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Interventions to address potentially inappropriate prescribing in community-dwelling older people: a systematic review of randomised controlled trials

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Abstract

Objectives To perform a systematic review to determine the effectiveness of interventions designed to reduce potentially inappropriate prescribing (PIP) in community-dwelling older people.

Design Systematic review and narrative synthesis.

Setting Primary and community care.

Participants Community-dwelling older people.

Measurements

The primary outcome was change in PIP, as measured using either implicit or explicit tools. Studies were grouped into organisational, professional, financial, regulatory and multifaceted interventions.

Results

12 RCTs were identified with baseline PIP prevalence of 18% to 100%. Four out of six organisational interventions reported a reduction in PIP, particularly through pharmacists conducting medication reviews. The evidence for the effectiveness of multidisciplinary teams was weak. Both professional (i.e. targeting prescriber's directly) interventions were computerised clinical decision support interventions and were effective in decreasing newly prescribed PIP but not existing PIP. Three out of four multifaceted approaches were

effective in reducing PIP. The risk of bias was often high, particularly in reporting selection bias.

Conclusion Interventions including organisational (pharmacist interventions), professional (computerised clinical decision support systems) and multifaceted approaches appear beneficial in terms of reducing PIP. However, the range of effect sizes reported are modest and it is unclear if such interventions can result in clinically significant improvements in patient outcomes. Ongoing assessment of interventions to reduce PIP is needed in community-dwelling older people, particularly in relation to preventing PIP initiation.

Introduction

Older people are among the highest consumers of prescription medication and evidence suggests that prescribing in this population can be potentially inappropriate.[1] Potentially inappropriate prescribing (PIP) comprises a number of suboptimal prescribing practices including inappropriate dose or duration of medications, drug-drug interactions, drug-disease interactions and the use of medications that carry a significant risk of an adverse drug event (ADE).[1, 2] Older people are more likely to have multimorbidity and be taking a number of medications (polypharmacy) and consequently, are more vulnerable to medication errors, adverse events and PIP.

Several criteria have been developed to quantify the appropriateness of prescribing. These criteria can be categorised as either explicit (criterion-based) or implicit (judgement-based). Explicit criteria are specific statements of appropriateness that are generally drug or disease orientated and commonly focus on specific drugs to avoid.[1] The US Beers criteria are the most commonly used explicit criteria for measuring PIP,[3] and the European Screening Tool for Older Peoples Prescriptions (STOPP) criteria has become increasingly popular in recent years.[4] Implicit measures are based on clinical judgement. The most commonly used implicit criteria is the Medicines Appropriateness Index (MAI), which assesses the appropriateness of prescribing across 10 elements: indication, effectiveness, dose, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and cost.[5]

The scale of the PIP problem has been well documented in older patients using both explicit and implicit criteria, with the prevalence of PIP in community dwelling older patients

estimated to be anywhere between 20 and 50%.[6-8] PIP has been found to be associated with increased morbidity, ADEs, lower health related quality of life, hospitalisations and expenditure.[7, 9-11]

As global populations age, PIP in older people is an important public health concern, particularly in primary care where the majority of prescribing for older people takes place. A number of interventions have been developed and tested to reduce PIP across healthcare settings. Recent systematic reviews have examined the evidence on interventions to decrease PIP in nursing home settings.[12-15] These reviews have produced mixed results, and due to the heterogeneity of included studies, robust conclusions about the effectiveness of such intervention are lacking.[13-15] Where strategies were found to be effective within the hospital or nursing home setting, there is little evidence to suggest that these would be effective for community dwelling older patients. The aim of this systematic review is to identify and determine the effectiveness of interventions to reduce PIP in community dwelling older people.

Methods

The PRISMA guidelines for the conduct and reporting of systematic reviews and meta-analyses were adhered to in the conduct of this systematic review.[16]

Data sources and search strategy

A literature search was performed including PubMed, Embase, Scopus and the Cochrane library databases (including the Central Register of Controlled Trials, Database of Systematic Reviews and Database of Abstracts of Reviews of Effect) in June 2014 (updated January 2015) using combinations of key words and MeSH terms (Figure 1). No language or date restrictions were applied. Hand searches of the references of retrieved full-text articles supplemented this search.

Study selection and data extraction

Studies were included if they met the following inclusion criteria:

1. Included community dwelling older adults (≥65 years or had an average age of ≥65 years) as the population of interest. Studies where >20% of the subject population were described as institutionalised (e.g. nursing homes, residential care homes or geriatric inpatients) were excluded.
2. An intervention intended to improve PIP in primary care, including but not restricted to: organisational, professional, financial, regulatory or multifaceted interventions compared to usual care or alternate intervention (see Table 1 for definitions).

3. The primary outcome was change in PIP measured using specified implicit or explicit tools (e.g. Beers, STOPP, MAI). Studies that focussed on the reduction of inappropriate prescribing in one drug class only were also excluded.
4. Study design was randomised controlled trials (RCT) only.

No language restrictions were applied. Studies were assessed against the inclusion criteria by three reviewers (AQ, CH, CF) by reading titles and/or abstracts. Eligible studies were read fully in duplicate and their suitability for inclusion was independently determined (RG, BC). Disagreement was managed by consensus. Data were extracted on study characteristics (setting, duration, outcome etc.) and participant demographics (age, gender etc.). Where available, data on secondary outcomes such as patient reported health status (e.g. psychosocial outcomes: quality of life, psychological health: well-being, physical health: adverse drug events), health behaviour (e.g. medication compliance) and resource use (e.g. health service utilisation, costs) were extracted.

