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SYSTEMATIC REVIEW

The Relationship between the Extent of Collaboration of General Practitioners and Pharmacists and the Implementation of Recommendations Arising from Medication Review

A Systematic Review

Henk-Frans Kwint · Lynette Bermingham · Adrianne Faber · Jacobijn Gussekloo · Marcel L. Bouvy

Abstract

Background Many studies have investigated the effect of medication review on a variety of outcomes, but the elements of the interventions have been quite diverse. Moreover, implementation rates of recommendations also vary widely between studies.

Objective The objective of this study was to investigate how the extent of collaboration between the general practitioner (GP) and the pharmacist impacts on the implementation of recommendations arising from medication review.

Methods MEDLINE, EMBASE and Web of Science were searched for studies published between January 2000 and April 2012. Keywords included medication review, medication therapy management, pharmaceutical services and drug utilization review. Sixteen articles (describing 14 randomized controlled trials [RCTs]) out of 620 titles met the inclusion criteria. Inclusion criteria for the review were medication review, RCT design, involvement of both pharmacist and GP, and home-dwelling patients (mean age >70 years) who had not been recently discharged. After quality assessment of the article, the presence of the following eight key elements reflecting collaboration were scored for each intervention: pharmacist with clinical experience, own pharmacist involved, sharing of medical records, patient interview by pharmacist, invitation of patients by GP, case conference between GP and pharmacist, action plan, follow-up. The primary outcome was the implementation rate of recommendations. Meta-regression analysis was used to assess the association between the implementation rate and the number of key elements present.

Results Twelve RCTs were included after quality assessment. The mean number of key elements within the intervention was 5.2 (range 1–8). The mean implementation rate of recommendations was 50 % (range 17–86). The association between the number of key elements present in the intervention and the implementation rate of recommendations was significant: $\beta = 0.085$ (95 % CI 0.052–0.128; $p < 0.0001$).

Conclusion This systematic review shows a significant association between the number of key elements of the intervention reflecting collaborative aspects in medication review and the implementation rate of recommendations.

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H.-F. Kwint (✉) · M. L. Bouvy
Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), PO Box 80082, 3508 TB Utrecht, The Netherlands
e-mail: h.f.kwint@uu.nl

H.-F. Kwint · A. Faber · M. L. Bouvy
SIR Institute for Pharmacy Practice and Policy, Leiden, The Netherlands

L. Bermingham · J. Gussekloo
Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, The Netherlands

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1 Introduction

Polypharmacy and drug-related morbidity is increasingly recognized as a major public health problem among the elderly [1, 2]. Medication review has been proposed as an important strategy to constrain the negative effects of polypharmacy, aiming at safer and more effective use of medicines [3, 4].

Medication review has been defined as "a structured, critical examination of a patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimizing the number of medication-related problems and reducing waste" [5]. Three types of medication review have been described, based on the purpose of the review: 'prescription review' [technical issues related to prescription(s)], 'concordance or compliance review' (issues relating to the patient's medicine behaviour) and 'clinical medication review' (issues relating to the patient's use of medicines in the context of their condition) [6]. Concomitantly, efforts have been made to standardize medication review [5–7].

However, systematic reviews of pharmacist-led medication review have not shown an effect on clinical outcomes such as hospital admissions or mortality [8–10]. In some studies, positive effects were reported on intermediate outcomes like drug knowledge and adherence [8]. The heterogeneity in patient populations, settings, interventions and outcomes in these studies made it difficult to draw definitive conclusions. There may be merit in combining the expertise of the pharmacist and physician with shared decision-making involving the patient in order to improve outcomes [11]. Previous systematic reviews did not take into account the variability in collaboration between pharmacists and general practitioners (GPs) in medication reviews.

Studies on barriers and facilitators in medication review reveal collaborative aspects that might be essential for conducting successful medication reviews [12–14]. The most commonly cited facilitators were having an established pharmacist–physician relationship [13, 14] and a face-to-face meeting (case conference) between pharmacist and physician to discuss the pharmacist's recommendations [13, 15, 16]. Using a pharmacist other than the patient's regular pharmacist was seen as a barrier, as was inadequate clinical training of the pharmacist [13]. Without access to medical records, the pharmacist may make tentative or inappropriate recommendations that are of little help [13]. The GPPC (General Practitioner–Pharmacist Collaboration) study [17] further suggested that a general practice-based service could be more facilitating than a community pharmacy-based service [17]. This could imply that patients are approached for medication review by the GP practice, which is also common in the Home Medicines Review (HMR) programme in Australia [12, 13]. They further suggested that the pharmacist should meet the patient for interview about their medicines in the physician's office [17–19], while a patient interview at home by an accredited pharmacist is the predominant step of the HMR programme [12, 13]. Finally, it is important for a collaborative medication review that responsibilities for implementation of the action plan and follow-up are clearly defined and divided between physician and pharmacist [13].

