The effect of a transitional pharmaceutical care program on the occurrence of ADEs after discharge from hospital in patients with polypharmacy

Uitvlugt, Elien B.; Heer, Selma En nasery de; van den Bemt, Bart J.F.; Bet, Pierre M.; Sombogaard, Ferdi; Hugtenburg, Jacqueline G.; van den Bemt, Patricia M.L.A.; Karapinar-Çarkit, Fatma

Published in:
Research in Social and Administrative Pharmacy

DOI:
10.1016/j.sapharm.2021.05.009

Publication date:
2022

Research in Social and Administrative Pharmacy 18 (2022) 2651–2658

Contents lists available at ScienceDirect

Research in Social and Administrative Pharmacy

journal homepage: www.elsevier.com/locate/rsap

The effect of a transitional pharmaceutical care program on the occurrence of ADEs after discharge from hospital in patients with polypharmacy

Elien B. Uitvlugt [a,1], Selma En-nasery-de Heer [b,1], Bart J.F. van den Bemt [c], Pierre M. Bet [b], Ferdi Sombogaard [b], Jacqueline G. Hugtenburg [b], Patricia M.L.A. van den Bemt [d], Fatma Karapinar-Çarkit [a,*]

[a] Department of Clinical Pharmacy, Jan Tooropstraat 164, 1061AE, Amsterdam, the Netherlands
[b] Department of Clinical Pharmacology and Pharmacy, De Boelelaan 1117, 1081, HV, Amsterdam, the Netherlands
[c] Department of Pharmacy, Sint Maartenskliniek, Nijmegen, The Netherlands. Department of Pharmacy, Radboud University Medical Centre, Nijmegen, the Netherlands
[d] University Medical Center Rotterdam, Department of Hospital Pharmacy. University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, the Netherlands

ARTICLE INFO

Keywords:
Adverse drug events
Hospital discharge
Medication reconciliation

ABSTRACT

Introduction: Transitional care programs (i.e. interventions delivered both in hospital and in primary care), could increase continuity and consequently quality of care. However, limited studies on the effect of these programs on Adverse Drug Events (ADEs) post-discharge are available. Therefore, the aim of this study was to investigate the effect of a transitional pharmaceutical care program on the occurrence of ADEs 4 weeks post-discharge.
Methods: A multicentre prospective before-after study was performed in a general teaching hospital, a university hospital and 49 community pharmacies. The transitional pharmaceutical care program consisted of: teach-back to the patient at discharge, a pharmaceutical discharge letter, a home visit by a community pharmacist and a clinical medication review by both the community and the clinical pharmacist, on top of usual care. Usual care consisted of medication reconciliation at admission and discharge by pharmacy teams. The primary outcome was the proportion of patients who reported at least 1 ADE 4 weeks post-discharge. Multivariable logistic regression was used to adjust for potential confounders.
Results: In total, 369 patients were included (control: n = 195, intervention: n = 174). The proportion of patients with at least 1 ADE did not statistically significant differ between the intervention and control group (general teaching hospital: 59% vs. 67%, OR_{adj} 0.70 [95% CI 0.38–1.31], university hospital: 63% vs 50%, OR_{adj} 1.76 [95% CI 0.75–4.13]).
Conclusion: The transitional pharmaceutical care program did not decrease the proportion of patients with ADEs after discharge. ADEs after discharge were common and more than 50% of patients reported at least 1 ADE. A process evaluation is needed to gain insight into how a transitional pharmaceutical care program could diminish those ADEs.

Introduction

Between 17 and 51% of patients experience Adverse Drug Events (ADEs) within 30 days after hospital discharge.[1] ADEs are any injuries resulting from medication use, including physical harm, mental harm or loss of function.[2] ADEs are responsible for 21% of hospital readmissions and 69% of these are deemed preventable.[3] Several circumstances may contribute to the occurrence of ADEs after discharge. Firstly, changes in medication regimens made during hospital stay are not always clear to the patient.[4,5] Whereas during hospital stay patients have little control over their medication management, after discharge patients regain full responsibility. Secondly, primary healthcare providers are not always

* Corresponding author.
E-mail addresses: e.uitvlugt@olvg.nl (E.B. Uitvlugt), s.en-nasery@amsterdamumc.nl (S.E.-n.-d. Heer), b.vandenbemt@maartenskliniek.nl (B.J.F. van den Bemt), pm.bet@amsterdamumc.nl (P.M. Bet), f.sombogaard@amsterdamumc.nl (F. Sombogaard), jg.hugtenburg@amsterdamumc.nl (J.G. Hugtenburg), m.l.a.van.den.bemt@umcg.nl (P.M.L.A. van den Bemt), f.karapinar@olvg.nl (F. Karapinar-Çarkit).
[1] both authors contributed equally to this study.

https://doi.org/10.1016/j.sapharm.2021.05.009
Received 11 September 2020; Received in revised form 13 May 2021; Accepted 16 May 2021
Available online 21 May 2021

informed on patient's hospitalization and the medication changes that have been made.[6] This could result in discontinuity of care and difficulties with monitoring the patient's actual medication regimen. Finally, because the length of stay in hospitals is decreasing, ADEs often reveal after discharge hampering recognition and adequate ADE management.[7] The period immediately after discharge could be a stressful period for patients as they have to recover mentally and physically from the hospital admission, which may increase the risk of ADEs.[8,9]

In order to improve medication safety at transitions of care, several interventions to support continuity of care have been developed and implemented.[10] Those interventions, including medication reconciliation, clinical medication review (CMR), patient education and counseling at discharge, are often implemented in just 1 setting, either in primary care or in-hospital. Studies on their effects report moderate and conflicting results.[11–14] However, transitional pharmaceutical care programs delivered both in the hospital and primary care setting, show promising effects.[15] The recent systematic review of Daliri et al. shows that transitional care interventions reduce overall hospital readmission rates within 30 days of hospital discharge.[16] This reduction is probably due to a reduction in ADEs, as medication-related interventions will especially affect ADEs. However, studies exploring the effect of multicomponent pharmaceutical transitional care programs on ADEs post-discharge are rare.[17–19] Therefore, the primary aim of this study was to investigate the effect of a transitional pharmaceutical care program on the occurrence of ADEs 4 weeks post-discharge in patients with polypharmacy compared to usual care. Secondary aims were to investigate the effect of the intervention on the Health related Quality of Life, medication satisfaction and the proportion of patients with 1 or more unplanned readmission(s) or emergency room visit(s), 4 weeks after discharge.