Data synthesis

The studies identified were too heterogeneous in terms of their outcome measures and intervention types to conduct a meta-analysis so a narrative summary was performed. Where appropriate, crude odds ratios and absolute risk reductions (ARR) were calculated. Interventions were categorised by the standard taxonomy of interventions developed by The Cochrane Effective Practice and Organization of Care Group (EPOC) including organisational, professional, financial and regulatory interventions, with the addition of multifaceted interventions (Table 1)**.** [17]

Ongoing studies

Where published protocols were identified during the search, study authors were contacted to ascertain if results were available for inclusion in the review. Where results were not available, ongoing studies were described in terms of methods, intervention used and outcome measures, together with an estimate of the reporting date, where available (Appendix 1).

Assessment of risk of bias

Three authors (BC, CH, AQ) independently assessed risk of bias using the Cochrane Collaboration's risk of bias tool including the standard domains of sequence generation, allocation concealment, blinding, outcome data, selective outcome reporting, protection against contamination, performance of baseline measurement and sample size. In cases of disagreement, a fourth reviewer (RG) was consulted. Some of the review authors were involved in the conduct of an RCT included in this review (the OPTI-SCRIPT study). The data extraction and methodological quality assessment was conducted independently by a researcher not involved in the review team (LM).

Results

Included studies

749 unique records were screened, and 30 full texts were reviewed. 11 RCTs met the inclusion criteria (Figure 1). Two studies were identified from conference abstracts/published protocols, one of which the review authors were involved in so study information was available, bringing the total of included studies to 12. The study author was contacted for details on the second protocol identified (Appendix 1).

Study description

Six studies were conducted in North America,[18-23] five in Europe,[24-28] and one in New Zealand.[29] The mean age of the 156,529 included patients ranged from 65 to 81 years (Table 2). Participants were eligible if they were community dwelling in all studies, had polypharmacy (defined as ≥3 or ≥5 drugs) in five studies[18, 19, 24, 25, 29] and were at high risk for medication-related adverse events in one study.[23] Included studies consisted of five patient randomised designs with sample sizes ranging from 81 to 59,860,[18-20, 23, 26] and seven cluster studies with 13 to 107 clusters randomised.[21, 22, 24, 25, 27-29] All but three studies compared the intervention to usual care (Table 2).[21, 25, 27] Three studies made reference to intervention design, [20, 27, 28] with one study publishing the intervention design and pilot process separately, referencing a specific theoretical framework for the intervention design.[28, 30] Process evaluations to explore intervention implementation and enactment were conducted in three studies. [18, 19, 28] All studies were funded by government bodies, university departments or professional bodies.

PIP measurement

Baseline PIP prevalence ranged from 18% to 100%. PIP was measured using implicit criteria in four studies and eight studies used explicit criteria. The MAI was the only implicit measure used. Three studies used a summated MAI score [19, 24, 29] and one reported the MAI score in terms of number of prescriptions with inappropriate medications.[23] Of the eight studies using explicit criteria, one used the Beers criteria 1997 iteration,[21] and one the 2003 iteration.[26] The McLeod criteria was used in one study.[22] The remaining five studies used combinations of existing criteria or study specific criteria.[18, 20, 25, 27, 28]

Risk of bias

Studies were heterogeneous with regard to risk of bias (Figure 2).

Detection, attrition and reporting bias were low in most studies. Randomisation, allocation concealment, and blinding were less reliably implemented or reported. Seven cluster designs ensured no contamination of control patients. [21, 22, 24, 25, 27-29] Protection against contamination was unclear in three patient randomised studies, [18, 20, 26] with one study finding it introduced no impact on the outcome.[18] All cluster RCTs had accounted for clustering so there were no unit of analysis errors.[21, 22, 24, 25, 27, 29] One RCT presented descriptive analysis only.[26] Half of the included studies reported an adequate sample size to detect a difference between groups.[18-20, 25, 27, 28]

Effects on medication appropriateness by intervention category

All studies could be divided into organisational (n=6), professional (n=2) or multifaceted interventions (n= 4) (Table 2). No study involved financial or regulatory interventions.

Organisational interventions

The six organisational studies included four pharmacist interventions, [19, 23, 25, 29] and two multidisciplinary teams (MDT) approaches.[18, 26] Out of six studies, four reported a positive effect on PIP (Table 3).

