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ORIGINAL ARTICLE

Effects of non-dispensing pharmacists integrated in general practice on medication-related hospitalisations

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Aims: To evaluate the effect of non-dispensing pharmacists (NDPs) integrated in general practice on medication-related hospitalisations, drug burden index and costs in patients at high risk of medication problems (being 65 years or older and using 5 or more chronic medications).

Methods: This was a multicentre, nonrandomised, controlled intervention study with pre–post comparison (2013 *vs* June 2014 to May 2015) in 25 general practices in the Netherlands, comparing NDP-led care (intervention) with 2 current pharmaceutical care models (*usual care* and *usual care plus*). In the intervention group, 10 specially trained NDPs were employed in general practices to take integral responsibility for the pharmaceutical care. They provided a broad range of medication therapy management services both on patient level (e.g. clinical medication review) and practice level (e.g. quality improvement projects). In the control groups, pharmaceutical care was provided *as usual* by general practitioners and community pharmacists, or *as usual plus*, when pharmacists were additionally trained in performing medication reviews.

Results: Overall, 822 medication-related hospitalisations were identified among 11 281 high-risk patients during the intervention period. After adjustment for clustering and potential confounders, the rate ratio of medication-related hospitalisations in the intervention group compared to *usual care* was 0.68 (95% confidence interval: 0.57–0.82) and 1.05 (95% confidence interval: 0.73–1.52) compared to *usual care plus*. No differences in drug burden index or costs were found.

Conclusions: In general practices with an integrated NDP, the rate of medication-related hospitalisations is lower compared to *usual care*. No differences with *usual care plus* were found.

Trial registration number NTR-4389, The Netherlands National Trial Register.

The authors confirm that the PIs for this paper are Dorien Zwart (d.zwart@umcutrecht.nl) and Niek de Wit (n.j.dewit@umcutrecht.nl) and that they had direct clinical responsibility for patients.

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KEYWORDS

general practice, medication safety, medication-related hospitalisation, non-dispending pharmacist, primary care

1 | INTRODUCTION

With the aging of the population, the number of patients with comorbidities and polypharmacy increases.[1] These elderly patients are especially prone to unsafe and ineffective pharmacotherapy, leading to adverse events and hospitalisations. In the Netherlands, 10.4% of acute hospitalisations in elderly patients in 2013 were related to medication and almost half of these hospitalisations were potentially preventable.[2]

Pharmacists can have an important contribution to safe and effective pharmacotherapy, but at present they cannot optimally fulfil this role. Several barriers are identified: pharmacists often do not have access to patient medical records and generally, they are insufficiently trained in clinical knowledge and consultation skills. Also, collaborative working relationships between pharmacists and general practitioners (GPs) are often suboptimal, despite working in the same geographical area. The workload of both GPs and pharmacists also contributes to a lack of focus on improving the quality of pharmaceutical care.[3,4] Full integration of a clinical *non-dispensing pharmacist (NDP)* in the primary care team could help to overcome these barriers.

Internationally, the role of pharmacists is developing from mainly dispensing medication towards providing pharmaceutical care in a clinical context.[5] In this new role, the clinical pharmacist takes overall responsibility for the patient's pharmacotherapy in close collaboration with the treating physician.[6] This new model of pharmaceutical care provision includes different pharmacist-led services, such as performing clinical medication reviews, conducting quality improvement projects, holding individual consultations for specific drug therapy problems and educating team members in pharmacotherapy.

Pharmacist-led services provided in general practice are demonstrated to reduce the number of drug therapy problems and improve intermediate outcomes, such as blood pressure, cholesterol and blood glucose.[7] So far, evidence on the effectiveness in terms of clinical outcomes such as morbidity or mortality is lacking. We conducted the POINT-study[8] (Pharmacotherapy Optimisation through Integration of a non-dispensing pharmacist in a primary care Team), to assess the effect of integration of an NDP in general practice on medication-related hospitalisations. As secondary outcomes, we assessed the effect on drug burden index (DBI) and costs.

What is already known about this subject

- Elderly patients with polypharmacy are at risk of medication-related morbidity and mortality.
- Non-dispensing pharmacists integrated in general practice are reported to improve safety and effectiveness of pharmacotherapy in single diseases and proxy endpoints.

