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The effectiveness of optimised clinical medication reviews for geriatric patients: Opti-Med a cluster randomised controlled trial

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ABSTRACT

Background.

Inappropriate drug use is a frequent problem in older patients and associated with adverse clinical outcomes and an important determinant of geriatric problems. Clinical medication reviews (CMR) may reduce inappropriate drug use.

Objective.

The aim of this study is to investigate the effectiveness of CMR on quality of life (QoL) and geriatric problems in comparison with usual care in older patients with geriatric problems in the general practice.

Methods.

We performed a cluster randomised controlled trial in 22 Dutch general practices. Patients of ≥65 years were eligible if they newly presented with pre-specified geriatric symptoms in general practice and the chronic use of ≥1 prescribed drug. The intervention consisted of CMRs which were prepared by an independent expert team and discussed with the patient by the general practitioner. Primary outcomes: QoL and the presence of self-reported geriatric problems after a follow-up period of 6 months.

Results.

518 patients were included. No significant differences between the intervention and control group and over time were found for QoL, geriatric problems, satisfaction with medication and self-reported medication adherence. After 6 months the percentage of solved Drug Related Problems (DRPs) was

significantly higher in the intervention group compared to the control group [B 22.6 (95%CI 14.1–31.1), $P < 0.001$].

Conclusion.

The study intervention did not influence QoL and geriatric problems. The higher percentage of solved DRPs in the intervention group did not result in effects on the patient's health. CMRs on a large scale seem not meaningful and should be reconsidered.

INTRODUCTION

Inappropriate drug use is a frequent problem in older patients. It is influenced by patient, prescriber, healthcare provider and system related factors (1) and is associated with adverse clinical outcomes such as functional decline, falling, adverse drug reactions, and hospital admissions. This has a negative impact on quality of life (QoL) (2–4) and may also increase the risk of the occurrence and persistence of the most common major impairments that appear in older people, also referred to as 'geriatric giants' (4), such as immobility, instability, incontinence and cognitive impairment (5–9).

Clinical medication reviews (CMRs) may reduce inappropriate drug use. A CMR is a structured, critical examination of the patient's medicines with the objective of reaching an agreement with the patient about treatment, optimising the impact of medicines, minimizing the number of drug related problems (DRPs) and reducing waste (10). Several studies have shown positive effects of CMRs on intermediate outcomes such as DRPs, medication adherence and knowledge. Although cost reduction might be an important motivation to CMRs, patient related effects are the most important. However, few effects have been established on clinical outcomes such as QoL, hospital admissions or mortality (11).

At present, CMRs have not yet been fully implemented because of lack of evidence for effectiveness and doubts about the target group who are assumed to benefit most. The feasibility in clinical practice and the consumption of time are barriers for implementation (12)

This study addresses the effects of CMRs on quality of life and geriatric problems in patients who newly present with geriatric problems in general practice, including immobility, instability, incontinence and impaired cognition, who use ≥1 drug chronically. Inappropriate drug use is considered an important determinant of geriatric problems and primary care is usually problem-oriented. We used a structured program for CMR that was designed to increase the feasibility of CMRs in primary care (13). In this paper we report on the effects of CMRs on QoL and geriatric problems in comparison with usual care. A process evaluation of the intervention and a cost-effectiveness evaluation will be published separately.

METHODS

Study design and setting

We performed a cluster randomised clinical trial in 22 general practices (mean 3890 listed patients) in Amsterdam, The Netherlands. The rationale to use a cluster design at practice level was to prevent contamination of structural attention to CMR activities within the GP practice. Non-institutionalised Dutch inhabitants are

obligatory listed at a general practice and most patients are registered with one community pharmacy. We included participants between November 2013 and February 2015 and followed them for 6 months. Randomisation of the intervention and control condition was carried out at practice level and was done before the patients were recruited. Randomisation was performed by a statistician blinded to characteristics of the practices using a computer generated list of random numbers. The practices were stratified by practice size (two strata), to ensure equally sized groups. Blinding to treatment allocation was not possible due to the nature of the intervention. The study protocol has been described elsewhere (13).