In three out of four pharmacist intervention studies, a pharmacist conducted a medication review with the patient and provided feedback either in person or in writing to the family physician.[19, 23, 29] All three studies reported a significant improvement in PIP with a mean improvement of -3.9 to 0.37 in MAI scores[1] post intervention in favour of the intervention group (Table 3).[19, 23, 29] Bryant *et al* found this approach resulted in an improvement in mean MAI scores, however, this study had a very high withdrawal rate, retaining with only 39% of recruited pharmacists.[29] In the remaining pharmacist intervention, Denneboom *et al* found shared pharmaceutical care (a pharmacist and family physician developed a patient pharmaceutical care plan together) resulted in significantly more appropriate prescribing than written feedback at 6 months, but this effect was not sustained at 9 months.[25]

The remaining organisational interventions involved a MDT approach. [18, 26] Allard *et al* reported no significant decrease in PIP following a medication review case conference involving two physicians, a nurse and a pharmacist.[18] Lampela *et al* reported that comprehensive geriatric assessment by two physicians, two nurses and two physiotherapists significantly changed overall prescribing in older patients (unadjusted OR 1.9, 95% CI 1.3-2.8).[26] The appropriateness of those changes was analysed descriptively and although PIP

[1] The MAI assesses appropriateness of a given medication across 10 elements of prescribing quality: indication, effectiveness, dose, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration and cost. Each medication is allocated a score for each element, the scores are then added together to give a single summated MAI score.

reductions were noted, particularly the use of amitriptyline and diazepam, the significance of those reductions was not reported.[26]

Professional interventions

Two studies were identified as professional interventions (i.e. targeting prescriber's directly). Both were computerised clinical decision support systems (CDSS) interventions which were effective (Table 3). Support was implemented at either the point of prescribing [22] or at the pharmacy level.[20] In both cases, CDSS was found to be effective in reducing new PIP.[20, 22] Raebel *et al* reported a 16% relative risk reduction and this effect was largely attributable to reductions in dispensings amitriptyline.[20] Tamblyn *et al* also demonstrated a significant reduction in patients receiving new PIP (relative risk 0.82, 95% CI 0.69 - 0.98), however, no effect on the discontinuation of existing PIP was noted.[22]

Multifaceted interventions

Four multifaceted (combining two or more techniques) interventions were identified.[21, 24, 27, 28] Rognstad *et al* found peer academic detailing with audit and feedback to be effective in reducing PIP (10.3%, 95% CI 5.9 -15.0 reduction relative to baseline).[27] The largest reductions were seen for drugs such as tricyclic antidepressants (TCAs) and 'old' antihistamines.[27] The OPTI-SCRIPT study also found that PIP was reduced by academic detailing, medicines review with web-based pharmaceutical treatment algorithms that provided alternative treatment options, and tailored patient information leaflets, particularly in the appropriate prescribing of proton pump inhibitor (adjusted OR 0.3, 95% CI 0.1 - 0.7).[28] In a population where drug-specific alerts were in operation, Simon *et al* analysed the effect of age-specific computerised alerts alone, and in combination with

intensive academic detailing.[21] They found that age-specific alerts resulted in a continuation of the effects of drug-specific alerts. Group academic detailing did not enhance the effect of the alerts. Using implicit criteria, Bregnhoj *et al* found a combined educational meeting with prescribing feedback resulted in a mean overall MAI change of -5. [24]

Effects on secondary outcomes: patient health status and behaviour

Three pharmacist interventions studies involving medication review, found no significant benefit on the psychosocial outcome of patient quality of life (SF-36).[19, 23, 29] In the only study powered to detect a difference, Bryant *et al* noted a significant decrease in the SF-36 domains of emotional role and social functioning in the intervention group which they attributed to the high withdrawal rate of pharmacists in the study leaving patients feeling abandoned.[29] One multifaceted intervention had no significant effect on patient psychological health in terms of well-being (WBQ-12). Pharmacist interventions had no significant impact on the physical health outcome of ADEs in one study. [19]

In terms of patient behaviour, one multifaceted intervention had no significant effect on beliefs about medication necessity.[28] One of two pharmacist intervention studies reported a significant improvement in medication compliance [19, 23].

Effects on secondary outcomes: health service utilisation and resource use (costs)

Health service utilisation was assessed in two studies, [23, 28] with one reporting a reduction in hospitalisations but not emergency department visits.[23] The data analysis is ongoing in the second study.[28] Two studies conducted economic evaluations. Denneboom *et al* found that

both shared pharmaceutical care and written feedback showed modest savings regarding medication costs but this was not statistically significant.[25] The data analysis is ongoing in the second study.[28]

Process evaluations

Of three process evaluations conducted, two incorporated quantitative and qualitative data.[19, 28] All studies assessed intervention implementation [18, 19, 28] with one study finding that two of the three components of a multifaceted intervention were utilised. Physicians were receptive to the intervention in two studies. [19, 28]

Discussion

This systematic review identified 12 RCTs of interventions to reduce PIP in community dwelling older people. There was considerable variation in the types of interventions with small numbers of studies grouped together. Overall, four out of six organisational interventions reported an improvement in PIP, particularly through pharmacists conducting medication reviews. The evidence for the effectiveness of MDTs was weak. Both professional interventions were CDSS studies and were effective in decreasing new PIP but not existing PIP. Three out of four multifaceted approaches were effective in reducing PIP.

