)).ti,ab. (25978)
4 ((over adj1 (prescrib$ or prescript$)) or (over-prescrib$ or overprescrib$) or ("or more" adj (medication$ or prescrib$ or prescript$))).ti,ab. (1899)
5 ((under adj1 prescrib$) or underprescrib$ or under-prescrib$).ti,ab. (493)
6 "medication appropriateness index$".ti,ab. (77)
7 (quality adj2 (prescribing or prescription$ or medication$)).ti,ab. (1133)
8 (improv$ adj2 (prescrib$ or pharmaco$ or prescription$)).ti,ab. (5406)
9 (Prescrib$ adj cascade$).ti,ab. (25)
10 ("assessing care of vulnerable elders" or ACOVE).ti,ab. (63)
11 ((multi-drug$ or multidrug$) adj2 (prescrib$ or prescription$ or regimen? or therap$ or treatment?)).ti,ab. (4569)
12 Medication errors/ [ML] (11633)
13 medication error/ [EM] (11633)
14 or/1-12 [ML Med Errors] (55104)
15 or/1-11,13 [EM Med Errors] (55104)
16 aged/ or frail elderly/ or very elderly/ or aged hospital patient/ [EM] (2996354)
17 exp Aged/ or Geriatrics/ [ML] (3025195)
18 (elder$ or geriatric$).ti,ab. (290024)
19 ((old$ or aged) adj (person$ or adult$ or people or patient$ or inpatient$ or outpatient$)).ti,ab. (147468)
20 Veteran/ [EM] (8332)
21 Veterans/ [ML] (8332)
22 veteran$.ti,ab. (27822)
23 or/16,18-20,22 [EM Aged] (3141205)
24 or/17-19,21-22 [ML Aged] (3163848)
25 -39 Deleted lines; not used

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. (1092914)
41 exp animals/ not humans.sh. (3522468)
42 40 not 41 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing] (1041587)
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$).tw. (1500575)
44 randomized controlled trial/ or crossover-procedure/ or double-blind procedure/ or single-blind procedure/ [EM] (505385)
45 or/43-44 [EM RCT per Cochrane 6.3.2.2] (1593955)
46 (random$ or placebo$ or double-blind$).tw. [EM RCT Wong J Med Libr Assoc 94(1) January 2006] (1077137)
47 14 and 24 and 42 (1643)
48 from 47 keep 646-1643 [MEDLINE Results RCT Filter 1950-] (998)
49 from 48 keep 1-998 (998)
50 (14 and 24 and 38) not 48 [PolyAge EPOC] (2981)
51 from 50 keep 1642-2891 [MEDLINE Results EPOC Filter 1950-] (1250)
52 15 and 23 and 45 (2030)
53 from 52 keep 1-941 (941) [EMBASE results before filters]
54 53 not (42 or 38) (226) [this line excludes results from Medline filters; will revisit in update searches to ascertain advisability of this exclusion]
55 from 54 keep 1-226 (226) [EMBASE RCT Results, 1980-]

Appendix 9. Cochrane Central Register of Controlled Trials (Wiley) 2010

ID	Search	Hits
#1	(polypharm*)	218
#2	("assessing care of vulnerable elders" or ACOVE)	7
#3	("beers criteria" or "beer's criteria")	10
#4	(#1 OR #2 OR #3)	230
#5	(overprescrib* or underprescrib*):ti,ab,kw	10
#6	((inappropriat* or suboptim* or sub-optim* or unnecessary or incorrect* or excess* or multip* or concurrent* or inadvert*) NEAR/2 (medici* or medicat* or prescrib* or prescription* or drug*)):ti,ab,kw	1794
#7	(overprescrip* or underprescrip*):ti,ab,kw	6
#8	((over NEAR/1 (prescrib* or prescript*)) or (over-prescrib* or overprescrib*) or ("or more" NEXT (medication* or prescrib* or prescript*))):ti,ab,kw	98

(*Continued*)

#9	((under NEAR/1 prescrib*) or underprescrib* or under-prescrib*):ti,ab,kw	12
#10	"medication appropriateness index*":ti,ab,kw	14
#11	(quality NEAR/1 (prescribing or prescription* or medication*)):ti,ab,kw	27
#12	(Prescrib* NEAR/1 cascade*):ti,ab,kw	0
#13	((multi-drug* or multidrug*) NEAR/2 (prescrib* or prescription* or regimen or regimens or regiment or therap* or treatment or treatments)):ti,ab,kw	265
#14	(improv* NEAR/1 (prescrib* or pharmaco* or prescription*)):ti,ab,kw	122
#15	(#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	2265
#16	MeSH descriptor Aged explode all trees	1277
#17	MeSH descriptor Geriatrics, this term only	174
#18	((old* or aged) NEXT (person* or adult* or people or patient* or inpatient* or outpatient*)):ti,ab	5817
#19	elderly:ti,ab	11641
#20	geriatric*:ti,ab	2065
#21	MeSH descriptor Veterans, this term only	368
#22	veteran*:ti,ab	1672
#23	(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)	20286
#24	(#4 OR (#15 AND #23))	367
#25	(#24), from 1800 to 2008	213
#26	(#24), in 2009	19
#27	(#24), in 2010	17

Appendix 10. 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. ANN PHARMACOTHER 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..

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 5, 2012

CONTRIBUTIONS OF AUTHORS

S Patterson (SP) prepared the protocol under the direction of C Hughes (CH), N Kerse (NK) and C Cardwell (CC). SP, MB and CH are pharmacists, NK is a GP and experienced researcher with an interest in geriatric medicine and CC is a biomedical statistician. MB, CH, NK and CC have been involved in systematic reviews in other areas. SP undertook the database searches and reviewed the literature identified. CH, MB and NK 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 for 2 years, 2 days per week.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

INDEX TERMS

Medical Subject Headings (MeSH)

*Medication Therapy Management; *Polypharmacy; *Quality Improvement; Drug Prescriptions [standards]; Drug Therapy [adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Humans