Practices

All 22 participating GP practices were member of the Academic Network Of General Practitioners of the VUmc Medical Centre. When the study started, most GP's used a electronical medical record system that warned for medication interactions. Pharmacies that filled the prescriptions would also check for interactions only. The inclusion criterion was that the practice was not performing CMRs on a regular basis and would not start doing so if randomized in the control group. All approached practices were willing to participate.

Study participants

Patients ≥65 years were eligible if they newly presented with a geriatric problem in general practice and used ≥1 prescribed drug chronically (i.e. ≥3 months). Patients with geriatric problems were identified based on ICPC coded diagnoses in their primary care electronic medical record (EMR) by an automated search strategy and an additional screening questionnaire. This questionnaire included questions on geriatric problems, actual medication use and DRPs. The geriatric problems included mobility problems, dizziness, fear of falling, falls, urinary incontinence and cognitive impairment. Patients were included if they scored ≥5 on the VAS scales (range 1–10) of the geriatric problems or reported ≥1 fall in the preceding 6 months.
We excluded those with a recorded dementia diagnosis and the GP excluded patients who had a recent CMR or were deemed unable to participate.
All participants returned an informed consent form together with the screening questionnaire.

Intervention

The intervention consisted of the following components:

- Preparation: Information from EMRs, the pharmacy and a screening questionnaire was collected, including the actual drug use of the patient, medication history, potential DRPs, the medical problems of the patient, recent laboratory test results and non-laboratory measurements. The questionnaire showed good agreement with a patient interview (14).
- Clinical medication review: Four trained independent expert teams consisting of a GP or nursing home physician and a community pharmacist performed the CMR analysis. They performed the medication review according to the adapted Systematic Tool to Reduce Inappropriate Prescribing (STRIP) method including the Screening Tool of Older Person's Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) criteria (15). A computerised version of STRIP, the STRIP-assistant was used (16).

- Pharmacotherapeutic treatment plan (PTP): The expert team made a PTP which was sent to the patient's GP by fax or encrypted e-mail.
- Implementation of the PTP: Patients were invited for a consultation with their GP in which the PTP was discussed and determined together with the patient. Changes in the medication were implemented usually by electronic communication from the practice to the pharmacy.

Usual care

The patients in control practices were identically selected as in the intervention practices but only received usual care. The expert teams also performed CMR analyses for control patients, but the GPs and patients did not receive the results.

Outcome measures

Measurements were administered at baseline, after 3 and 6 months through patient questionnaires. We chose the two most generally used generic measures for Qol: SF-12 and the EuroQol (EQ-5D-3L) and the presence and severity of geriatric problems. This was assessed with questions on the presence and self-perceived severity of geriatric problems using VAS (1–10). The primary geriatric problem per patient and two dichotomous outcome measures were defined (Fig. 1).

[FIGURE 1.]

Definition and operationalization of geriatric problems outcome measure based on the information in the patient questionnaires.

The number of DRPs per patient was determined at baseline and the number of solved DRPs after 6 months. Contrary to the study protocol (due to capacity problems) only one researcher (FW), rather than an independent expert team, only one categorised the DRPs after 6 months based on the results of the CMR analyses by the expert team using the DOCUMENT checklist and the EMR information (17) In case of doubt this was discussed with another researcher (JH).

Patient satisfaction about medication was assessed by the single-item Medication Satisfaction Questionnaire (MSQ) on a 7-point Likert scale at baseline, 3 and 6 months. The MSQ has acceptable reliability and validity. A 1-point change on the MSQ score was considered clinically meaningful (18)

Self-reported medication adherence was measured in the screening and follow-up questionnaires after 6 months.

Sample size

A sample size calculation, as described in the study protocol, was performed based on a clinically relevant change of 7.4 in the EQ-5D VAS (score range 0–100) (19). Two groups of 225 patients were required (13).