Method

Study design and setting

A multicentre prospective before-after study was performed in the Amsterdam area of the Netherlands and was called the MARCH-study. The departments of internal medicine and cardiology of a general teaching hospital (OLVG) and the departments of internal medicine, cardiology and surgery of a university hospital (Amsterdam UMC, location VUmc) collaborated with 49 community pharmacies. These departments were selected to focus on the most common causes of medication-related hospital (re)admissions, including falls, syncope and hypoglycaemia.[20] The control period was from September 2018–April 2019, the implementation of the program took place in May 2019, whereas the intervention patients were included from June–December 2019.

Study population

Consecutive patients counselled for medication reconciliation at discharge were eligible for inclusion. Inclusion criteria were: use of at least 5 chronic medicines at discharge, at least 1 change in chronic medication during hospitalization and informed consent. These criteria were chosen because studies showed that a higher number of medication and medication changes were risk factors for ADEs after discharge.[21] Exclusion criteria were: length of stay shorter than 24 h, discharge to a nursing a home, life expectancy shorter than 6 months, not willing or unable to participate due to physical/mental constraints or language barrier and having a community pharmacy that was not participating in the study.

Usual care

See appendix 1 for the description of the usual care in the hospital and community pharmacy. In brief, medication reconciliation was performed at admission and discharge by pharmacy teams. Medication surveillance during hospital admission took place based on computerized surveillance alerts (e.g. interactions, duplication, dose) and were assessed daily by clinical pharmacists. Community pharmacies received a medication overview and did not perform home visits on a regular basis. Discharge letters, composed by the hospital doctors, were used to inform the general practitioner about the admission and generally contain a medication list. Previous studies of our research group have shown that discharge letters frequently arrive relatively late and are often incomplete regarding medication related information.[6,22]

Intervention

In addition to usual care, a transitional pharmaceutical care program was implemented, consisting of 4 components. See appendix 1 for a comprehensive description of the program components performed by the hospitals and community.

The intervention included:

1) Teach-back at discharge[19]

Teach-back communication was added to the patient reconciliation at discharge. Patients were asked to restate the medication related information on medication changes that had been presented to them, to check their understanding. If teach-back was unsuccessful, this was communicated to the community pharmacist (see 2).

2) Pharmaceutical discharge letter composed by clinical pharmacist

Within 1 working day after discharge, a pharmaceutical discharge letter was sent by mail to the community pharmacist. This letter contained: date, department and reason of hospitalization, medication list, reason for medication changes, indications of medication, relevant laboratory results, management of drug-drug interactions, side effects, practical and teach-back problems.

3) Post-discharge home visit by community pharmacist

Within 5 working days after discharge a home-visit was performed by the patient's community pharmacist, to discuss medication use. A home-visit was performed as previous studies have shown several benefits.[19,23] During a home-visit, medication related problems can be identified in the patient's own surrounding, so all medicines are available and user problems (e.g. expired medication, problems with opening medication) or inappropriate storage conditions can be identified. Unnecessary medication can be discarded. In addition, a home visit may be beneficial due to the personal touch of face-to-face contact.

The home visit was based on a protocol from a previous study[19] consisting of 3 parts: 1. Inventory of discussion items of the patient, 2. Current medication use (indication, identity, dosage, time of administration, knowledge of medication changes), 3. patients' experience, concerns and beliefs regarding medication. Findings from the home visit were used as input for the transitional CMR (see 4).

4) CMR performed by both the community pharmacist and clinical pharmacist

A transitional CMR was performed within 10 working days after discharge, using teleconference. These teleconferences were coordinated by the study pharmacists (EU, SE). During this meeting, medication related problems (MRPs) identified during the home visit were discussed. MRPs were defined as "an event or circumstance involving medication treatment that actually or potentially interferes with the patient experiencing an optimum outcome of medical care".[24]

In case of MRPs that could be solved by physicians in the hospital, the clinical pharmacist contacted the responsible physician to discuss the

recommendation. In case of MRPs that could be solved by the general practitioner, the community pharmacist contacted the general practitioner to discuss the recommendation. The outcomes of the discussions with the physician in the hospital or the general practitioner were shared with the study pharmacists by means of email or telephone. Recommendations were then categorized (e.g. recommendation accepted, not accepted or unknown).

Training

To prepare participating pharmacists for the program, a training was developed. Ten medication-related readmission cases from a previous studies were selected for their educational value using the Delphi method.[25] These cases were used as material to train pharmacists to timely recognize and identify ADEs that occur after hospital discharge. In total 97 community pharmacists were trained by the pharmacist-researchers (EU, SE, FK, JH), and 49 community pharmacists participated in the study. Additionally, information and instructions on the performance of the study were presented, including how to properly and consistently register the home visit outcomes. In total 3 clinical pharmacists (EU, PB, FS) participated in the study and got the same training.

Data collection and main outcomes

Patient and hospital admission characteristics were extracted from the medical records in the hospital information system (Epic, Verona, Wisconsin, United States) and stored in a cloud-based data platform (Castor Electronic Data Capture, Amsterdam, the Netherlands).

The characteristic 'one or more hospitalizations ≤6 months before index admission' was collected to compare the control and intervention group, as previous hospitalisations are linked to a higher risk for readmissions.[25]Comorbidities were used to calculate the updated Charlson comorbidity score.[26] Level of education (primary, secondary or higher) and country of birth were collected by a telephone or online questionnaire within 1 week after discharge.