A variety of interventions can be effective in improving prescribing practice and medication safety, including CDSS, educational outreach and audit and feedback.[31-34] Consistent with these findings and previous reviews of PIP specific interventions in other healthcare settings, this review found various strategies may be useful in reducing PIP.[1, 12, 15, 35] This would suggest that PIP is amenable to change, however, there was a range of modest effect sizes. Regardless of the explicit criteria utilised, absolute risk reductions of less than 3% were common. The largest absolute risk reduction was 25% in a study where all participants had PIP at baseline.[28] There was evidence to suggest that certain drug classes responded better to certain interventional strategies as TCAs and 'old' antihistamines were reduced by multifaceted interventions,[27] and CDSS,[20] while appropriate prescribing of proton pump inhibitors improved with a multifaceted intervention.[28] In all studies, these drugs were the most frequently occurring in the patient population so a significant effect was arguably more likely to be found. Both CDSS studies were effective in decreasing the initiation of PIP, but not the discontinuation of existing PIP, while three pharmacist medication review studies were effective in increasing the appropriateness of current prescribing. It is unclear

if this reflects differences in the areas where the interventions can be effective, or differences in applying explicit or implicit criteria. Most studies using the MAI criteria reported an improvement in appropriateness across all ten elements. The largest overall decrease was a mean MAI change of 5 points. However, it is difficult to determine what the clinical importance of a change in MAI score is as it unclear what impact a reduction in score has on actual patient risk and outcomes such as quality of life or ADEs. A reduction in PIP, measured using implicit or explicit criteria, may not equate to a change in health outcomes.[35, 36]

Few studies examined the impact of interventions on patient outcomes or patient preferences, which may be of greater importance to patients overall. This may reflect the difficulty in selecting such outcomes as until the recent publication of the CONSORT guidelines on patient-reported outcomes in RCTs, guidance has been lacking.[37] Three studies that demonstrated an improvement in MAI scores using a pharmacist intervention did not report an effect on quality of life or ADEs.[19, 23, 29] While higher MAI scores have been found to be associated with ADEs,[38] there is little evidence to suggest that a decrease in MAI score equates to a decrease in adverse outcomes. It remains unclear if this is an effect of the studies being underpowered to detect differences in patient outcomes, the follow-up period being too short to detect a difference, or the outcome measures not being responsive to the intervention.

While various strategies may reduce PIP, little attention has been paid to understanding how or why interventions worked or failed. In order to develop feasible and appropriate interventions, they should be theoretically informed, modelled and pilot tested prior to RCT

implementation, and the long-term implementation evaluated.[39] This review has highlighted a deficit in intervention development and evaluation. Little detail on intervention development, underlying theoretical frameworks, and pilot studies was given, even in the more recent publications, a common issue in behaviour change interventions.[40, 41] Very few studies in this review conducted a process evaluation to gain insight into the intervention implementation. Such evaluations can also offer insights into how study findings can be generalised to other settings. In relation to multifaceted interventions, too few studies were identified to draw conclusions about which combinations of interventions may be most effective.

Strengths and weaknesses of this review

This review is timely as the prevalence of PIP remains high in community dwelling older people. However, there are some limitations. Potential limitations in the search strategy arise from the diversity in MeSH terms and key words used to describe interventions and PIP. Furthermore, publication bias is an important source of potential bias in systematic reviews. RCT designs were included in this review. While this may have resulted in the exclusion of other studies of interest, this criterion allowed for the inclusion of more robust evidence as nonrandomised studies frequently report larger treatment effects than randomised studies.[42] A broad definition of PIP was utilised and studies that focussed on the reduction of inappropriate prescribing in one drug class only were excluded. Due to the heterogeneity of the interventions and their outcome measures, a meta-analysis was not possible. Few studies conducted process evaluations or presented adequate detail which would allow for an analysis of the impact of contextual factors on intervention

effectiveness. Usual care can vary greatly across settings and few studies described it in great detail. Many studies were limited by potential bias, particularly in relation to selection bias, and only half of the studies had adequate sample size, undermining the robustness of the findings.

Implications for clinical practice and future research

A significant body of observational research has been published on PIP over the last number of years. There are at least 36 published tools available to assess inappropriate prescribing in older people. [43] Numerous individual studies have utilised these tools to establish the prevalence and outcomes of PIP across healthcare settings.[4, 10, 38] In primary care, Opondo *et al* identified 19 studies estimating PIP prevalence using drug-age criteria, excluded wider criteria (e.g. drug-disease criteria).[44] This may therefore be a conservative estimate. To improve the empirical knowledge in this field, greater emphasis on well-designed and rigorous RCTs of interventions to reduce PIP are necessary. Future research should provide detail on intervention design and evaluation processes to enable identification of elements of successful interventions.

Increased emphasis should be placed on the selection of appropriate outcome measures, particularly in terms of comparability across studies as considerable variation in the application of implicit and explicit measures was identified. Although the interventions reviewed here appear beneficial in terms of reducing PIP, the clinical impact this may have on patient outcomes such as ADEs and quality of life is not known. The link between improved medication appropriateness based on the criteria such as MAI or Beers criteria

and patient-related outcomes requires further investigation. Future research should consider involving patients to explore patient preference in relation to PIP and interventions to decrease it.

Future research should explore whether the differences in decreasing the initiation of PIP, as opposed to the discontinuation of existing PIP results from differences in the interventions, or differences in applying explicit or implicit criteria.

Conclusions

This review highlights various interventions including organisational (pharmacist interventions), professional (CDSSs) and multifaceted approaches appear beneficial in terms of reducing inappropriate prescribing. However, effects sizes are often small and it is unclear if such interventions can result in clinically significant improvements in patient outcomes.

Future research should place greater emphasis on intervention development and process evaluations to provide rigorous evaluations that will add to understanding how effective interventions can be sustained and ultimately translated into improvements in patient outcomes, particularly in relation to preventing the initiation of PIP drugs.