Statistical analyses

We used descriptive statistics to describe the patient characteristics and compared baseline values between study groups using independent sample *t*-tests, chi-square tests and Mann-Whitney-U tests. We performed effect analyses according to the 'intention to treat' principle. Multilevel linear and logistic regression analyses were performed to establish differences between the intervention and the control group taking clustering on the GP level and repeated measurements in patients into account Imputation methods for missing data were not applied, because this is not needed in multi-level analyses as the total number of missing was low (max 15%). Fixed

effects were time (baseline, 3 and 6 months) and the study group × time interaction. We assumed a random intercept for the second level (patients). Adjustment for baseline values was done by retaining baseline as part of the outcome vector and by assuming that the group means are equal at baseline, as appropriate in RCTs (20).Regression coefficients and odds ratios are shown adjusted for baseline and adjusted for baseline and number of chronic diseases, because this number differed significantly between intervention and control group.
The addition of the GP as third level variable and the interaction of the different expert teams were analysed. For DRPs solved after 6 months a linear multilevel regression analyses was performed with a random intercept at the second level and a random slope for the number of DRPs at baseline. Residuals were checked for normal distribution.
Two per protocol analyses were performed; (i) all intervention patients that had a consultation with the GP and (ii) all intervention patients that had the consultation within 1.5 months. We also performed subgroup analyses for polypharmacy patients and for each geriatric problem separately.
The data was analysed using IBM SPSS statistics version 22 software and MLWIN v2.28 for the multilevel analyses.

RESULTS

Baseline characteristics

Figure 2 provides an overview of randomisation, recruitment and follow-up. In total 518 patients were included. Apart from more frequent use of multidose dispensing systems, more chronic diseases and DRP's there were no significant differences for patient characteristics between intervention and control group at baseline. (Table 1) The distribution of DRP types did not differ between the two groups, with the most frequent DRPs being drug selection and undertreatment. (Table 2).

[FIGURE 2.] [TABLE 1.][TABLE 2]

Fifty nine GP's worked in the 22 practices. . There were no significant differences between the intervention and control practices for practice and GP characteristics (practice size, number of GPs, gender and years of working experience).

Declined to participate and non-responders

378 (18.6%) subjects declined to participate. They did not differ in age from participants, but among them were significantly fewer women ($P = 0.02$) and they used fewer drugs ($P < 0.001$). Indicated reasons for non-participation included no interest or no time, older age, health problems or the patient deemed the CMR not useful. Age and gender of the non-responders ($n = 840$) were similar to the participants.

Performed intervention

A CMR was performed for 274 of 275 participants in the intervention group (one drop-out before expert team started). $N = 247$ (90%) of the CMR's were discussed with the patient. The median (IQR) number of days between inclusion and the consultation was 33.0 (15–51) days and 42% of the patients had their consultation within the planned 1 month after inclusion.

The implementation rate of the proposed interventions was 47.8%.

Primary outcomes

No significant differences between the intervention and control group and over time were found for QoL at 3 and 6 months, with either the EQ5D-3L and SF-12. There were also no significant differences in improvement of the primary geriatric problem. (Table 3) In the intervention group, for 24.8% of the patients the primary geriatric giants was resolved and for 44.7% this was improved, compared to 23.0% and 41.5% in the control group.

Per protocol and subgroup analyses did not show different results. For EQ5D utility scores and SF12 MCS, we found a statistical significant intervention effect after 3 months among intervention patients who had their consultation within 1.5 months, this effect was absent at 6 months.

Adding general practice as a third level and the expert team as interaction term did not significantly improve the models and were not added to the final model.

Secondary outcomes

The percentage of solved DRPs after 6 months was significantly higher in the intervention group compared to the control group B:22.6 (95%CI 14.1–31.1). (Table 3) A higher number of DRPs at baseline decreased the difference between the two groups. Subgroup analyses with only polypharmacy patients gave lower regression coefficients, but the effect remained highly significant 19.3 (95%CI 10.6–27.4). Patient satisfaction with medication and self-reported medication adherence did not change over time, nor in the intervention nor in the control group. (Table 3) General practice as second level had no effect. Per protocol analyses and subgroup analyses did not show different results. The effect on the percentage solved DRPs after 6 months was higher in the per protocol analyses, in favour of the intervention group.

DISCUSSION

We investigated the effectiveness on QoL and geriatric problems of an optimally facilitated, prepared and structured CMR in comparison with usual care in older patients presenting their GP with a new geriatric problem. No significant effects were found for QoL and improvement in geriatric problems. The secondary outcomes patient satisfaction with medication and self-reported medication adherence did not show any effects either. However, after 6 months significantly more DRPs were solved in the intervention group compared to the control group. Subgroup analyses showed no other effects of the intervention, in the per protocol analyses a small significant difference in favour of the intervention group after 3 months for QoL was found. This effect disappeared after 6 months. The capability of CMRs to solve DRPs did not result in an improved QoL or a reduction of geriatric problems.