Primary outcome was the proportion of patients who reported at least 1 ADE 4 weeks post-discharge. A period of 4 weeks was chosen to have enough time to resolve medication related problems and is based on previous studies.[19] A questionnaire, see appendix 2, based on the face- and content validated questionnaire developed by Willeboordse et al.[27] was used to determine the type and occurrence of ADEs (part a) and practical problems (part b). The patient was asked whether he or she suffers from 1 or more complaints of a predetermined list of adverse events (AEs), using a 4-point scale ranging from 0 (no complaints) to 3 (severe complaints). A score higher than 0 was considered as having a complaint and in that case, the patient was asked whether he or she thought it was caused by medication (ADEs). Patients could choose to receive a telephone or online questionnaire. The telephone questionnaire was conducted by 2 blinded medical students, supervised by EU and SE.

Secondary outcomes were: the number of ADEs, AEs and practical problems with medication use per patient within 4 weeks. In addition, Health related Quality of Life (EQ-5D-5L),[28] medication satisfaction and the proportion of patients with 1 or more unplanned readmission(s) or emergency room visit(s), 4 weeks after discharge, were determined. Index values (range −0.329 to 1) were calculated for EQ-5D-5L, with a higher score reflecting a better health state.[29] Patient's medication satisfaction was measured by the Medication Satisfaction Questionnaire (MSQ) (7-point scale rated as follows: 1 = extremely dissatisfied, 2 = very dissatisfied, 3 = somewhat dissatisfied, 4 = neither satisfied nor dissatisfied, 5 = somewhat satisfied, 6 = very satisfied, 7 = extremely satisfied).[30]

Finally, the number of MRPs identified by the community and clinical pharmacist as well as the percentage of accepted interventions was measured. MRPs were classified according to the DOCUMENT system (e.g. medication errors and compliance issues).[24] Two main categories were added: overtreatment and presence of superfluous medication. MRPs were categorized into pharmacotherapy-related and patient-related MRPs (see appendix 3).

Protocol fidelity was assessed for the 4 components of the transitional pharmaceutical care program. For teach-back the date was registered on the inclusion form after the interview for medication reconciliation. For the pharmaceutical discharge letter the date of sending was registered. For the home visit and transitional CMR the date of performing was registered. The number of components performed per patient were scored. If all 4 components were performed, the full transitional pharmaceutical care program was performed.

Statistical analysis

Based on results from a comparable study,[19] a sample size of at least 195 patients per group was calculated to show a decrease from 30% to 18% of the patients reporting at least 1 ADE (2-sided chi-square test with alpha of 0.05 and power of 80%).

Given the differences between the 2 hospitals as described in appendix 1, no overall analysis was possible and stratification per hospital was applied.

Statistical analysis was performed in IBM SPSS version 22.0 (IBM Corporation, Armonk, New York, U.S.). Categorical variables were reported as percentages. Normally and non-normally distributed continuous variables are reported as mean with the standard deviation (SD) and median with the interquartile range (IQR) respectively. Univariable and multivariable logistic regression analysis were performed to compare the proportion of patients with 1 or more ADEs between the control and intervention group, and to compare the proportion of patients with 1 or more unplanned readmission or emergency room visit. Parameters showing a significant association ($p < 0.10$) in the univariable analysis were added to the multivariable analysis. Data were analysed according to intention-to-treat (ITT) analysis. The primary outcome was also analysed in all patients, who received all the 4 components from the transitional pharmaceutical care program, in the per protocol analysis. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) were reported. A Mann-Whitney test was used to compare number of ADEs, AEs, practical problems, quality of life and medication satisfaction between the control and intervention group.

Results

Patient characteristics

Of 835 patients screened for inclusion 369 patients were included in the study (195 in the control group, 174 in the intervention group) (Fig. 1). Of the 466 excluded patients, 229 (49%) did not give informed consent whereas 237 (51%) reported other reasons (e.g. patient was already discharged, participation in conflicting study).

Due to loss to follow up, complete data for the primary outcome ADEs were available for 277 patients (75%). No statistically significant differences were found between the baseline characteristics of patients with complete data (n = 277) and patients with missing primary outcome (n = 92), based on gender (male 56% vs. 57%, p = 0.925), age (70.5 vs. 70.5 years, p = 0.976), number of medications (11.5 vs. 11.5, p = 0.92) and CCI score (1.64 vs. 1.59, p = 0. 795).

The baseline characteristics of both groups were similar, see Table 1. However, for teaching hospital patients, the control patients were more often admitted at the internal medicine ward (55% vs. 42%. P = 0.042).

Protocol fidelity

In the general teaching hospital 71 patients (66%) received the full transitional pharmaceutical care program and in the university hospital 49 patients (72%) (Table 2). In total 49 community pharmacies