What this study adds

- This study demonstrates a lower risk on medication-related hospitalisations in patients with nondispending pharmacist-led care compared to usual care.
- To optimise the quality of pharmacotherapy, pharmaceutical care needs to be fully integrated in primary care.

2 | METHODS

A multicentre, nonrandomised, pragmatic, controlled intervention study with pre–post comparison was conducted between January 2013 and June 2015, comparing pharmaceutical care by an NDP as integral member of the primary care team (intervention group) with 2 current models of pharmaceutical care (control groups). For a detailed description of the study design, see the study protocol.[8]

2.1 | Setting

This study was conducted in general practice in the Netherlands. Participating practices were affiliated to 1 of 3 research networks: Julius General Practitioners Network (University Medical Centre Utrecht), healthcare network Almere (Zorggroep Almere) and the Registration Network of General Practitioners Associated with Leiden University (RNUH-LEO).[9-11]

2.2 | Participating practices

For the intervention group, we included practices that were explicitly willing to host an NDP. These practices had to meet the following additional criteria: availability of a consultation room for the NDP; access to the GPs' electronic medical records; a minimum of 5000 registered patients; at least 1 practice nurse working on chronic disease management programmes.

For the control groups, we included practices that matched the characteristics of practices in the intervention group as much as possible with regard to practice size, degree of urbanisation, socioeconomic status and patients' age distribution.

2.3 | The intervention group: NDP-led care

Ten NDPs (all PharmD) were embedded in 10 general practices in the intervention group, on a full-time basis. Concurrently, they

participated in a newly developed 15-month Clinical Pharmacy Training Program based on interprofessional workplace learning.[12]

The NDPs were given integral responsibility for the pharmaceutical care in the practice, with a main focus on *high-risk patients*: patients aged 65 years or older and using 5 or more chronic medications.[13] At the patient level, the NDPs performed clinical medication reviews for patients with polypharmacy, medication reconciliations for patients discharged from the hospital and individual patient consultations for patients with specific drug therapy problems. Patients were either invited by the NDPs, referred by the GPs or could consult on their own request. At the practice level, the NDPs organised quality improvement projects to systematically identify and treat patients at risk of medication errors, and educated GPs and staff members on pharmacotherapy.

In addition to these predefined fixed tasks, the NDPs' responsibilities could be tailored to the specific needs of the practices. During the Clinical Pharmacy Training Program, alignment to the predefined tasks was evaluated and discussed regularly to increase fidelity of the intervention. No modifications to the original predefined tasks were made.

2.4 | The control groups: usual care and usual care plus

The *usual care* group consisted of general practices where pharmaceutical care was provided in the traditional way, i.e. in collaboration with community pharmacists. In the *usual care plus* group, pharmaceutical care was provided in collaboration with community pharmacists who had completed a nationally accredited training programme in performing medication reviews.[14,15]

2.5 | Data collection

Data were collected between 2013 and 2015. The period between 1 January 2013 and 31 December 2013 served as baseline period (pre).[8] The intervention period started on 1 June 2014 and ended on 31 May 2015 (post). Three months prior to the intervention period, NDPs already started working in the practices. These months were considered necessary for the NDPs to learn basic clinical skills and to establish their position in the practice[16]; no data were collected in these months. For outcome measurements, we only included high-risk patients.

Patient characteristics, such as patients' medical history, medication records and laboratory results, were extracted anonymously from the GPs' electronic medical records. The number of chronic conditions was based on a standardised morbidity index list[17] and a national prevalence list[18] of chronic diseases and multimorbidity. Data on acute, unplanned hospitalisations in above described periods were collected by research assistants. They visited participating practices to collect anonymised discharge letters of acute hospitalisations. Data from the GPs' electronic medical records were used for the analyses of medication-related hospitalisations and drug burden index. For the cost-analyses, anonymised healthcare cost reimbursement data from the major health insurance company[19] were used.