Our results are comparable to findings of other studies (11,21). The recent Cochrane review concluded that CMRs demonstrated improvements in appropriate prescribing, however it remains unclear whether such interventions can improve clinical outcomes on the patient level, no effects were found for QoL (22). Apparently, expert opinion and guideline recommendations (10,15,23) do not match with available evidence.

There are several explanations for the absence of effects. First, the selected target group for Opti-Med may have been not complex. Other studies showed some effects

of medication reviews on patient outcomes in specific more complex subgroups such as patients having more than five comorbidities (24) or patients with heart failure (25). Because of the large number of patients that did not respond (41%) or declined to participate (18.5%) we cannot exclude selection bias. In our study only 57% had polypharmacy and a mean of three chronic diseases, however subgroup analyses showed no differences. Since our inclusion criterion was a cut-off value on a VAS regarding geriatric problems, one could argue that the scores and cut-off value for the VAS for geriatric problems might have been too low. However over half of the participants had multiple geriatric problems and all contacted their GP for their complaints. Our target group is very heterogeneous, which could partially explain the absence of effects.

Another explanation for the lack of effects could be related to the outcome measures. QoL is difficult to measure in elderly people due to the diversity of problems in multimorbidity. The EQ5D-3L and SF12 questionnaires appear unresponsive measures and the VAS for geriatric problems are limited. Ideally CMRs should lead to less hospitalizations and mortality, for which much larger sample sizes are needed and one previous attempt failed (24). More specific outcomes might be more appropriate, such as Medication related QoL or exposure to specific high-risk medications (26,27); however, these are still intermediate outcomes.

Another explanation could be the intensity and implementation of intervention. Only one face to face contact with the patient was performed, since we chose to replace the patient interview with a questionnaire. Our previous study showed reasonable agreement between a patient interview and a questionnaire (13). The level of implementation of the intervention was good, with 90% having had a consultation with the GP and 47.8% of the proposed interventions was implemented by GP and patients, which is also high for an intervention with an external expert team. The number of DRPs identified by the expert teams is within the range found in other studies (28,29). The non-published process evaluation of Opti-Med including a patient survey and qualitative interviews among healthcare workers showed that all those involved were satisfied with the intervention and thought it was useful. This suggests that low fidelity is not the explanation for the absence of effects.

Finally, the follow-up may have been too short to detect changes in QoL due to changes in medication. Resolved DRPs related to e.g. preventative medication are not expected to influence QoL in the short term.

A limitation was that the external expert teams that performed the medication reviews were not blinded, for practical reasons and as result of the protocol deviation as described earlier. This might be the explanation that more DRPs were identified in intervention than the control group. However, we corrected for this in the analyses. Moreover, we think that the protocol deviation did not influence the results.

Our study indicates that there are no (measurable) effects of medication reviews on QoL or geriatric problems in this population or that the effects of CMR in the selected population are so small that the number needed to review is very high. The study had sufficient power, with a representative primary care population, the implementation of the intervention was good and patients were involved through a questionnaire and during a consultation with the GP. An additional factor might be that the quality of usual primary care in the Netherlands is high leaving only limited room for improvement.

Implications for practice and research

Intervention studies to reduce inappropriate medication and prescribing so far have not resulted in measurable changes in clinical patient outcomes. The evidence for medication reviews is mainly based on expert opinions and not on the evidence for the effectiveness of medication reviews. However, in clinical practice and guidelines, patients and policymakers demand CMRs, based on ethical considerations regarding possible future medication complications. Therefore future initiatives for implementation in clinical practice should focus on efficient and less costly methods, in which the Opti-Med intervention elements such as the questionnaire to evaluate patients' medication use and DRPs (13) and the use of external expert teams seem suitable.

Future research initiatives should focus on the characteristics of high risk patient groups for whom medication reviews might be of added value.