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Conflicts of interest:

BC, TF and SS were involved in the conduct of the OPTI-SCRIPT trial which is included in this review.

Author Contributions: Study concept and design: BC, RG, TF, SS. Literature search, data extraction, quality assessment: BC, CF, AQ, CH, RG. Data analysis: BC, RG, TF, SS. Preparation of manuscript: BC, AQ. Critical review of the manuscript: SS, TF, RG. Final approval of the version to be published: All authors.

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Graphics

Table 1 Taxonomy of interventions and studies included in this review

Intervention	Description	Included RCTs
Organisational interventions	**Involve a change in the structure of health care services or a change in how health care services are delivered.**	**Total = 6**
Multidisciplinary teams (MDT)	Creation of new team of providers of different disciplines or additions of new members to existing team.	2 (Allard,[18] Lampela[26])
Pharmacist interventions	An intervention delivered by a pharmacist or where a pharmacist is a member of the intervention team.	4 (Bryant,[29] Hanlon,[19] Taylor,[23] Denneboom[25])
Professional	**Target professionals themselves directly with a view to improving some aspect of practice.**	**Total = 2**
Computerised clinical decision support systems (CDSS)	Information systems to assist clinical decision making. Patient characteristic matched to knowledge base, software algorithms generate patient specific recommendations for clinician.	2 (Raebel,[20] Tamblyn[22])
Audit and feedback	Any summary of clinical performance of health care over a specified time period, given in a written, electronic or verbal format.	
Academic detailing	A personal visit by a trained person to a health professional in their own setting.	
Patient-mediated	1. New clinical information collected from patient & given to provider	

approach	2. Information provided to patients to change interaction with provider.	
Local consensus process	Inclusion of all providers in discussion to ensure agreement on importance and approach to chosen problem.	
Financial interventions	**Changes in reimbursement/payment mechanisms**	**Total = 0**
Provider orientated	Changes to the ways providers are reimbursed, incentivised and penalised.	
Patient orientated	Interventions include approaches such as the use of co-payments and user fees.	
Regulatory interventions	**Change to professional practice and patient outcomes through regulation or law.**	**Total = 0**
Multifaceted interventions	Combine a number of professional, organisational, financial or regulatory interventions within a single intervention: CDSS and academic detailing Education and feedback Academic detailing and audit and feedback Academic detailing, medicines review and patient information leaflets	**Total =** 4 Simon[21] Bregnhoj[24] Rognstad[27] Clyne[28]

Table 2 Characteristics of Studies

Author (Year, country)	Study Design	Study Duration	Number of Participants		Intervention Type and Comparison	Outcome Measures	Results
			Healthcare Professionals	*Patients*			
Organisational interventions							
Allard [18] (2001, Canada)	RCT	12 months	N/A	266 (≥75 years, ≥3 drugs) Intervention 136 Control 130 *Baseline PIP:* Intervention 56.7% Control 61.2%	**MDT:** Team of 2 physicians, 1 pharmacist and 1 nurse reviewed medications in a case conference, mailed feedback to family physician **Comparison:** Usual care (normal social and health care services)	**Primary:** Number of PIP drugs (Quebec consensus panel) **Secondary:** Number of drugs taken per day	**Primary:** No effect on decreasing PIP (adjusted OR 1.83, 95% CI 0.94 - 3.57) **Secondary:** Mean number of drugs per patient declined by 0.24 in intervention and 0.13 in control (P > 0.05)

Lampela[26] (2010, Finland)	RCT	12 months	N/A	781 (≥75 years) Intervention 404 Control 377 *Baseline PIP:* Intervention 21.4% Control 19.5%	**MDT:** Team of 2 physicians, 2 nurses and 2 physiotherapists performed a comprehensive geriatric assessment including medication review and clinical examination **Comparison:** Usual care	a) Medication changes b) Number of PIP drugs (Beers criteria 2003)	a) 83.7% of intervention patients had changes to regular medication compared to 72.8% in control (unadjusted OR 1.9, 95% CI 1.3-2.8) b) **Descriptive analysis of PIP** Number of PIP drugs decreased by 15.6% in intervention compared to 2.9% in control.

Bryant[29] (2011, New Zealand)	Cluster RCT	6 months	Pharmacists 26 GPs 63	498 (≥65 years, ≥5 drugs) Intervention 269 Control 229 *Baseline PIP:* Intervention mean MAI = 5.1 Control mean MAI = 4.5	**Pharmacist interventions:** Pharmacist conducted medication review, met with family physician to discuss recommendations **Comparison:** Usual care. After 6 months the control group received the intervention	**Primary:** a) Change in MAI score b) Quality of life (SF-36) **Secondary:** a) Change in overall medicine use b) Recommendations implemented	**Primary:** a) MAI score improved more in intervention (mean change -2.0) than in control (mean change -0.3; P = 0.003) b) Improvement in emotional role (13.4 unit difference, P = 0.024) and social functioning (7.7 unit difference, P = 0.019) for control. No effect on other domains. **Secondary:** a) More medication were started in the control group than the intervention group (P < 0.0001); more dosage reductions and medicine switches in the intervention group than the control group (P = 0.037). b) 46% of recommendations were implemented, 16% partially implemented