The aim of this systematic review was to investigate how the extent of collaboration between the GP and the pharmacist impacts on the implementation of recommendations arising from medication review.

2 Methods

2.1 Search

Our search strategy identified research on medication review interventions involving pharmacists and GPs. MEDLINE, EMBASE and Web of Science were searched for articles published between 1 January 2000 and 1 April 2012. These dates were chosen because relatively few studies with an elaborate description of the medication review process were published before 2000. Interventions were identified using the following keywords and medical subject headings (MeSH): medication review, medication therapy management, pharmaceutical services and drug utilization review (see Appendix S1 for detailed search terms [Online Resource 1]). Different publications on the same group of patients were considered as one study.

2.2 Study Selection

All titles were reviewed by two investigators (H.K. and L.B.). Studies were excluded if both agreed that the title clearly indicated that the study did not concern medication review and/or focussed on only one drug or drug class. H.K. and L.B. assessed all remaining abstracts independently in this manner. Studies were included if they fulfilled the following criteria: medication review, randomized clinical trial (RCT), pharmacist and GP involved, home-dwelling patients in primary care, mean age $\geq$70 years, patients not recently discharged (<1 month).

Only studies in English were included. Finally, full papers from potential studies were assessed independently by the two investigators for their suitability for inclusion. Differences were resolved by discussion, or a third investigator (either A.F. or M.B.) was consulted.

2.3 Quality Assessment of the Studies

Trial quality was assessed according to the Delphi list [20]. This list consists of ten criteria: randomization, treatment allocation, similar groups at baseline, eligibility criteria, blinding of outcome assessor, blinding of care provider, blinding of patient, point estimates and measures of variability, intention-to-treat analysis and reporting of

withdrawal/drop-out rate. In addition, we added 'power calculation' to this list. Studies with a low score on the quality assessment (5 or fewer items scored 'yes') were excluded for analysis of outcomes.

2.4 Study Characteristics

2.4.1 Categorization

Studies were categorized by study author, year of publication, number of pharmacists and GPs, country, number of patients, duration of the study, mean age and sex of patients, mean number of drugs, description of the intervention, setting, number of recommendations in the intervention group, the clinical, intermediate and process outcomes assessed and the quality score.

2.4.2 Outcomes

The primary outcome was the implementation rate of recommendations following drug-related problems (DRPs) identified during medication review. The implementation rate was defined as the percentage of recommendations fully or partly implemented and/or the percentage of DRPs resolved. Partial implementation of recommendations means that an action other than that originally proposed by the pharmacist was implemented. Fully and partly implemented recommendations were counted equally. Data on clinical outcomes (hospital admissions, quality of life), intermediate outcomes (adherence) and other process outcomes (drug changes, number of drugs) were also extracted. The effect on clinical, intermediate and process outcomes was described as a significant effect in favour of the intervention group, a significant effect in favour of the control group or no significant effect.

2.4.3 Key Elements of the Intervention

The intervention was characterized by the presence or absence of eight key elements reflecting collaborative aspects between a GP and a pharmacist, based on the aforementioned facilitators and barriers in medication review [12–14]. The choice of the key elements was supported by scientific discussion with experienced pharmacist reviewers who regarded these elements as having 'face validity'. The following key elements were assessed: (1) 'pharmacist with clinical experience' means that the study pharmacist had adequate clinical training and expertise to perform medication reviews; (2) 'own pharmacist involved' means that the study pharmacist is the patient's regular pharmacist who has a longer lasting therapeutic relationship with his or her patient; (3) 'sharing of medical records' describes full access for the care provider performing the medication review to GP data on diseases of the patient and clinical values; (4) 'patient interview by pharmacist' means a face-to-face consultation between a pharmacist and a patient—this pharmacist must have a relationship with the GP; (5) 'invitation of the patients by GP' means that the patient is invited to the study or referred for medication review by the GP (practice); (6) 'case conference GP and pharmacist' indicates a face-to-face meeting between at least the GP and the pharmacist to discuss the DRPs and recommendations for specific patients; (7) 'action plan' means that the study investigators reported that the agreed recommendations were formulated as an action plan and that there were designated persons responsible for implementation of this plan; and (8) 'follow-up' has taken place to assess whether the actions have been implemented, and to assess the patient's experience with these actions.