Conclusions

The Opti-Med study intervention did not influence QoL and geriatric problems. The higher percentage of solved DRPs in the intervention group did not translate into effects on the patient level. Clinical medication reviews on a large scale seem not meaningful and should be reconsidered.

Declarations

Funding: this study was supported by a research grant by the Dutch Organization for Health Research and Development (ZonMw).

Ethical approval: the Opti-Med study is registered in the Netherlands Trial Register (NTR4264) and was approved by the Medical Ethics Committee of the VU University Medical Center (2011/408).

Conflict of interest: none of the authors report conflicts of interest.

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FIGURES AND TABLES

Figure 1. Definition and operationalization of geriatric problems outcome measure based on the information in the patient questionnaires.

Definition primary geriatric problem based on decision rules: 1. Two or more falls in the previous 6 months 2. Highest VAS for the geriatric problems Dizziness, Mobility, Cognition problems or Incontinence. When equal VAS: 1. Check with EMR for matching ICPC code for identification 2. Dizziness>Mobility>Cognition problems>Incontinence 3. One fall in the previous 6 months 4. Fear of falling
The geriatric problem outcome measure was operationalised in two ways (dichotomous); 1. improvement versus worsening or stabilization of the primary geriatric problem o A difference after 6 months of two or more points on the VAS was considered as either an improvement or worsening. o For falls an improvement or worsening was absolutely more or less falls in the previous 6 months (T1 and T2 combined). 2.'Resolved' geriatric problem: Absence of the geriatric problem versus the presence of the primary geriatric problem; o Resolved: Absence of the primary geriatric problem is defined as a VAS of two or less after 6 months or no falls in the previous 6 months o Unsolved: Presence of the primary geriatric problem is a VAS or three or more after 6 months or at least one fall.

Figure 2. Flowchart of the Opti-Med study participants. GP, General Practitioner.