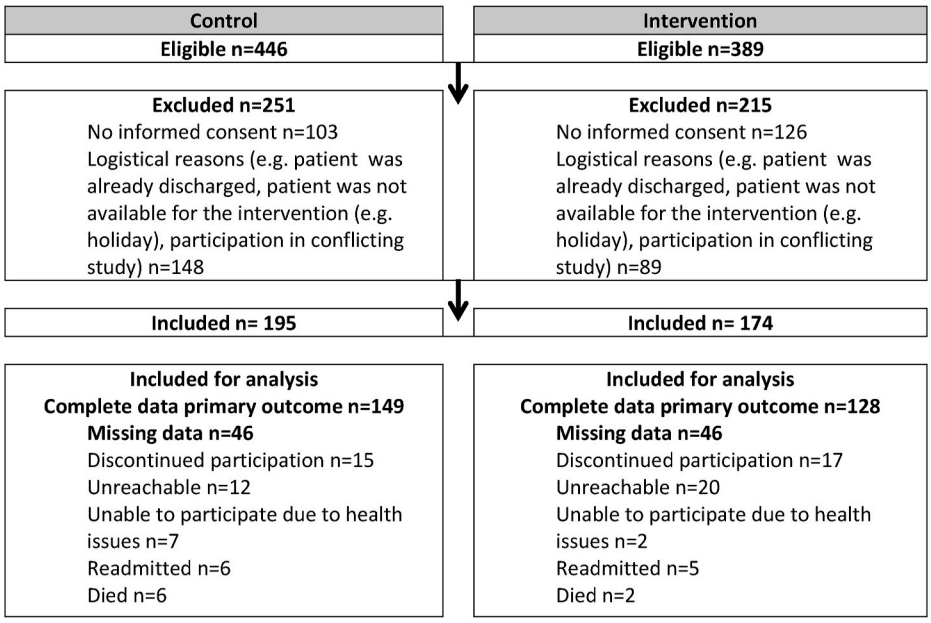

Fig. 1. Study flow.

Table 1
Baseline characteristics.

	General Teaching Hospital			University Hospital		
	Control N = 146	Intervention N = 106	*p-value*	Control N = 49	Intervention N = 68	*p-value*
Age, mean ± SD	71.3 (13.6)	72.0 (12.2)	*0.67*	65.4 (14.6)	69.9 (12.3)	*0.08*
Gender, male, n (%)	70 (48)	63 (59)	*0.07*	32 (65)	42 (62)	*0.70*
CCI score, median (IQR)	2 (1–3)	1 (0–2.25)	*0.25*	1 (0–2.5)	1 (0–2)	*0.83*
Country of birth, n (%)[a]			*0.62*			*0.76*
Netherlands	77 (53)	58 (55)		32 (65)	48 (71)	
Other	49 (34)	32 (30)		10 (20)	13 (19)	
Living Situation, n (%)[b]			*0.83*			*0.18*
Alone	62 (42)	46 (43)		20 (41)	21 (31)	
Together	63 (43)	44 (42)		22 (45)	40 (59)	
Education, n (%)[c,d]			*0.93*			*0.78*
Primary	56 (38)	45 (42)		11 (22)	19 (28)	
Secondary	56 (38)	29 (27)		16 (33)	20 (29)	
Higher	13 (9)	14 (13)		15 (31)	22 (32)	
Department, n (%)			*0.04*			*0.54*
Cardiology	65 (45)	61 (58)		27 (55)	35 (51)	
Internal Medicine	81 (55)	45 (42)		17 (35)	23 (34	
Surgery	–	–		5 (10)	10 (15)	
Unplanned admission, n (%)	142 (97)	106 (100)	*0.99*	34 (69)	49 (72)	*0.75*
Length of hospitalization, mean ± SD	7.2 (6.8)	7.3 (8.2)	*0.91*	9.0 (6.0)	10.0 (7.9)	*0.46*
Hospitalization ≤ 6 months before index admission, n (%)[e]	39 (27)	32 (30)	*0.44*	11 (22)	21 (31)	*0.35*
missing	20 (14)	17 (16)		7 (14)	8 (12)	
Multi-dose drug dispensing system, n (%)	55 (38)	40 (38)	*0.99*	7 (14)	11 (16)	*0.78*
Help with medication use, n (%)[e]	88 (60)	57 (54)	*0.37*	12 (24)	15 (22)	*0.69*
EQ5D-5L, Index value, <1 week after discharge, median (IQR) [f]	0.7 (0.4–0.8)	0.6 (0.3–0.8)	*0.52*	0.7 (0.6–0.8)	0.7 (0.5–0.8)	*0.77*
MSQ <1 week after discharge, median (IQR)[f]	3 (3–4)	3 (3–4)	*0.76*	3 (3–3)	3 (2–4)	*0.54*
Number of medicines at discharge, mean ± SD	12.4 (4.4)	11.6 (4.4)	*0.39*	10.5 (4.7)	9.6 (3.1)	*0.23*
Number of medication changes, mean ± SD	4.4 (2.4)	4.1 (2.4)	*0.30*	5.4 (4.7)	5.0 (3.5)	*0.60*
Medication changes						
New, n (%)	113 (77)	78 (74)	*0.49*	41 (84)	58 (85)	*0.81*
Stop, n (%)	92 (63)	60 (57)	*0.43*	24 (49)	39 (57)	*0.59*
Dosage change, n (%)	79 (54)	55 (52)	*0.73*	24 (49)	34 (50)	*0.91*
Switch, n (%)	35 (24)	30 (28)	*0.44*	14 (29)	26 (38)	*0.28*

IQR: Interquartile range.
[a] 27 missing values in control group and 23 missing values in intervention group.
[b] 28 missing values in control group and 23 missing values in intervention group.
[c] Primary education: elementary or primary school. Secondary education: pre-vocational, senior general or pre-university. Higher education: higher professional or university.
[d] 28 missing values in control group and 25 missing values in intervention group.
[e] 27 missing values in control group and 25 missing values in intervention group.
[f] 35 missing values in control group and 29 missing values in intervention group.

Table 2
Protocol fidelity.

Component	General Teaching Hospital		University Hospital	
	Patients, n (%) N = 106	**Working days after discharge, median (IQR)**	**Patients, n (%) N = 68**	**Working days after discharge, median (IQR)**
Teach-back	106 (100)	0	68 (100)	0
Pharmaceutical discharge letter	105 (99)	1 (0–2)	68 (100)	2 (1–2.8)
Home visit	73 (69)	6 (4–11)	54 (79)	7 (6–12)
Transitional CMR	75 (71)	10 (7–16)	52 (75)	12 (10–18.5)
Complete transitional pharmaceutical care program	71 (66)	–	49 (72)	–
Reasons for incomplete program fidelity	**Patients, n (%) n = 35**		**Patients, n (%) n = 19**	
Study discontinuation of the patient	19 (54)		6 (32)	
Patient readmitted	6 (17)		3 (16)	
Patient unreachable	2 (6)		3 (16)	
No community pharmacist available (e.g. holiday)	5 (14)		2 (11)	
Patient died	1 (3)		0	
Transitional CMR performed after study period	2 (6)		5 (26)	

CMR = clinical medication review.

participated in the intervention. Table 2 shows how often the components of the program were performed. Main reasons for an incomplete transitional pharmaceutical care program were due to unavailability of the patient, e.g. study discontinuation or readmission of the patient.