2.6 | Primary outcome

The primary outcome was the number of medication-related hospitalisations in high-risk patients. If patients had multiple medication-related hospitalisations, all hospitalisations were included. Only acute hospitalisations were included, as planned hospitalisations are rarely related to medication.[20]

2.7 | Assessment of hospitalisations

We performed a case-by-case assessment of all acute admissions, based on a modified version of the algorithm by Kramer *et al*.,[21] to identify medication-related hospitalisations. We applied the following procedure, in which all assessors were blinded for the corresponding study groups:

STEP 1: a medical doctor or a senior medical Master student determined whether the reason(s) for admission could be related to a known side-effect of the used medication. Side-effects with an incidence of at least 1% according to Dutch standard reference sources[22-24] and side-effects explicitly described in the discharge letter were included for further assessment.

STEP 2: An expert duo, consisting of a medical doctor (J.P., V.S.) and a clinical pharmacist (A.H., P.H., S.H., M.B.) assessed whether the hospitalisations selected in step 1 were *possibly* or *unlikely* to be medication related. For this assessment, 2 elements were taken into account: first, whether alternative causes (other than the suspected medication), such as a pre-existing clinical condition, explained the reason for admission; second, the time relationship between the potential side effect and the start of medication administration. Admissions that were beyond the scope of the NDPs were excluded, such as admissions in patients treated for malignancies, post-transplantation, patients on renal dialysis and psychiatric admissions.

STEP 3. Results of step 1 and 2 were compared. In case of disagreement, consensus meetings with an experienced GP (D.Z., N. d.W.) and/or clinical pharmacist (A.L.) were arranged. Differences were resolved in discussion.

STEP 4. Of all cases excluded in step 1, a random 10% sample was double checked by a medical doctor (V.S.) and a clinical pharmacist (A.H.). In case of disagreement about the exclusion, the case was reassessed. According to a preset protocol, all excluded cases would be reassessed in case the percentage of disagreement exceeded 10%.

2.8 | Secondary outcomes

2.8.1 | DBI

The DBI[25] measures a patient's total exposure to anticholinergic and sedative medications, taking medication dosage into account:

$DBI = \sum\left(\frac{D}{D+\delta}\right)$, with D being the daily medication dose and δ being the minimum recommended daily dose, we used those stated in Dutch reference sources.[22] We calculated the DBIs at the start and at the end of the intervention period for each high-risk patient. A reduction in DBI of at least 0.5 was considered clinically relevant, as this is the average effect of stopping 1 anticholinergic or sedative drug.[26]

2.8.2 | Costs

We calculated direct primary and secondary healthcare costs and total medication costs, in both the pre and the post periods for each high-risk patient, using cost reimbursement data of the major health insurance company. We compared intervention practices with *usual care* practices, as in *usual care plus* practices too few patients were insured with this company.

2.9 | Sample size

We assumed the annual incidence rate of medication-related hospitalisations in the high-risk population to be 4.5.[27] We expected a 50% reduction of medication-related hospitalisations.[28] To demonstrate a statistically significant difference between the intervention and control groups, at least 2850 high-risk patients needed to be present in each study group. As the high-risk population comprises 6.4% of an average general practice in the Netherlands, 45 000 patients were needed for each study group.[27] Assuming an average practice size of 5000 patients, we aimed to include 10 practices per study group. This was based on a 2-sided α of 0.05 and a power (1 – β) of 0.8.[8]

2.10 | Data analysis

The primary outcome, the number of medication-related hospitalisations in high-risk patients (count data), was analysed with a Poisson mixed model to compare the intervention and control groups, with adjusted rate ratios. The model included a random intercept to adjust for clustering at practice level and a residual (i.e. generalised estimating equations type) covariance matrix to account for patients that were included in both the baseline and intervention period. The intervention effect was assessed with the interaction between study group and study period. We adjusted for patients' age, sex, number of chronically used medications and number of comorbidities (medications and comorbidities as measured in the corresponding study period). On practice level, we adjusted for the degree of urbanisation and socioeconomic status.

In a sensitivity analysis, we excluded those types of medication-related hospitalisations that were previously not used in research of medication-related hospitalisations (fever/infection/inflammation) because of an unclear or weak association between medication and hospitalisation.

The secondary outcome DBI was analysed with a linear mixed model to compare treatment-effects between the intervention and both control groups. A subanalysis was performed excluding patients with a DBI-score of 0 at baseline. Costs were split into direct primary healthcare costs, direct secondary healthcare costs and medication costs, and analysed with linear mixed models on log-transformed data to compare the intervention and *usual care* group. All models included elements comparable but somewhat different to the primary outcome model; for details please see Appendix 1.