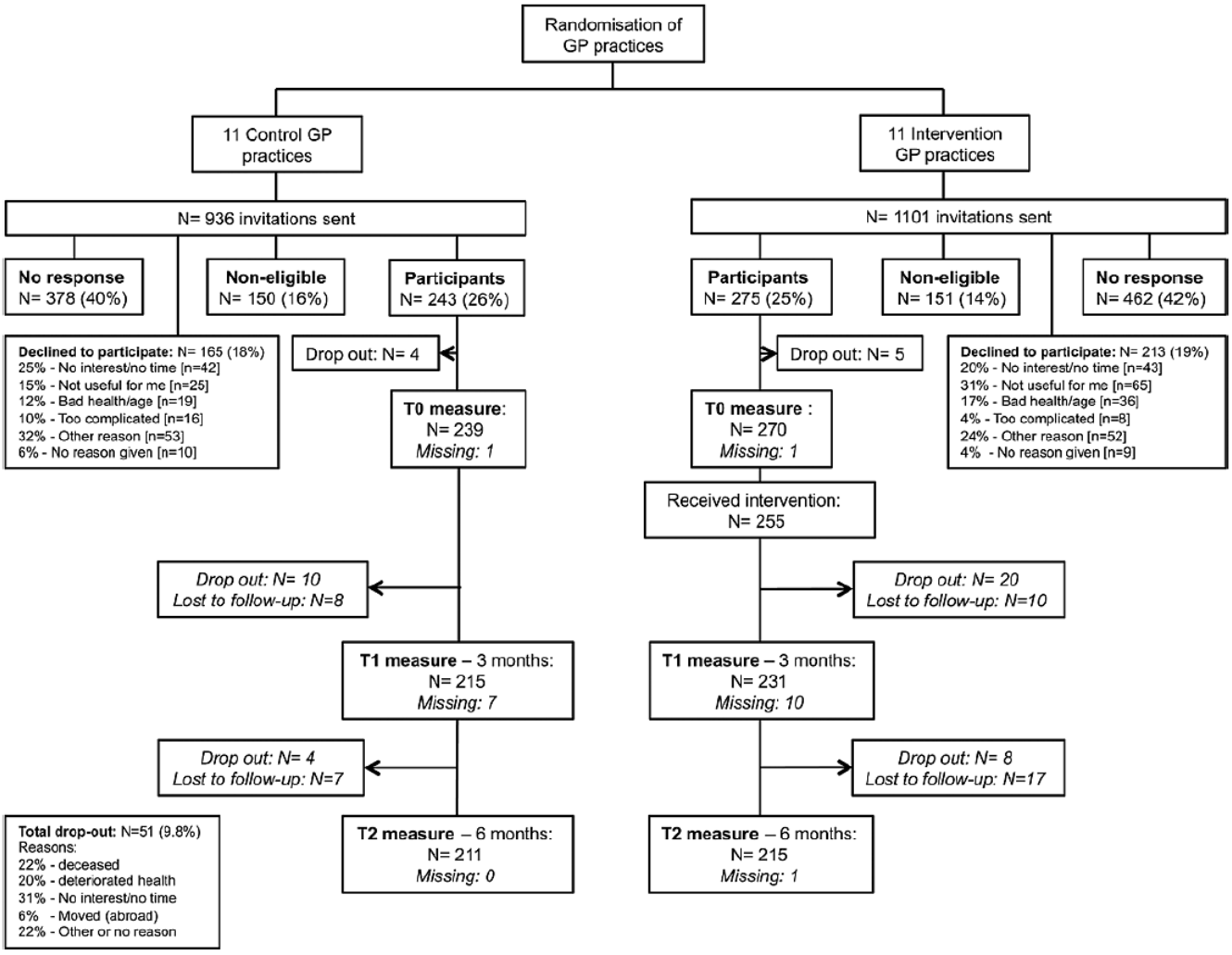

Table 1. Patient characteristics of the participants at baseline of the Opti-Med study

Demographic characteristics	Intervention	Usual care	Total	*P* value
Number of participants	275	243	518	
Women *n* (%)	177 (64.4)	159 (65.4)	336 (64.9)	0.80
Age, mean (sd) [range]	77.8 (7.7)	77.8 (8.0)	77.7 (7.9) [65–102]	0.94
≥80 year, %	38.8	40.6	39.6	0.67
≥90 year, %	5.8	7.4	6.5	0.47
Country of birth				0.43
Dutch and other European, %	91.7	93.6	92.6	
Non-Western, %	8.3	6.4	7.4	
Education level[a]				0.25
Low, %	26.6	20.5	23.7	
Middle, %	44.9	46.6	45.7	
High, %	28.5	32.9	30.6	
Living situation				0.60
Alone, %	59.4	57.1	58.3	
Together, %	40.6	42.9	41.7	

Health characteristics	Intervention	Usual care	Total	*P* value
EQ-5D-3L utility, mean (sd)	0.72 (0.22)	0.75 (0.20)	0.73 (0.21)	0.15
EQ5D VAS (0–100), mean (sd)	68.5 (15.6)	68.5 (14.5)	68.5 (15.1)	0.93
SF12 PCS, mean (sd)	47.9 (24.0)	47.2 (25.7)	47.6 (24.8)	0.76
SF12 MCS, mean (sd)	63.4 (23.1)	64.0 (22.6)	63.7 (22.9)	0.78
Mean chronic diseases (sd)[b]	2.77 (1.76)	3.23 (2.19)	2.99 (1.98)	**0.01**
≥2 chronic diseases[b], %	73.8	78.6	76.1	0.20
≥3 chronic diseases[b], %	48.4	53.9	51.0	0.21
≥4 chronic diseases[b], %	30.9	41.6	35.9	**0.01**
≥5 chronic diseases[b], %	17.5	26.7	21.8	**0.01**
BMI, mean (sd)	26.7 (5.4)	26.8 (5.4)	26.7 (5.4)	0.86
Pain VAS (0–10), mean (sd)	3.7 (3.0)	3.6 (2.9)	3.7 (3.0)	0.82

Geriatric problems	Intervention	Usual care	Total	*P* value
Mobility problems, % ≥5 VAS	57.9	62.6	60.1	0.28
Falling				0.70
% ≥1 times last 6 months	33.9	33.3	33.7	—
% ≥2 times last 6 months	17.4	20.1	18.7	—
Fear of falling, % ≥5 VAS	36.6	41.2	38.7	0.29
Dizziness, % ≥5 VAS	17.2	15.8	16.5	0.67
Incontinence, % ≥5 VAS	22.9	25.2	24.0	0.54
Cognition problems, % ≥5 VAS	25.5	26.9	26.1	0.72
≥ 2 geriatric problems, %	56.5	61.3	58.8	0.27
≥ 3 geriatric problems, %	32.3	35.7	33.9	0.54