2.5 Data Synthesis and Analysis

For each trial, we extracted data on the primary outcome, 'implementation rate'. When the implementation rate was not present, we derived this rate from the percentage of DRPs resolved or the decrease in the number of potentially inappropriate prescriptions (PIPs). Trial quality and key elements of interventions were assessed independently by the two investigators (H.K. and L.B.) for each included study. Differences were resolved by discussion, or a third investigator (either A.F. or M.B.) was consulted.

Meta-regression analysis was used to assess the association between the number of key elements and the implementation rate, with the number of recommendations in the different studies as possible effect moderator. This mixed-effects analysis was conducted using the 'metafor' statistical package in R (version 2.12.2, R Project for Statistical Computing, Vienna, Austria, 2011, http://www.R-project.org).

3 Results

3.1 Search Results

A total of 620 titles were identified, 16 of which (describing 14 RCTs) met the inclusion criteria and were included in this review (Fig. 1) [3, 15–17, 19, 21–32].

3.2 Quality Assessment of Studies

The methodological quality of 12 of the 14 studies was assessed as adequate (i.e. 6 or more of 11 items scored 'yes') 3, 15–17, 19, 21, 23–27, 29–32] (see Table S1 in Appendix S2 [Online Resource 1]). The quality of the trial

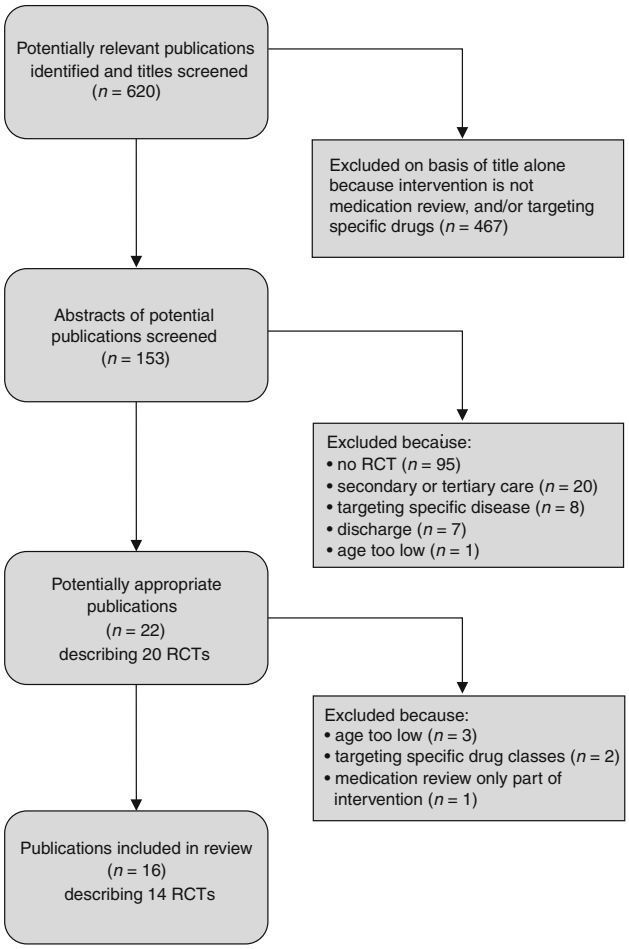

Fig. 1 Flow chart describing study selection and excluded studies. RCT randomized, controlled trial

in the two remaining studies was scored as 'low' [22, 28] and they were therefore excluded from further analysis. These studies were related; one trial formed part of a larger co-ordinated project with more countries, which was described in the other paper [22, 28].

In all included studies, a method of randomization was performed and eligibility criteria were specified. The majority of studies reported a method of treatment allocation [3, 15–17, 22–26, 29–31], while in three studies this was either not clearly described or not conducted [19, 21, 27, 32]. All except two studies reported similar groups at baseline [28–30]. An independent outcome assessor who was blinded to the intervention allocation was clearly described in only two studies [17, 21]. Because of the nature of the studied intervention, the care provider was never blinded to the intervention allocation. The patient was blinded for the intervention allocation in three studies [3, 15, 16, 23]. In two of these studies, patient interviews were conducted for both the intervention and the control group, but a pharmaceutical care plan was implemented only for the intervention group [3, 23]. In the third study, no patient interview was conducted and there was no description of patient involvement with the study [15, 16]. Point estimates and measures of variability were described in all studies. Intention-to-treat analysis was conducted in five studies [19, 21, 23, 25, 27, 32]. The withdrawal rate was likely to have caused bias in 3 of 14 studies [3, 15, 16, 19, 21, 23–27, 29–32].