All analyses were performed using both SAS software Version 9.4 for Windows and IBM SPSS Statistics for Windows Version 23.0 (Armonk, NY).

2.11 | Ethical considerations

The Medical Ethical Committee of the University Medical Center Utrecht waived formal medical–ethical assessment (METC protocol number 13-432C).

3 | RESULTS

3.1 | Study practices

Ten NDPs were embedded in 10 general practices in the intervention group. One NDP was unable to finish the training programme and was withdrawn from the study. This resulted in 9 intervention practices with an embedded NDP. For the *usual care* and *usual care plus* groups, we approached approximately 125 general practices and included 10 and 6 participating practices, respectively.

The practices in the 3 study arms did not differ in multidisciplinary composition, professional accreditation status, GP training site or urbanisation level (Table 1).

The mean proportion of high-risk patients per practice was highest in the *usual care plus* group: 7.4% compared to 5.6 and 6.4% in the intervention and *usual care* groups. The mean socioeconomic status of patients was higher in the intervention practices (0.9) than in the control practices (0.6; Table 1).

The median number of medication reviews at baseline in the intervention group was 8 per 100 high-risk patients, compared to 15 in the *usual care* group and 3 in the *usual care plus* group. These medication reviews were conducted by community pharmacists and/or GPs, and were part of care as usual.[13] No information on the quality of medication reviews was available. Almost all practices had a high standard of quality of pharmacotherapy audit meetings.[31,32]

3.2 | Patients

A total of 11 928 high-risk patients was included in the analysis. Of 647 patients (5.4%) only pre period data were available, as they were deregistered from the participating practices because of death (55%), moving (9%), or for unknown reason (36%). Of 317 patients who newly registered in the practices during the post period, no pre period data were available (Figure 1). The number of patients who were deregistered or newly registered was not equally distributed between

TABLE 1 Practice and patient characteristics at baseline

		Intervention group (9 practices)	Usual care group (10 practices)	Usual care plus group (6 practices)
Practice	Practice size			
	Patients ≥18 years, median (IQR)	8669 (4765–10 689)	5973 (5371–6646)	6907 (4474–13 981)
	High-risk patients, median (IQR)	427 (312–587)	344 (271–501)	523 (285–1087)
	Setting and organisation			
	Degree of urbanisation[a], mean ± SD (range)	1.8 ± 1.1 (1–4)	2.1 ± 0.7 (1–3)	2.2 ± 0.8 (1–3)
	Socioeconomic status[b], mean ± SD (range)	0.9 ± 1.0 (−1.2–2.2)	0.6 ± 0.9 (−2.1–1.7)	0.6 ± 0.5 (0–1.2)
	Healthcare Centre, *n* (%)	7 (78)	7 (70)	3 (50)
	GP training practice, *n* (%)	8 (89)	7 (70)	4 (67)
	Indoor pharmacy, *n* (%)	6 (67)	6 (60)	4 (67)
	Collaborating pharmacies, mean ± SD (range)	1 ± 1 (1–4)	2 ± 1 (1–4)	2 ± 2 (1–5)
Patient	High-risk patients, *n*	3879	3941	3791
	Male sex, *n* (%)	1703 (44)	1756 (45)	1693 (45)
	Age, mean ± SD	75 ± 8	75 ± 8	75 ± 8
	Patients <75 years, *n* (%)	2069 (53)	1901 (48)	1893 (50)
	Patients 75–85 years, *n* (%)	1318 (34)	1414 (36)	1296 (34)
	Patients ≥85 years, *n* (%)	492 (13)	626 (16)	602 (16)
	Chronic medications, median (IQR)	6 (5–7)	6 (5–8)	6 (5–8)
	Comorbidities[c], median (IQR)	4 (3–6)	4 (3–6)	5 (3–7)

SD, standard deviation; GP, general practitioner; IQR, interquartile range.