Teach-back took place at the day of discharge and the discharge letter was sent in the general teaching hospital within a median of 1 (IQR 0–2) working day and in the university hospital within a median of 2 (IQR 1–2.75) working days after discharge. The transitional CMR took place in the general teaching hospital within a median of 10 (IQR 7–16) working days and in university hospital within in a median of 12 (IQR10–18.5) working days.

Patient reported Adverse Drug Events 4 weeks after discharge

In both hospitals, the proportion of patients with at least 1 ADE 4 weeks post-discharge was not statistically significant different between the intervention and usual care group general teaching hospital: 59% vs. 67% (OR_{adj} 0.70 [95% CI 0.38–1.31]), university hospital: 63% vs 50%, OR_{adj} 1.76 [95% CI 0.75–4.13] (see Table 3). According to the per protocol analysis in the general teaching hospital (n = 60), the proportion of patients with at least 1 ADE 4 weeks post-discharge was lower in the intervention group (52% vs. 67%, OR_{adj} 0.51 [95% CI 0.26–0.99]). The per protocol analysis in the university hospital (n = 41) showed no statistically significant difference between the intervention and usual care group (68% vs. 50%, OR 2.15 [95% CI 0.86–5.38]).

Secondary outcomes 4 weeks post-discharge

No effect of the transitional pharmaceutical care program on the number of ADEs, AEs and practical problems per patient, or on the quality of life and medication satisfaction was found, see Table 4.

The EQ5D-5L index value did not differ between baseline and at 4 weeks in the control group in the general teaching hospital (0.69 vs. 0.71, p = 0.92). In the intervention group in the general teaching hospital the EQ5D-5L index value increased between baseline and at 4 weeks (0.63 vs. 0.67, p = 0.04). In the university hospital an increase was found between baseline and at 4 weeks in both the control as intervention group (control group: 0.69 vs. 0.78, p = 0.01) (intervention group: 0.69 vs. 0.75. p < 0.01). No statistical significant difference was between the MSQ scores between baseline and at 4 weeks.

The EQ5D-5L index value did not differ between baseline and 4 weeks post-discharge in the control group in the general teaching hospital (0.69 vs. 0.71, p = 0.92). In the intervention group in the general teaching hospital the EQ5D-5L index value increased between baseline and 4 weeks post-discharge (0.63 vs. 0.67, p = 0.04). In the university hospital an increase was found between baseline and 4 weeks post-discharge in both the control and intervention group (control group: 0.69 vs. 0.78, p = 0.01, intervention group: 0.69 vs. 0.75. p < 0.01). No statistical significant difference were found between the EQ5D-5L VAS score and the MSQ scores between baseline and at 4 weeks.

The other secondary outcomes (the proportion of patients with 1 or more unplanned readmission(s), and with 1 or more ER-visits) were not affected by the transitional pharmaceutical care program as well.

Type of medication related problems

In the general teaching hospital 237 MRPs were detected in 71 patients during the transitional pharmaceutical care program: of these patients, 77% (n = 55) of patients had at least 1 pharmacotherapy-related MRP and 78% (n = 56) had at least 1 patient-related MRP (appendix 3). In the university hospital 217 MRPs were detected in 49 patients during the transitional pharmaceutical care program: of these patients, 92% (n = 45) of patients had at least 1 pharmacotherapy-related MRP and 86% (n = 42) had at least 1 patient-related MRP. Of the pharmacotherapy-related MRPs, overtreatment, dosing and drug selection problems were the most common problems in both hospitals. Of the recommendations to resolve MRPs, 64% was accepted by the physician involved, 7% was not accepted and of 29% the acceptance was unknown in the general teaching hospital. In the university hospital 49% was accepted, 8% was not accepted and of 44% the acceptance by

Table 3
Patient reported Adverse Drug Events (ADEs) 4 weeks post-discharge in patients from general teaching and university hospital.

	General Teaching Hospital					University Hospital				
	Control	Intervention				Control	Intervention			
		Intention-to-treat		Per-protocol			Intention-to-treat		Per-protocol	
	n = 111	**n = 76**	**OR (95% CI)**	**n = 60**	**OR (95% CI)**	**n = 38**	**n = 52**	**OR (95% CI)**	**n = 41**	**OR (95% CI)**
Patients with any ADE, n (%)	74 (67)	45 (59)	0.73 (0.39–1.33) Adj[a]: 0.70 (0.38–1.31)	31 (52)	0.53 (0.28–1.02) Adj[a]: 0.51 (0.26–0.99)	19 (50)	33 (63)	1.74 (0.74–4.06) Adj[b]: 1.76 (0.75–4.13)	28 (68)	2.15 (0.86–5.37) Adj[b]: 2.15 (0.86–5.38)

[a] Adjusted for department and gender.
[b] Adjusted for age.

Table 4
Number of ADEs, patient reported Adverse Events (AEs) and practical problems per patient, Quality of Live, Medication Satisfaction, Unplanned readmissions and emergency room visits 4 weeks after discharge.