3.3 Study Characteristics

In Table 1, the study characteristics and outcomes are presented for the 12 included studies. The number of participants in these studies ranged from 118 to 1,188. The mean age of the participants was 76.6 years (range 71.8–84.3) and 66 % were females (range 56–90). The mean number of prescribed drugs was 7.2 (range 4.5–12). Three of these studies were performed in the US [23, 29–31], three in the UK [3, 19, 25, 32] and two in The Netherlands [15, 16, 24].

3.3.1 Outcomes

Seven of 12 studies provided data on clinical outcomes [3, 17, 19, 25–27, 29, 32]. Six of these studies reported on quality of life measured using the 36-item Short Form Health Survey (SF-36) [3, 17, 19, 26, 27, 29, 32] or the EuroQoL-5D/visual analogue scale (VAS) [25]. No effects were found on total scores for quality of life, and one study reported only negative effects on some domains in one study [17]. Data on hospital admissions were provided by four studies [19, 25–27, 32], and no significant effects were reported. Twelve studies provided data on intermediate outcomes. Two studies reported on adherence, either self-reported [29, 30] or measured by refill rate [23], with no effect. Two studies reported on DRPs in both the intervention and the control group, with positive effects on DRPs resolved [3, 24]. Two studies [17, 21] reported on potentially inappropriate medications (PIMs), with positive effects for one study [17]. Process outcomes were reported in all studies. Two studies reported a reduction in the number of (prescribed) drugs [19, 31, 32], while in four studies no effect was reported [21, 23, 25, 26]. Five studies reported an increase in the number of drug changes [15–17, 19, 24, 31, 32].

Implementation rates of recommendations in the intervention group are shown in Table 2. The percentage of implemented recommendations was reported in seven studies [15–17, 19, 23, 25–27, 32], while a percentage of resolved DRPs was mentioned in three studies [3, 24, 29, 30]. In two studies, the implementation rate was derived from the decrease in the number of PIPs compared with the total number of PIPs [21, 31].

Table 1 Description of included studies: effect on clinical, intermediate and process outcomes

Study	Year of publication	No. of pharmacists and GPs (country)	Pts [*n* (%F); mean age (y)]	Duration	No. of drugs	Intervention (setting)	No. of recommendations (mean per pt)	Clinical outcomes (significant effect)	Intermediate and process outcomes (significant effect)	Quality score
Allard et al. [21]	2001	Team of 2 physicians, pharmacist and nurse; 52 GPs (Can)	266 (90); 80.5	12 mo	6.3	Nurse met pts at home for inventory of drugs. MR was performed by a multidisciplinary team and mailed to GPs (Faculty of Medicine, University)	147 (1.1)	–	No. of PIMs (↔); no. of pts with ≥1 PIM (↔); no. of pts with drug improvements (↔); no. of prescribed drugs (↔)	8
Bryant et al. [17]	2011	26 CPs, 57 GPs (NZ)	498 (59.0); 75.4	12 mo	5.0	Home MR followed by CC with GP (community pharmacies)	462 (1.7)	QoL (SF-36): emotional role (↓); social functioning (↓); other domains (↔)	MAI (↑); no. of PIMs (↑); no. of drug changes (↑)	7
Denneboom et al. [15]	2007	29 CPs, 84 GPs (NL)	738 (62.1); 81.0	9 mo	7.2	MR without pt interview ('treatment review') followed by CC with GP (study arm A) or written feedback (study arm B) (community pharmacies)	(A) 141 (0.5) (B) 128 (0.3)	–	No. of drug changes: 6 months (↑); 9 months (↔)	7
Grymonpre et al. [23]	2001	Pharmacists NS, 35 GPs (US)	135 (79.3); 77	12 mo	6.2	Home medication history taken by 'lay person' and reviewed by pharmacy consultant (1 interdisciplinary health clinic)	794 (11.5)	–	Adherence (refill rate) (↔); drug knowledge (↔); no. of prescribed drugs (↔)	9
Krska et al. [3]	2001	Pharmacists NS, 6 general practices (UK)	332 (60.5); 75.1	3 mo	7.5	Home-based MR. Care plan sent to GP, agreed actions implemented by pharmacist assisted by practice staff (general practices)	1,206 (6.3)	QoL (SF-36) (↔)	Proportion of PCIs resolved (↑); use of health services (↔)	6
Kwint et al. [24]	2011	6 CPs, GPs NS (NL)	118 (68.5); 79.3	6 mo	10.1	MRs without pt interview were performed by external pharmacist reviewers at distance, but the following CC with GP was conducted by pt's own CPs (community pharmacies)	249 (4.0)	–	No. of DRPs leading to recommendation for drug change (↑); no. of drug changes related to a recommendation (↑); no. of drug changes (↑)	7
Lenaghan et al. [25]	2007	1 CP; 9 GPs (UK)	136 (65.7); 84.3	6 mo	7.4	Home-based MR (1 dispensing general practice)	71 (1.0)	No. of hospital admissions (↔); deaths (↔); QoL (EuroQoL-5D/VAS) (↔)	No. of prescribed drugs (↔)	7