[a]Using a 5-point scale of degree of urbanisation (1 = highly urbanised area, 5 = rural area).[29]

[b]Data from Dutch Social and Cultural Planning Office, using status scores of zip code area of the general practice (a higher score represents a higher status).[30]

[c]Using the UK Quality and Outcomes Framework and overview of chronic diseases developed by the Dutch National Institute for Health and Environment.[17,18]

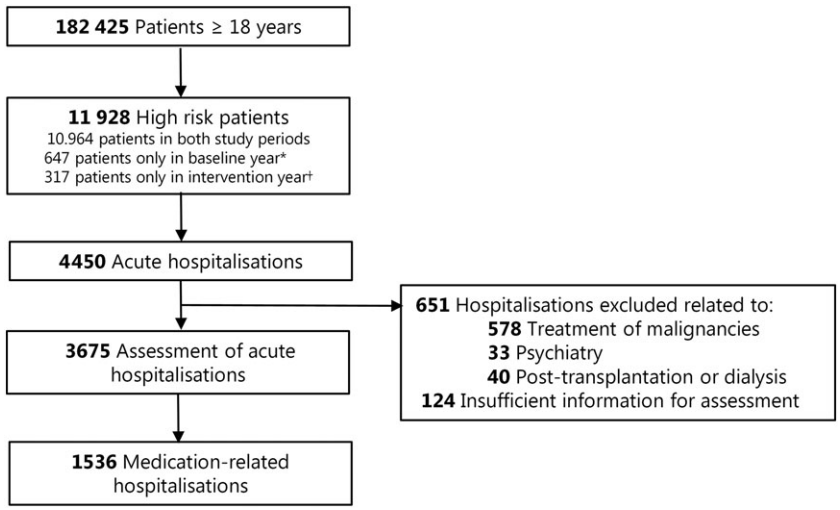

FIGURE 1 Flowchart of medication-related hospitalisations in the total study population in both study periods.
*deregistered high-risk patients in general practice during the pre period. † newly registered high-risk patients in the general practice after the pre period

the study groups. In the intervention, *usual care* and *usual care plus* groups, 3.9, 5.1 and 7.3% of patients were deregistered, and 1.8, 3.9 and 2.1% of patients were newly registered, respectively.

Differences in age and sex distribution between the 3 study groups were insignificant. The proportion of patients aged 85 years or older was 13% in the intervention group and 16% in both control groups (Table 1). The median number of chronically used medications was 6 in all study groups and the median number of registered comorbidities was 4 in both the intervention and *usual care* group and 5 in the *usual care plus* group.

3.3 | Primary outcome: medication-related hospitalisations

In the intervention period, we identified a total of 822 medication-related hospitalisations among 11 281 high-risk patients in the 3 study groups (Table 2). The adjusted mean rate of medication-related hospitalisations was 4.4 per 100 high-risk patients per year in the intervention group, 6.4 in the *usual care* group and 4.2 in the *usual care plus* group (Table 3). The adjusted rate ratio for medication-related hospitalisations in the intervention group compared to *usual care*

TABLE 2 Unadjusted numbers of medication-related hospitalisations in high-risk patients

Study group	Intervention group		Usual care group		Usual care plus group	
Study period	Pre	Post	Pre	Post	Pre	Post
High-risk population, *n*	3879	3798	3941	3894	3791	3589
Acute hospitalisations, *n* (%)	542 (14.0)	584 (15.4)	691 (17.5)	841 (21.6)	517 (13.6)	500 (13.9)
Medication-related hospitalisations, *n* (%)	213 (5.5)	230 (6.1)	297 (7.5)	355 (9.1)	204 (5.4)	237 (6.6)
Patients with medication-related hospitalisations, *n* (%)	172 (4.4)	187 (4.9)	236 (6.0)	289 (7.4)	166 (4.4)	199 (5.5)

TABLE 3 Adjusted rates and rate ratios of medication-related hospitalisations in high-risk patients, per study group[a]

Adjusted rate, *n* medication-related hospitalisations per 100 high-risk patients per year		Rate ratio (95% CI)
	Post	
Intervention group	4.4	Intervention group
Usual care group	6.4	*vs usual care* group: 0.68 (0.57–0.82)
Usual care plus group	4.2	*vs usual care plus* group: 1.05 (0.73–1.52)

CI, confidence interval

[a]Adjusted at patient level for age, sex, number of chronic medications and comorbidities as measured in the corresponding study period; at practice level for the degree of urbanisation and socioeconomic status; and adjusted for clustering, using a Poisson mixed model. These adjustments resulted in estimates for an average patient in the total database

was 0.68 (95% confidence interval [CI] 0.57–0.82) and compared to *usual care plus* 1.05 (95% CI 0.73–1.52; Table 3). Of the patients with a medication-related hospitalisation, 5% had >1 medication-related hospitalisation.