	General teaching hospital			University hospital		
	Control	Interven-tion	p-value	Control	Interven-tion	p-value
	n = 111	n = 76		n = 38	n = 52	
Number of ADEs per patient, median (IQR)	1 (0–3)	1 (0–2)	0.30	0.5 (0–2)	1 (0–1)	0.26
Number of AEs per patient, median (IQR)	4 (2–8)	4 (2.25–6)	0.45	4 (2–6)	4.5 (3–9)	0.44
Number of practical problems per patient, median (IQR)	0 (0–0)	0 (0–0)	0.59	0 (0–0)	0 (0-0)	0.78
EQ5D-5L, Index value, median (IQR)[a]	0.71 (0.39–0.83)	0.67 (0.44–0.85)	0.64	0.78 (0.66–0.86)	0.75 (0.67–0.83)	0.56
Medication Satisfaction, median (IQR)[a]	3 (3–4)	3 (3–4)	0.79	3 (3–4)	3 (3–4)	0.23
	n = 140	**n = 104**	**p-value**	**n = 49**	**n = 68**	**p-value**
≥1 Unplanned readmission <4 weeks after discharge, n (%)	18 (13)	14 (13)	0.89	8 (16)	5 (7)	0.14
≤10 days after discharge, n (%)	10 (56)	8 (57)		3 (38)	2 (40)	
within 11–28 days after discharge, n (%)	8 (44)	6 (43)		5 (62)	3 (60)	
Patients with any ADE, n (%)[b]	9 (50)	8 (57)		3 (38)	2 (40)	
≥1 ER-visit <4 weeks after discharge, n (%)	12 (9)	12 (12)	0.44	3 (6)	3 (4)	0.68
≤10 days after discharge, n (%)	5 (42)	5 (42		1 (33)	2 (67)	
within 11–28 days after discharge, n (%)	7 (58)	7 (58)		2 (67)	1 (33)	

[a] 2 missing values in control group of the general teaching hospital.
[b] 11 missing ADE questionnaires in the readmitted patients in the general teaching hospital and 6 missing ADE questionnaires in the readmitted patients in the university hospital.

physicians was unknown.

Discussion

In this study, no effect of a transitional pharmaceutical care program on the proportion of patients with at least 1 ADE 4 weeks post-discharge was found. Only in the per protocol analysis of the general teaching hospital data a reduction of ADEs were found. No effect of the program was found on secondary outcomes.

Three previous studies have investigated the effect of a transitional pharmaceutical care program on the occurrence of ADEs post-discharge. Only the study of Daliri et al. found a reduction in the proportion of patients with ADEs from 25% to 16% (p = 0.04).[19] The proportion of patients with ADEs in the current study is higher. This may be due to the way ADEs were questioned: in both studies ADEs were self-reported by patients. In our study a check-list based questionnaire was used, while in the study of Daliri et al. an open-ended questionnaire was used. Previous studies show that more adverse events are reported in a check-list based questionnaire compared to an open-ended questionnaire.[31] However, as no validated questionnaire to examine post-discharge ADEs exists, further research is needed to find out the best way to gather post-discharge ADEs. The composition of the intervention in study of Daliri et al. was comparable with our transitional pharmaceutical care program. Both programs contained a pharmacist education and both pharmacotherapeutic and clinical information transfer. In contrast, the studies from Kripalani et al. and Phatak et al. investigated the effect of a combined in- and out-hospital intervention with only educational and pharmacotherapeutic components,[17,18] and they found no effect of their intervention on ADEs 30 days after discharge. This suggests that including all 3 components is essential to be effective.[15] This is also confirmed in two studies from the UK, that showed that a combination of electronic transmission of medication related information between the hospital and community pharmacy in combination with medication reconciliation and medication review after discharge may result in lower rates of readmissions.[32,33]

Some explanations for the lack of an effect of our transitional pharmaceutical care program can be given. First, the intended sample size was not reached. One third of the eligible patients did not give informed consent and also 25% of the included patients did not complete the ADE questionnaire. Patients indicated that they already had to arrange a lot around the period after discharge and were reluctant to fill out the questionnaire. Second, only 66% (n = 71) of the patients in the general teaching hospital and 72% (n = 49) of the patients in the university hospital received the complete transitional pharmaceutical care program. In contrast, in the study of Daliri et al. nearly 90% (n = 197) of the patients received a complete intervention.[19] Fourteen percent of the patients discontinued the intervention and in 8% of the patients there was no pharmacist available or the pharmacists were unable to complete the program within 4 weeks. Pharmacists mentioned that additional pharmacy team members were required to perform the intervention and this was not always available.

Third, in 29% (general teaching hospital) and 44% (university hospital) of the suggested recommendations to resolve pharmacotherapy related MRPs, it was unknown whether they were accepted or not. Previous studies have shown that a lack of effect of pharmacist-led home visits could be caused by insufficient collaboration between physicians and pharmacists.[34–36] Pharmacists are not authorized to adjust prescriptions independently, so there is a dependence on general practitioners or hospital physicians to read and act on recommendations. Even if recommendations were accepted, we did not know whether they were implemented as the period of 4 weeks may have been too short to implement changes. The transitional CMR took place in the general teaching hospital within a median of 10 working days and in the university hospital within a median of 12 working days, which was later than the intended time frame of 10 working days. Therefore, maybe more than 4 weeks were needed to solve ADEs. In addition, the study of Parekh et al. showed that the highest risk period for medication-related harm after leaving the hospital is up to 8 weeks.[21] So the follow-up period of 4 weeks after discharge may have been too short to detect and resolve medication related harm.