Table 1 continued

Study	Year of publication	No. of pharmacists and GPs (country)	Pts [*n* (%F); mean age (y)]	Duration	No. of drugs	Intervention (setting)	No. of recommendations (mean per pt)	Clinical outcomes (significant effect)	Intermediate and process outcomes (significant effect)	Quality score
Sellors et al. [26]	2003	24 CPs; 48 GPs (US)	889 (62.8); 74	5 mo	7.9	Clinic-based MR, then telephone interviews (family practices in 24 sites)	1,093 (2.5)	No. of hospital admissions (↔); no. of drug-related hospital admissions (↔); QoL (SF-36) (↔)	No. of daily units of drugs taken (↔); no. of drugs taken (↔)	7
Sorensen et al. [27]	2004	32 CPs; 84 GPs (Aus)	400 (63.8); 71.8	6 mo	8.0	Home visit and MR by pharmacist and team conferences with GP and implementation at next pt/GP visit (general practices and community pharmacies)	564 (3.2)	No. of hospital admissions (↔); no. of hospital services (↔); QoL (SF-36) (↔); severity of illness (DUSOI-A) (↔); ADEs (↔)		7
Volume et al. [29]	2001	5 CPs; GPs NS (US)	363 (66.9); 74.0	15 mo	4.5	Pharmaceutical care services including clinical MR (community pharmacies)	559 (3.5)	QoL (SF-36) (↔)	Adherence (self-reported) (↔)	6
Williams et al. [31]	2004	1CP, 1GP (US)	140 (57.1); 73.7	6 wk	12.0	Clinical MR (1 health centre ambulatory clinic)	257 (4.1)	–	No. of prescribed drugs (↓)	7
Zermansky et al. [32]	2001	1 clinical pharmacist, 4 GPs (UK)	1188 (56); 73.5	12 mo	4.7	1 clinical pharmacist held pt consultations in GP office followed by clinical MR (4 general practices)	502 (0.8)	No. of hospital admissions (↔)	No. of drug changes (↑); frequency of dose (↔); no. of prescribed drugs (↓); no. of hospital outpatient attendances (↔); no. of GP consultations (↔)	7

ADEs adverse drug events, *Aus* Australia, *Can* Canada, *CC* case conference, *CP* community pharmacist, *DUSOI-A* Duke's Severity of Illness Visual Analogue Scale, *DRP* drug-related problem, *F* female, *GP* general practitioner, *MAI* Medication Appropriateness Index, *MR* medication review, *NL* Netherlands, *NS* not specified, *NZ* New Zealand, *PCIs* pharmaceutical care issues, *PIMs* potentially inappropriate medications, *pt(s)* patient(s), *QoL* quality of life, *SF-36* 36-item Short Form Health Survey, *VAS* visual analogue scale, ↑ significant effect in favour of intervention group, ↓ significant effect in favour of control group, ↔ no significant difference

Table 2 Key elements of intervention versus implementation rate of recommendations

Study	Year of publication	Pharmacist with clinical experience	Own pharmacist involved	Access to medical records	Patient interview (location/care provider)	Invitation by GP	Case conference GP and pharmacist	Action plan (care provider)	Follow up (care provider)	Implementation rate (%)	Outcome measurement (months)
Denneboom et al. [15] (study arm B)	2007		✔							17	6
Allard et al. [21]	2001			✔	✔ h/O				✔ O	25	12
Grymonpre et al. [23]	2001	✔			✔ h/P + O				✔ P	29	NS
Denneboom et al. [15] (study arm A)	2007		✔				✔	✔ NS	✔ CP	30	6
Kwint et al. [24]	2011	✔	✔				✔	✔ NS		30	6
Williams et al. [31]	2004	✔		✔	✔ NS/CP				✔	33	1.5
Sorensen et al. [27]	2004	✔	✔	✔	✔ h/CP	✔	✔	✔ GP + CP	✔ GP	54	NS
Sellors et al. [26]	2003	✔	✔	✔	✔ GPO/CP		✔	✔ GP	✔ CP	56	5
Volume et al. [29]	2001	✔	✔	✔	✔ NS/CP			✔	✔	58	NS
Bryant et al. [17]	2011	✔	✔	✔	✔ h/CP	✔	✔	✔ NS	✔ CP	62	12
Krska et al. [3]	2001	✔		✔	✔ h/P	✔		✔ P + O	✔ P	83	3
Lenaghan et al. [25]	2007	✔	✔	✔	✔ h/CP	✔	✔	✔ GP + O	✔ CP	85	NS
Zermansky et al. [32]	2001	✔		✔	✔ GPO/P	✔	✔	✔ P	✔ P	86	12

CP community pharmacist, *h* patient's home, GP general practitioner, *GPO* GP's office, *NS* not specified, *O* other care provider, *P* pharmacist

3.3.2 Key Elements of the Intervention

Key elements of 13 interventions from the 12 studies are shown in Table 2. One study compared outcomes between two intervention groups (case conference and written feedback [15, 16]), and therefore both study arms (A and B) are shown.