Primary geriatric problems	Intervention	Usual care	Total	*P* value
Mobility, %, mean VAS (sd)	41.4 [7.1 (1.7)]	37.3 [7.1 (1.6)]	39.2 [7.1 (1.7)]	
Falling ≥1 times last 6 months, %	18.5	12.8	15.8	
Falling ≥2 times last 6 months, %	17.4	20.1	18.7	
Fear of falling, %, mean VAS (sd)	1.6 [6.4 (1.8)]	2.9 [5.5 (1.0)]	2.3 [6.1 (1.6)]	
Dizziness, %, mean VAS (sd)	6.5 [7.1 (1.7)]	4.9 [7.1 (1.9)]	5.8 [7.1 (1.7)]	
Incontinence, %, mean VAS (sd)	8.7 [7.8 (1.7)]	9.8 [7.0 (1.4)]	9.2 [7.4 (1.6)]	
Cognitive problems, %, mean VAS (sd)	9.0 [6.8 (1.4)]	8.7 [6.1 (1.2)]	8.8 [6.5 (1.3)]	

Medication characteristics	Intervention	Usual care	Total	*P* value
No of drugs in pharmacy records, mean (sd)	6.2 (3.2)	5.8 (3.3)	6.0 (3.2)	0.22
No of drugs reported by patient, mean (sd)	6.1 (3.1)	5.6 (3.2)	5.9 (3.2)	0.12
No of chronic drugs GP EMR, mean (sd)	5.6 (3.4)	5.5 (3.2)	5.6 (3.3)	0.74
Polypharmacy, %[c]	58.0	55.7	56.9	0.60
OTC medication use, %	81.3	83.1	82.1	0.62
Multidose drug dispensing system use %	13.0	7.0	10.2	**0.02**
Self-reported adverse event %	28.7	19.9	24.6	**0.02**

Medication characteristics	Intervention	Usual care	Total	*P*
Adherence problems %	34.8	29.1	32.2	0.17
Effectiveness problems %	18.8	16.6	17.8	0.51
User or practical problems %	23.5	21.3	22.5	0.54
MSQ score (1–7)[d], mean (sd)	5.4 (0.9)	5.3 (0.9)	5.3 (0.9)	0.43

P values <0.05 in bold are considered statistically significant.

BMI, Body Mass Index; EMR, Electronic Medical Record; MSQ, Medication Satisfaction Questionnaire; NA, not applicable; OTC, over the counter; SF-12, Short Form 12-item health survey; SF12, Physical Health Summary Scales; SF-12 MCS, SF12 Mental Health Summary Scales.

[a]low education level: No education, primary education or first stage of basic education; middle education level: Lower secondary education or second stage of basic education; high education level: Upper secondary education or higher.

[b]Chronic diseases according to set list of 29 diseases (30).

[c]Definition of polypharmacy is the use of ≥5 indicated for the treatment of a chronic disease at the ATC-5 level in in the 4 months preceding baseline. ATC codes were derived from prescription data from the EMR records. Excluded were anti-infectives (ATC-class J,G01,S01A,C,S02A,C), topical products (ATC-class M02 and dermatologicals (ATC-class D) and preparations for sensory organs, except drugs intended for long-term use were included (ATC-class S01E,F,G).

[d]Range is from 1 (extremely dissatisfied) to 7 (extremely satisfied) with all medications in general (17).

Table 2. Drug Related problems identified by the expert team at baseline according to the DOCUMENT classification

	Intervention	Usual care	Total	*P* value
DOCUMENT (16) DRP Category				0.44
Drug selection, %	38.6	37.0	37.9	
Over or underdose prescribed, %	8.0	9.9	8.8	
Compliance, %	3.8	3.1	3.5	
Un(der)treated indications, %	28.5	29.0	28.7	
Monitoring, %	11.9	13.8	12.7	
Education or Information, %	3.2	2.1	2.7	
Not classifiable, %	1.4	1.5	1.5	
Toxicity or ADR, %	4.5	3.7	4.1	
Total number of DRPs, mean (sd)	4.4 (1.9)	3.7 (1.9)	4.1 (2.0)	**<0.01**
Total number of DRPs, median (IQR)	4 (3–5)	4 (2–5)	4 (2–5)	**<0.01**

P values <0.05 in bold are considered statistically significant.