Fourth, in both hospitals a high standard of usual care was already implemented during hospitalization (including medication reconciliation both at hospital admission and discharge[37]). This made it more challenging to show a further improvement with the transitional pharmaceutical care program. On the other hand, in 77% of the patients in the general teaching hospital and 92% patients in the university hospital at least one MRP was identified during the intervention. This indicates there is ample room for improvement. To address the explanations as described above, more attention should be paid to the implementation of the transitional pharmaceutical care program e.g. by conducting a process evaluation and contextual analysis (33). During this study differences in the implementation of the intervention between the general teaching and the university hospital were experienced. In the general teaching hospital the usual care was more extensive than in the university hospital, as described in appendix 1, making it easier to implement the intervention compared to the university hospital. Also, the type of patients differed between the hospitals. In general, in the university hospital more complex patients are hospitalized compared to the general

teaching hospital. However, no more ADEs were found in the patients from the university hospital. Meanwhile, the higher age and number of medications at discharge, together with the more unplanned admissions, use of multi-drug dispensing systems and help with medication use in patients from the general teaching hospital compared to patients from the university hospital, suggest that patients from the general teaching were at higher risk for ADEs. This could explain the higher proportion of patients with an ADE in the general teaching hospital in the control group. The differences in the implementation of the intervention and patient characteristics may explain why there was an effect of the intervention in the per-protocol-analysis in the general teaching hospital but not in the university hospital. Barriers and facilitators that impact the implementation of the program should be investigated to identify how the program should be adapted for the setting.

The strengths of this study were the participation of both a general teaching and university hospital and the design of the intervention consisting of components performed in- and outside the hospital by both clinical and community pharmacists. However, some limitations need to be discussed. First, this study was performed in one urban region of the Netherlands, limiting generalizability. Especially for the university hospital, many patients could not be included as the their community pharmacy was outside the urban region and was not participating in this study. Second, patients were not randomized because of the risk of contamination bias at the hospital and community pharmacy level. Instead a before-after design was used. This design has some sources of potentially bias, including the comparability of patients before and after the intervention and the influence of developments in the services over the time. Multivariable statistics may partly correct for these biases but unmeasured confounders and bias remains a concern. Third, detection bias could have occurred as patients in the intervention group were triggered by the home visit to report ADEs. No causality assessment of the ADEs by healthcare professionals has been performed, so overestimation of ADEs in the intervention group is possible. No causality assessment was performed as we did not know the actual medication use at 4 weeks after discharge, which is necessary to make a valid statement about the causality. To find out the medication use 4 weeks after discharge, medication reconciliation should have been performed again and this was not included in our study protocol. However, previous studies have identified patients' valuable in reporting ADEs.[38,39] Fourth, we measured protocol fidelity by scoring whether the different components of the intervention were performed, but we did not measure the quality of the performance of the interventions. In total 49 community pharmacists participated in the study and 120 patients received the complete intervention, so most of the participating pharmacists performed the intervention only a few times. This limited the opportunity to gain experience in performing the intervention and could lead to differences in the implementation between hospitals. Also, as the general teaching hospital had already performed several studies on medication related admissions and transitional interventions, some of the components of the intervention, e.g. teach-back, had already been adopted in the usual care. This could have diluted the effect of the transitional pharmaceutical care program as healthcare providers could perform the components for both patients in the control and intervention group.

In conclusion, this study shows that a transitional pharmaceutical care program did not decrease the proportion of patients with ADEs after discharge. This indicates that another approach is needed to reduce ADEs, especially since ADEs 4 weeks post-discharge were common, affecting more than 50% of the patients in both control group and intervention group. A process evaluation is needed to gain insight into how a transitional pharmaceutical care program could diminish those ADEs.

Trial registration

Netherlands Trial Register; Trial NL7788.

CRediT authorship contribution statement

Elien B. Uitvlugt: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. **Selma Ennasery-de Heer:** Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – review & editing. **Bart J.F. van den Bemt:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **Pierre M. Bet:** Writing – review & editing, Methodology, Supervision. **Ferdi Sombogaard:** Writing – review & editing, Methodology, Supervision. **Jacqueline G. Hugtenburg:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Patricia M.L.A. van den Bemt:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition. **Fatma Karapinar-Çarkit:** Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

None.

Acknowledgement

We are grateful to all the participating patients and the contribution of all pharmacists, pharmaceutical consultants and pharmacy technicians. Also, we thank the patient organization for their input in this study and the students Salwa el Ghouch, Natasha Lemmens, Kubra Pulato, Roos-Marije Schotsman, Nursel Uslu and Atiya Mohammad for their help. Special thanks to Joost Vanhommerig for statistical advice. This work was supported by The Royal Dutch Pharmacists Association (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, KNMP). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sapharm.2021.05.009.

References

1. Parekh N, Ali K, Page A, Roper T, Rajkumar C. Incidence of medication-related harm in older adults after hospital discharge: a systematic review. *J Am Geriatr Soc*. 2018; 66:1812–1822.
2. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *Jama*. 1995;274:29–34.
3. El Morabet N, Uitvlugt EB, van den Bemt BJF, van den Bemt P, Janssen MJA, Karapinar-Carkit F. Prevalence and preventability of drug-related hospital readmissions: a systematic review. *J Am Geriatr Soc*. 2018;66:602–608.
4. Knight DA, Thompson D, Mathie E, Dickinson A. Seamless care? Just a list would have helped!' Older people and their carer's experiences of support with medication on discharge home from hospital. *Health Expect*. 2013;16:277–291.
5. Eibergen L, Janssen MJA, Blom L, Karapinar-Carkit F. Informational needs and recall of in-hospital medication changes of recently discharged patients. *Res Soc Adm Pharm*. 2018;14:146–152.
6. Uitvlugt EB, Siegert CE, Janssen MJ, Nijpels G, Karapinar-Çarkit F. Completeness of medication-related information in discharge letters and post-discharge general practitioner overviews. *Int J Clin Pharm*. 2015;37:1206–1212.
7. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. *Ann Intern Med*. 2003;138:161–167.
8. Fylan B, Armitage G, Naylor D, Blenkinsopp A. A qualitative study of patient involvement in medicines management after hospital discharge: an under-recognised source of systems resilience. *BMJ Qual Saf*. 2018;27:539–546.
9. Fylan B, Marques I, Ismail H, et al. Gaps, traps, bridges and props: a mixed-methods study of resilience in the medicines management system for patients with heart failure at hospital discharge. *BMJ open*. 2019;9. bmjopen-2018-023440.
10. World Health Organization. Medication without harm WHO global patient safety challenge. https://www.who.int/patientsafety/medication-safety/en/; 2017. Accessed May 20, 2020.
11. Huiskes VJB, Burger DM, van den Ende CHM, van den Bemt BJF. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. *BMC Fam Pract*. 2017;18:5.