Pharmacists had clinical experience in 10 of the 13 interventions [3, 17, 19, 23, 25–27, 29–31]. Pharmacists were accredited pharmacists [17, 27], consultant pharmacists [23, 31] or clinical pharmacists [19, 32]. They followed a university accredited externship programme [26], were clinically trained [3], experienced in medication reviews [24, 25] or had a post-graduate qualification in pharmacy practice [25]. In 8 of 13 interventions, the patient's own GP was involved [15–17, 25–27, 29, 30]. In the other interventions, the study pharmacist had no existing therapeutic relationship with the patient or this was not described [3, 19, 21, 23, 31, 32] (see also Table 1). Pharmacists had full access to GP's medical records of the patient in 8 of the 13 interventions [3, 17, 19, 25–27, 29, 32]. Patient interviews were conducted in 11 of 13 interventions, at home [3, 17, 21, 23, 25, 27] or in the GP's office or clinic [19, 26, 31, 32]. In 3 of 13 interventions, eligible patients were invited by the GP to participate in the study [17, 19, 27, 32]. Case conferences between GPs and pharmacists were conducted in 7 of 13 interventions [15–17, 19, 24–27, 32]. In three interventions, letters with recommendations or care plans were sent to the GPs ('written feedback') [3, 15, 16, 23]. As mentioned earlier, one study compared the process outcomes of case conferences with written feedback [15, 16]. As part of two interventions, case conferences were held by external multidisciplinary teams without the patient's own GP [21, 31] and recommendations were mailed to the GP [21] or implemented with endorsement of the GP [31]. Action plans were used for implementation of agreed recommendations in 9 of 13 interventions [3, 15–17, 19, 24–27, 29, 32]. A follow-up of the implementation of actions was described in 11 of 13 interventions [3, 15–17, 19, 21, 23, 25–27, 29, 31, 32], most often conducted by a pharmacist [15, 17, 19, 23, 25, 26, 31, 32].

3.4 Association between Number of Key Elements and Outcomes

Key elements of the intervention and the implementation rate are shown in Table 2. The mean number of key elements present in the interventions was 5.2 (range 1–8). The mean implementation rate was 50 % (range 17–86).

The association between the number of key elements present in the intervention and the implementation rate of recommendations was positive: an increase in number of key elements was related to an increase in implementation rate, $\beta = 0.085$ (95 % CI 0.052–0.128; $p < 0.0001$) (Fig. 2). Figure 3 is a forest plot showing the observed and expected implementation rates, estimated on the meta-analysis association between number of key elements and the implementation rate. In all but three interventions, the observed implementation rate was within the 95 % confidence interval of the expected value [3, 19, 27, 32].

No meta-regression analyses were possible for the association between the number of key elements and the number of hospital admissions ($n = 4$ studies), the number of drug changes ($n = 5$ studies) and the number of prescribed drugs ($n = 5$ studies), because of the low number of studies and participants with these outcomes.

4 Discussion

This systematic review shows a significant association between the number of key elements of the intervention reflecting collaborative aspects in medication review and