Hanlon[19] (1996, USA)	RCT	13 months	N/A	208 (≥65 years, ≥5 drugs) Intervention 105 Control 103 *Baseline PIP:* Intervention mean MAI = 17.7 Control mean MAI = 17.6	**Pharmacist interventions:** Pharmacist conducted medication review, written recommendations sent to family physician; patient counselling at each clinic visit **Comparison:** Usual care. Pharmacist reviewed prescribing and written recommendations were filed for review at study completion.	**Primary:** Change in MAI score **Secondary:** a) Quality of life (SF-36) b) ADEs c) Medication compliance	**Primary:** MAI score improved more in intervention (mean change -4.9) than in control (mean change -1.1; P<0.001) **Secondary:** a) No significant difference between groups in SF-36 change scores b) No significant difference between intervention and control in ADEs (30.2% V 40.0%, P=0.19) c) No significant difference between groups in medication compliance

Taylor[23] (2003, USA)	RCT	12 months	N/A	81 (≥18 years, mean age 65) Intervention 41 Control 40 *Baseline PIP:* Not reported	**Pharmacist interventions:** Pharmacist conducted medication review, provided family physician with recommendations and also provided patient education **Comparison:** Usual care	a) MAI (expressed as number of PIP drugs) b) Quality of life (SF-36) c) Health service utilisation d) Medication compliance e) Clinical outcomes	**a) Descriptive analysis of PIP** The % of inappropriate prescriptions decreased in all 10 MAI domains in intervention group and increased in five domains in the control group. **b)** No significant difference between groups in SF-36 **c)** Fewer hospitalisations (11 V 2, P=0.003) and ED visits (4 V 6, p=0.044) in intervention patients compared to control **d)** Medication compliance scores improved in the intervention group but not in the control group (p=0.115). **e)** Compared to control, intervention patients were

Denneboom[25] (2007, The Netherlands)	Cluster RCT	6, 9 months	Pharmacists 29 GPs 84	738 (≥75 years, ≥5 drugs) Pharmaceutical care 387 Written Feedback 351 *Baseline PIP:* Not reported	**Pharmacist interventions:** Shared pharmaceutical care, family physician and pharmacist developed pharmaceutical care plan for patient **Comparison:** Written-feedback group - pharmacists listed all recommendations per patient and delivered them to family physician	**Primary:** Number of medication changes following clinically relevant recommendations (own criteria based on existing published) **Secondary:** Costs	**Primary:** More clinically relevant medication changes made in pharmaceutical care plan group than feedback (42 vs 22 changes, P=0.02). This was still significant at 6 months (36 vs 19 changes, p=0.02) but not at 9 months (33 vs 19 p=0.07). **Secondary:** Both groups showed modest savings regarding medication costs but there was no statistically significant difference between groups
Professional interventions							

Raebel[20] (2007, USA)	RCT	12 months	N/A	59,860 (≥65 years) Intervention 29,840 Control 29,840 *Baseline PIP:* Not reported	**CDSS:** Age-specific alerts sent to pharmacists prior to dispensing when 1 of 11 PIMs prescribed; pharmacists phoned prescriber to suggest alternatives **Comparison:** Usual care - prescribing and dispensing per usual clinical practice	Number of PIP drugs dispensed across 11 indicators (Beers criteria, Zhan criteria)	1.8% of intervention versus 2.2% of control had newly dispensed PIP (P = 0.002). Dispensing rates differed between groups for amitriptyline (P<0.001; 37% RRR) and diazepam (P=0.02; 21% RRR)

Tamblyn[22] (2003, Canada)	Cluster RCT	13 months	107 Intervention 54 Control 53	12,560 (≥66 years) Intervention 6,284 Control 6,276 *Baseline PIP:* Intervention 31.8% Control 33.3%	**CDSS:** Point of prescribing age-specific alerts for 159 prescribing problems, including drug-disease interactions, drug-drug interactions, drug-age interactions, and drug duplication **Comparison:** Usual care	Initiation and discontinuation rates of PIP (McLeod criteria)	New PIP was significantly lower (18%) in intervention than control group (RR 0.82, 95% CI 0.69 - 0.98). No effect on discontinuation of pre-existing PIP (RR 1.06, 95% CI 0.89–1.26).
Multifaceted interventions							

Clyne[28] (2013, Ireland)	Cluster RCT	12 months	GP practices 21 Intervention 11 Control 10	196 (≥70 years, ≥ 1 drug) Intervention 99 Control 97 *Baseline PIP:* 100%	**Multifaceted:** Pharmacist led academic detailing, GP-led medicines review supported by web-based pharmaceutical treatment algorithms with alternatives to PIP; and patient information leaflets **Comparison:** Usual care	**Primary:** a) Proportion of patients with PIP (34 criteria from based Beers, STOPP) b) Mean number of PIP drugs at intervention completion **Secondary:** a) Drug specific outcomes b) Patient beliefs about medication (BMQ) c) Patient Well-being	**Primary:** a) 52% of intervention compared to 77% of control had PIP (adjusted OR 0.3, 95% CI 0.1 - 0.7, P=0.02) b) Mean number of PIP drugs in the intervention was 0.7 and 1.2 in control (P0.02) Number of PIP drugs per person less in intervention than control (IRR 0.71, 95% CI 0.5 to 1.0, P=0.49) **Secondary:** c) 23% of intervention compared to 47% of control had a proton pump inhibitor (adjusted OR 0.3, 95% CI 0.1-0.6, P0.04). No significant difference between groups in benzodiazepines or therapeutic duplication