ADR, Adverse Drug Reaction; DRP, Drug Related Problem; IQR, Inter Quartile Range.

DRPs were identified by the expert team at baseline and classified by the researchers according to the validated DOCUMENT (17) classification system to categorize DRPs into 8 categories.

Table 3. Intervention effects from multilevel linear and logistic regression analyses

Continuous outcome measures	obs/total[a]	3 months				6 months			
		Adjusted for T0 *B* (95% CI)	*P* .	Adjusted[a] *B* (95% CI)	*P* .	Adjusted for T0 *B* (95% CI)	*P* .	Adjusted[a] *B* (95% CI)	*P* .
Quality of Life (EQ5D-3L utility -0.20–1)	1338/155	0.03 (0.00 to	0.06	0.02 (−0.00 to	0.14	0.02 (−0.02 to 0.05)	0.32	0.01 (−0.02 to 0.04)	0.53
Quality of Life (EQ5D-3L VAS	1332/155	0.91 (−1.69 to	0.51	0.38 (−2.03 to	0.76	2.30 (−0.16 to 4.76)	0.06	1.82 (−0.55 to 4.18)	0.13
Quality of Life (SF-12 MCS 0–	1319/155	3.33 (0.35 to	0.03	2.76 (−0.19 to	0.07	0.16 (−2.89 to 3.22)	0.92	−0.39 (−3.43 to 2.65)	0.81
Quality of Life SF-12 PCS (0–	1305/155	2.36 (−0.67 to	0.13	1.88 (−1.13 to	0.22	−0.06 (−3.19 to 3.06)	0.96	−0.58 (−3.69 to 2.53)	0.72
Medication Satisfaction MSQ	1344/155	0.01 (−0.17 to	0.89	0.00 (−0.19 to	0.97	0.11 (−0.08 to 0.30	0.25	0.09 (−0.10 to 0.28)	0.35
Percentage of solved DRPs 6 months	470/507	—	—	—	—	20.2 (12.2 to 28.1)[b,c]	**<0.001**	19.9 (12.0 to 27.9)[b,c]	**<0.00**

Dichotomous outcome	*N*	6 months							
						OR (95% CI)	*P*	OR[a] (95% CI)	*P*
Resolved primary geriatric	406	—	—	—	—	1.10 (0.69 to 1.74)	0.68	0.99 (0.62 to 1.57)	0.96
Improved versus worsened/ primary geriatric problem[e]	406	—	—	—	—	1.14 (0.77 to 1.69)	0.52	1.09 (0.73 to 1.63)	0.67
Persistence of self-reported problems	406	—	—	—	—	0.83 (0.54 to 1.27)	0.38	0.81 (0.53 to 1.25)	0.35

P values <0.05 in bold are considered statistically significant.

B, regression coefficient; CI, confidence interval; DRP, Drug Related Problem; ICC, Intraclass Correlation Coefficient; MSQ, Medication Satisfaction Questionnaire; OR, odds ratio; SF-12, Short Form 12-item health survey; SF12, Physical Health Summary Scales; SF-12 MCS, SF12 Mental Health Summary Scales; VAS, Visual Analogue Scale.

[a]Adjusted for T0 and number of chronic diseases at baseline.

[b]Adjusted for number of DRPs at baseline.

[c]Total observations is 1554 (3 times 518) for QoL and MSQ. For solved DRPs after 6 months total is 507, no DRPs at baseline and deceased were excluded from analyses.

[d]A 'solved' primary geriatric problem is defined as a VAS of two or less after 6 months or no falls in the previous 6 months.

[e]A difference after 6 months of two or more points on the VAS was considered as either an improvement or worsening. For falls an improvement or worsening was absolutely more or less falls in the previous 6 months (T1 and T2 combined).