12. Redmond P, Grimes TC, McDonnell R, Boland F, Hughes C, Fahey T. Impact of medication reconciliation for improving transitions of care. *Cochrane Database Syst Rev*. 2018;8(8), CD010791.
13. Hohl CM, Wickham ME, Sobolev B, et al. The effect of early in-hospital medication review on health outcomes: a systematic review. *Br J Clin Pharmacol*. 2015;80:51–61.
14. Spinewine A, Claeys C, Foulon V, Chevalier P. Approaches for improving continuity of care in medication management: a systematic review. *Int J Qual Health Care*. 2013;25:403–417.
15. Tomlinson J, Cheong V-L, Fylan B, et al. Successful care transitions for older people: a systematic review and meta-analysis of the effects of interventions that support medication continuity. *Age Ageing*. 2020;49:558–569.
16. Daliri S, Boujarfi S, el Mokaddam A, et al. Medication-related interventions delivered both in hospital and following discharge: a systematic review and meta-analysis. *BMJ Qual Saf*. 2020;30:146–156.
17. Phatak A, Prusi R, Ward B, et al. Impact of pharmacist involvement in the transitional care of high-risk patients through medication reconciliation, medication education, and postdischarge call-backs (IPITCH Study). *J Hosp Med*. 2016;11:39–44.
18. Kripalani S, Roumie CL, Dalal AK, et al. Effect of a pharmacist intervention on clinically important medication errors after hospital discharge: a randomized trial. *Ann Intern Med*. 2012;157:1–10.
19. Daliri S, Hugtenburg JG, ter Riet G, et al. The effect of a pharmacy-led transitional care program on medication-related problems post-discharge: a before—after prospective study. *PloS One*. 2019;14.
20. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in The Netherlands. *Arch Intern Med*. 2008;168:1890–1896.
21. Parekh N, Ali K, Davies JG, et al. Medication-related harm in older adults following hospital discharge: development and validation of a prediction tool. *BMJ Qual Saf*. 2019;29(2):142–153.
22. Uitvlugt EB, Suijker R, Janssen MJ, Siegert CE, Karapinar-Çarkit F. Quality of medication related information in discharge letters: a prospective cohort study. *Eur J Intern Med*. 2017;46:e23–e25.
23. Ensing HT, Koster ES, Stuijt CC, van Dooren AA, Bouvy ML. Bridging the gap between hospital and primary care: the pharmacist home visit. *Int J Clin Pharm*. 2015;37:430–434.
24. Williams M, Peterson GM, Tenni PC, Bindoff IK, Stafford AC. DOCUMENT: a system for classifying drug-related problems in community pharmacy. *Int J Clin Pharm*. 2012;34:43–52.
25. Uitvlugt EB, Janssen MJ, Siegert CE, et al. Medication-related hospital readmissions within 30 days of discharge: prevalence, preventability, type of medication errors and risk factors. *Front Pharmacol*. 2021;12.
26. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173:676–682.
27. Willeboordse F, Grundeken LH, van den Eijkel LP, Schellevis FG, Elders PJ, Hugtenburg JG. Information on actual medication use and drug-related problems in older patients: questionnaire or interview? *Int J Clin Pharm*. 2016;38:380–387.
28. EQ-5D instruments. https://euroqol.org/eq-5d-instruments/. Accessed 20 May 2020.
29. Versteegh MM, Vermeulen KM, Evers SM, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. *Value Health*. 2016;19:343–352.
30. Vernon MK, Revicki DA, Awad AG, et al. Psychometric evaluation of the Medication Satisfaction Questionnaire (MSQ) to assess satisfaction with antipsychotic medication among schizophrenia patients. *Schizophr Res*. 2010;118:271–278.
31. Bent S, Padula A, Avins AL. Brief communication: better ways to question patients about adverse medical events: a randomized, controlled trial. *Ann Intern Med*. 2006;144:257–261.
32. Mantzourani E, Nazar H, Phibben C, et al. Exploring the association of the discharge medicines review with patient hospital readmissions through national routine data linkage in Wales: a retrospective cohort study. *BMJ open*. 2020:10.
33. Nazar H, Brice S, Akhter N, et al. New transfer of care initiative of electronic referral from hospital to community pharmacy in England: a formative service evaluation. *BMJ open*. 2016;6.
34. Kwint H-F, Bermingham L, Faber A, Gussekloo J, Bouvy ML. The relationship between the extent of collaboration of general practitioners and pharmacists and the implementation of recommendations arising from medication review. *Drugs Aging*. 2013;30:91–102.
35. Holland R, Lenaghan E, Smith R, et al. Delivering a home-based medication review, process measures from the HOMER randomised controlled trial. *Int J Pharm Pract*. 2006;14:71–79.
36. Abbott RA, Moore DA, Rogers M, Bethel A, Stein K, Coon JT. Effectiveness of pharmacist home visits for individuals at risk of medication-related problems: a systematic review and meta-analysis of randomised controlled trials. *BMC Health Serv Res*. 2020;20:39.
37. Karapinar-Çarkit F, Borgsteede SD, Zoer J, Egberts TC, van den Bemt PM, Tulder Mv. Effect of medication reconciliation on medication costs after hospital discharge in relation to hospital pharmacy labor costs. *Ann Pharmacother*. 2012;46:329–338.
38. Zhu J, Stuver SO, Epstein AM, Schneider EC, Weissman JS, Weingart SN. Can we rely on patients' reports of adverse events? *Med Care*. 2011:948–955.
39. Weingart SN, Gandhi TK, Seger AC, et al. Patient-reported medication symptoms in primary care. *Arch Intern Med*. 2005;165:234–240.