Rognstad[27] (2013, Norway)	Cluster RCT	24 months	CME groups 81 Intervention 41 Control 40 GPs 465 Intervention 265 Control 209	81,810 (≥70 years) Intervention 46,737 Control 35,073 *Baseline PIP:* Intervention 19.9% Control 18.6%	**Multifaceted:** Peer academic detailing on PIP with audit and feedback **Comparison:** Peer academic detailing on antibiotics with audit and feedback	Changes in PIP across 13 indicators (Beers criteria; Swedish national board of health and welfare)	10.3% (95% CI 5.9 to 15.0) reduction relative to baseline for 13 selected PIMs per 100 patients Largest reductions were for TCAs and 'old' antihistamines (18.9%)

Bregnhoj[24] (2009, Denmark)	Cluster RCT	12 months	GP practices 41	212 (≥65 years, ≥5 drugs) Group 1 79 Group 2 61 Control 62 *Baseline PIP:* Group 1 mean MAI = 10.8 Group 2 mean MAI = 9.1 Group 3 mean MAI = 9.8	**Multifaceted:** Interactive educational meeting with feedback **Single:** Interactive educational meeting **Comparison:** Usual care	Changes in MAI score	Combined intervention resulted in mean MAI change of -5 (95% CI -7.3 to -2.6)

				26,805 (≥65 years) Intervention 24,119 Control 26,805			
Simon[21] (2006, USA)	Cluster RCT	18 months	Clinics 13 Doctors 126	*Baseline PIP:* Intervention mean 146.3 per 10,000 Control 155.2 per 10,000	**Multifaceted:** Point of prescribing, age-specific alerts for drugs to avoid with alternatives and academic detailing **Comparison:** Age-specific alerts for drugs to avoid with alternatives	Number of times target PIP drugs dispensed per 10,000 patients per quarter (Beers 1997)	There was a decrease of 19.7 PIP per 10,000 in the intervention group compared to 13.0 per 10,000 in control but this was not significant (p=0.52)

CDSS (computerised clinical decision support systems); CME (continuing medical education); CI (confidence interval); MAI (Medicines Appropriateness Index); MDT (Multidisciplinary teams); OR (odds ratio); N/A (not applicable); PIP (potentially inappropriate prescribing); RCT (randomised controlled trial)

Table 3 Table of effect sizes for primary outcomes

Author (Year)	No. of participants Baseline PIP prevalence	PIP measurement continuous (mean MAI, 95% CI)	PIP measurement categorical (explicit criteria)	
			Odds ratio (OR) of PIP in intervention versus control (95% CI)[a]	Absolute risk reductions (ARR)[b]
Organisational				
Allard (2001) [18]	266 58.9%	MAI not utilised	Adjusted OR 1.83 (0.94 -3.57)	-7.28%
Lampela (2010) [26]	781 20.4%	MAI not utilised	Crude OR 0.70 (0.50 – 1.03)	6%
Bryant (2011) [29]	498 *Mean MAI per group* Intervention: 5.1 Control: 4.5	Standardised mean difference 0.37	MAI criteria utilised	MAI criteria utilised
Hanlon (1996) [19]	208 *Mean MAI per group* Intervention: 17.7 Control: 17.6	Mean difference -3.9 (-5.84, -1.96) Standardised mean difference -0.54	MAI criteria utilised	MAI criteria utilised

Taylor (2003) [23]	81 Not reported	Mean MAI scores not reported	MAI criteria utilised	MAI criteria utilised
Denneboom (2007) [25]	738 Not reported	MAI not utilised	Data not presented	Data not presented
Professional (CDSS)				
Raebel (2007) [20]	59,860 Not reported	MAI not utilised	Crude OR 0.84 (0.75 – 0.94)	0.3%
Tamblyn (2003) [22]	12,560 32.5%	MAI not utilised	Crude OR 0.81 (0.73 – 0.89)	2.5%
Multifaceted				
Clyne (2013) [28]	196 100%	MAI not utilised	Adjusted OR 0.3 (0.1 - 0.7)	25%
Rognstad[27] (2013)	81,810 19.2%	MAI not utilised	Crude OR 0.95 (0.92 – 0.99)	0.7%
Bregnhoj[24] (2009)	212 *Mean MAI per group* Group 1: 10.8 Group 2: 9.1 Group 3: 9.8	Mean difference -5 (-7.3 - -2.6)	MAI criteria utilised	MAI criteria utilised

Simon[21] (2006)	26,805 150.7 per 10,000	MAI not utilised	Data presented as rates per 10,000	Data presented as rates per 10,000

a. Crude odds ratio calculated based on the number of cases of PIP in intervention and control at follow-up as follows: (number of participants in intervention with PIP/ number of participants in intervention with PIP)/ (number of participants in control with PIP/ number of participants in control with PIP). This approach does not account for changes from baseline