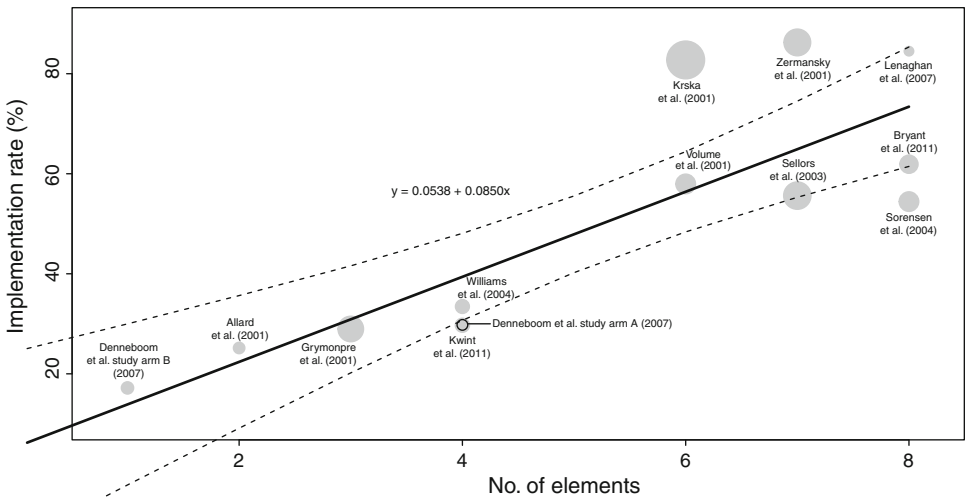

Fig. 2 Bubble plot of number of key elements of intervention vs. implementation rate of recommendations. The size of the circles reflects the number of recommendations in the intervention group of the different studies [3, 15, 17, 21, 23–27, 29, 31, 32]

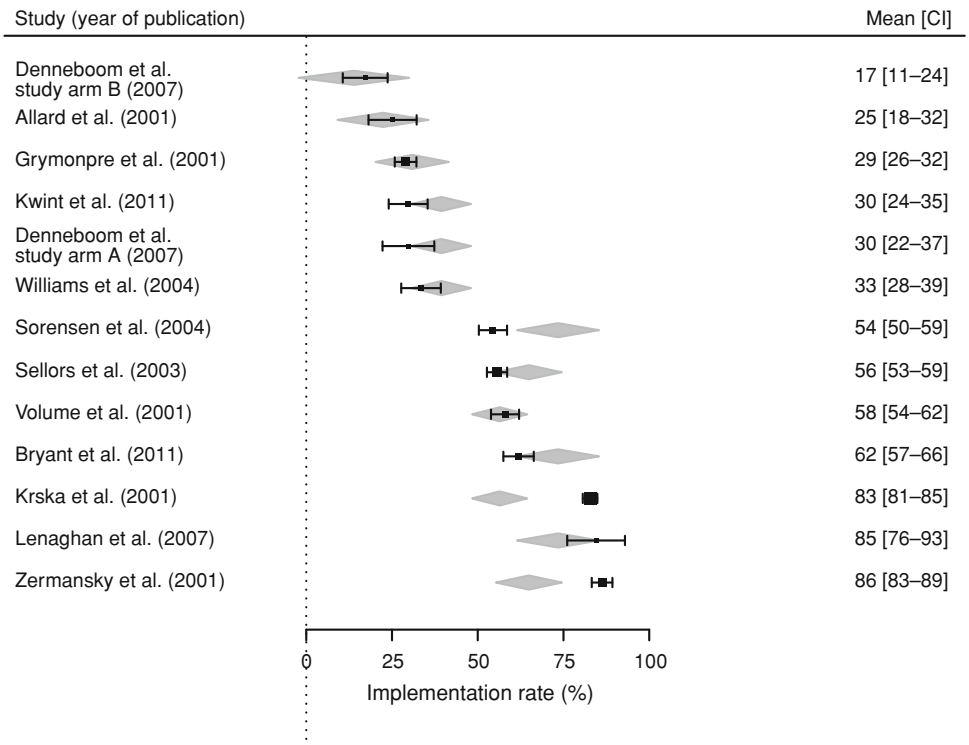

Fig. 3 Forest plot of observed and expected implementation rate of recommendations [3, 15, 17, 21, 23–27, 29, 31, 32]. Mean observed implementation rate with confidence intervals (95 % CIs). The grey diamonds represent the CIs of the expected implementation rate estimated on the meta-regression analysis association between the number of key elements and the implementation rate

the implementation rate. This suggests that more intensive collaboration between GP and pharmacist in medication review leads to higher recommendation implementation rates.

The expected implementation rate could be predicted from the number of key elements estimated from this association (Fig. 3). This model gives a good prediction of the implementation rate for the majority of the studies. For three studies, the expected implementation rate was different from the observed value [3, 19, 27, 32]. A higher implementation rate than expected was observed in the studies by Krska et al. [3] and Zermansky et al. [19, 32]. In the study by Zermansky et al. [19, 32], one pharmacist collaborated with only a few GPs, similar to the study by Lenaghan et al. [25], resulting in comparably high implementation rates. The major difference with the Lenaghan study was that the patient's own pharmacist was not involved. However, it is conceivable that this (clinical) pharmacist established a good relationship with this small number of GPs and their patients whilst he was consulting patients in the GP's office. Studies with pharmacists working at a GP practice yielded high rates of acceptance of recommendations [18, 19, 26, 32]. Conversely, Krska et al. [3] was the only study with a high implementation rate without a case conference. This face-to-face meeting between GPs and pharmacists to discuss the pharmacist's recommendations is often considered one of the most important and key elements of the collaborative approach in medication review [13, 15, 16, 33]. In the study by Krska et al. [3], pharmacists were assisted by practice staff in the implementation of accepted actions. Possibly, this partly explains the high implementation rate. Furthermore, the nature and number of pharmacists and their relationship with patients was not specified [3]. On the other hand, a lower than expected implementation rate was observed in the intervention by Sorensen et al. [27]. In this study, a large number of pharmacists collaborated with an even larger number of GPs, which could have made it difficult to achieve high implementation rates. The implementation rate and numbers of GPs and pharmacists in the study of Sorensen et al. [27] were similar to those in the study by Sellors et al. [26]. The major difference was that, in the study of Sorensen et al. [27], patients were invited by the GP.