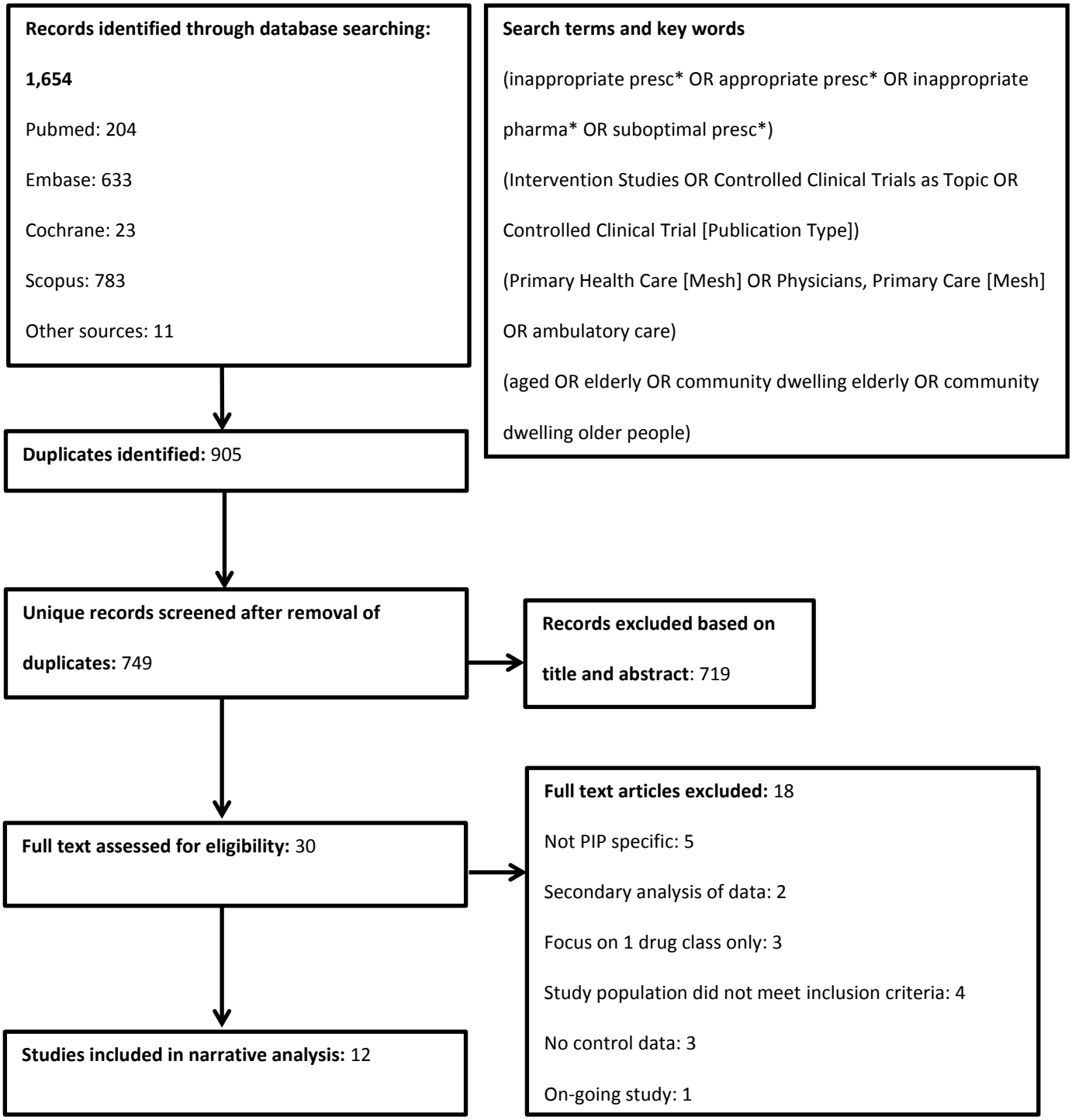
b. Absolute risk reduction calculated as the difference between the control group's event rate (i.e. number in control with PIP/total in control) and the experimental group's event rate (i.e. number in intervention with PIP/total in (intervention).

Appendix 1: Characteristics of ongoing studies

	Cedilnik Group
Title	Use of web-based application to improve prescribing in home-living elderly: A randomised controlled study protocol[45]
Study design	RCT
Participants	Home dwelling adults ≥ 65 years
Intervention	Web-based application will screen for PIP using STOPP and START criteria. Identified potentially inappropriate prescriptions will be presented to participants' physicians for consideration and change.
Outcome measure	Decrease of PIP
Start date	Unknown

RCT (randomised controlled trial); START (Screening Tool to Alert doctors to Right Treatment); STOPP (Screening Tool for Older Peoples Prescriptions)

Figure 1 Flow diagram of included risk studies



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants/personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Baseline characteristics (other bias)	Protection against contamination (other bias)	Sample size calculation (other bias)
Allard 2001	U	U	U	L	L	L	L	L	L
Bregnhoj 2009	L	U	L	L	L	U	L	L	H
Bryant 2010	U	U	U	L	H	L	L	U	U
Clyne 2013	L	L	H	L	L	L	U	L	L
Denneboom 2007	U	U	U	U	L	L	L	L	L
Hanlon 1996	L	U	L	L	L	U	L	H	L
Lampela 2010	L	U	U	U	L	U	L	L	H
Raebel 2007	L	U	L	U	L	L	L	U	L
Rognstad 2013	U	U	U	U	L	L	L	L	L
Simon 2006	U	U	U	L	U	L	L	L	H
Tamblyn 2003	U	U	H	U	U	L	L	L	U
Taylor 2003	U	U	U	U	L	L	L	H	H

H high risk L low risk U unclear risk

Figure 2 Risk of bias summary