There have been no earlier systematic reviews investigating the implementation rate of recommendations. We found a significant association between the number of key elements reflecting collaborative aspects and the implementation rate. This finding is in agreement with other medication review studies in secondary and tertiary care where direct communication between healthcare providers revealed higher acceptance rates of recommendations [34, 35]. For clinical and intermediate outcomes, no association could be assessed, because the number of studies reporting these outcomes was too low. Earlier systematic reviews reported no effect on hospital admissions and quality of life [8, 10]. Compared with these reviews, our scope was more focused, as we included only RCTs, home-dwelling patients in primary care, a mean age of 70 years and no recent discharge, yielding only 12 trials after quality

assessment. However, due to our inclusion criteria, patients in our review were relatively healthy and not directly at risk for hospital admission. In contrast, studies on medication review in hospitals were more successful in preventing hospital (re)admissions because they generally reviewed patients who were admitted to hospital and at high risk for readmission [36, 37].

There may be additional reasons for low implementation rates. Sellors et al. [26] showed that these reasons might include patient reluctance, previous failed attempts at the same strategy and a relatively short period for implementation combined with the occurrence of more urgent issues. In particular, the periods over which implementation rates were measured varied between the different studies in this review. Nor do we know if the recommendations in the different studies were clinically appropriate [17]. GP's perceptions of pharmacists' recommendations in the GPPC study revealed that they generally found the recommendations useful although at times theoretical [38]. Pharmacist's recommendations may be less appropriate if a high proportion of patients are already receiving the recommended treatment, for example, in the MEDMAN study ('ceiling effect') [39].

There were several strengths to this study. First of all, like in other systematic reviews on medication review, trials reported very heterogeneous outcomes that could not be pooled. In this systematic review, we could compare different trials using the implementation rate as the common (process) outcome. Implementation rates are also reported in many (observational) studies in home-dwelling patients [40, 41] as well as for patients in nursing homes [34, 42]. Implementation rate has a greater significance than acceptance rate of pharmacist's recommendations by physicians because it includes enactment of the recommendation by a care provider and the level of acceptance of recommendations by the patient. Secondly, we described eight different elements of the intervention that reflect collaborative aspects between GPs and pharmacists. These key elements were based on described facilitators and barriers in medication review [12–14]. Thirdly, the importance of patient involvement in medication review was also reflected by the key elements 'own pharmacist involved', 'patient interview' and 'follow-up'.

Our decision to consider all eight key elements of the intervention as equivalent weighted determinants for the implementation rate could be seen as a limitation. For example, the face-to-face discussion between pharmacists and GPs seemed a key element that could have more weight. The small number of studies precluded us from studying the association of the individual key elements in a multivariate design. Also, there could have been other key elements reflecting collaborative aspects that we may have missed. Furthermore, it was not possible to discriminate between the clinical relevance of the implemented recommendations in the different studies. This clinical relevance was only described in the study by Denneboom et al. [15, 16]. Finally, it cannot be ruled out that some relevant RCTs may have been missed or excluded.

5 Conclusion

This systematic review showed that the number of key elements reflecting collaborative aspects of medication review was significantly associated with the recommendation implementation rate. Further clinical trials could demonstrate whether an increase in collaborative aspects leads to higher implementation rates.

Based on this model, future studies for elderly in primary care could consider these key elements of intervention to design a standardized medication review process. More research is needed to assess which key elements of this collaborative approach are the most important and if there are additional elements that may influence implementation rates. Next to the physician and the pharmacist, the patient is the third main player in the medication review process. Future studies could focus on the influence of the patient on the implementation rate. Large multicentre trials in primary care are needed to draw definitive conclusions on whether a standardized collaborative approach in medication review could affect clinical outcomes. Such trials may be expensive, difficult to organize in practice settings and it may be questioned how many and which elderly home-dwelling patients in primary care are at greatest risk for negative clinical outcomes.

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