The types of medication-related hospitalisations and associated medications are reported in Table 4. Most frequent hospitalisations were those related to infections, falls and bleeding. Most medication-related hospitalisations were associated with a single medication, but those related to falls and constipation were often associated with a combination of medications.

The sensitivity analysis excluding medication-related hospitalisations related to infections, showed similar adjusted rate ratios of the intervention compared to *usual care* and *usual care plus*: 0.70 (95% CI 0.55–0.89) and 0.97 (95% CI 0.68–1.39), respectively.

3.4 | Secondary outcomes

3.4.1 | DBI

The DBI scores in all groups did not differ. When comparing the treatment effects on DBI scores per patient with a mixed model, we found no differences between the intervention group and both *usual care* groups (Table 5 and 6). The subanalysis, excluding patients with a DBI score of 0 in the pre year, did not alter the results.

3.4.2 | Costs

Mixed model comparison of average direct healthcare costs revealed no differences between the intervention group and *usual care* group in primary care costs, secondary care costs and medication costs (Table 7 and 8). Also, when looking more closely into secondary healthcare costs related to hospitalisations, we found no differences: adjusted ratio 0.82 (95% CI 0.64–1.06).

4 | DISCUSSION

This study demonstrates a lower rate of medication-related hospitalisations among high-risk patients in general practices with fully integrated NDPs compared to *usual care*. No difference with *usual care plus* practices was found. Also, no differences in DBI scores nor in direct healthcare costs were found. Despite the absence of an effect on DBI scores and costs, results on medication-related hospitalisations suggest that in order to improve medication safety, the current model of pharmaceutical care provision should be replaced by new concepts of pharmaceutical care provision, centred around full integration of pharmaceutical care in medical practice — such as the NDP care model.

4.1 | Comparison with existing literature

To our knowledge, this is the first study evaluating the effect of NDPs integrated in general practice on medication-related hospitalisations. Studies measuring the impact of such NDP-led care on relevant clinical patient outcomes are sparse. Lowrie *et al*. reported no effect of NDP-led care on death or hospitalisation in patients with heart failure.[34] Maybe this lack of effect was due to the fact that this intervention had insufficient patient follow-up. Moreover, NDPs in Lowrie's study, so-called *non-specialist pharmacists*, only received a very short additional training.

TABLE 4 Reason for medication-related hospitalisation and associated medications, including both pre and post periods

Reason for admission[a]	*n* (%)	Most associated medications (*n*)[b]
Fever/infection/inflammation (e.g. pneumonia, urinary tract infection)	394 (23)	Corticosteroids (377), immunosuppressive drugs (23), sympathicomimetics (19), opiates (10), diuretics (8), antibiotics (7), antimuscarinics (7), antiepileptics (7), statins (7), benzodiazepines (7)
Dizziness/collapse/hypotension/ syncope[c]	352 (21)	Beta-blockers (152), benzodiazepines (98), ACE inhibitors (96), diuretics (81), angiotensin II receptor blockers (62), antidepressants (54), opiates (53), nitrates (51), calcium channel blockers (47)
Bleeding (non-GI; e.g. haematuria, epistaxis, anaemia)	162 (10)	Vitamin K antagonists (102), antiplatelets (74), heparins (10)
Gastrointestinal complication/bleeding (e.g. ulcer, gastritis, melena)	139 (8)	Antiplatelets (87), vitamin K antagonists (71), NSAIDs (12)
Congestive heart failure	122 (7)	Beta-blockers (53), calcium channel blockers (36), diuretics (32), corticosteroids (13), ACE inhibitors (7), NSAIDs (4)
Arrhythmia (e.g. bradycardia, atrial fibrillation)	82 (5)	Beta-blockers (40), antiarrhythmics (32), antidepressants (7), ACE inhibitors (7)
Renal insufficiency/electrolyte imbalance (e.g. hypokalaemia, hyponatremia)	85 (5)	Diuretics (59), ACE-inhibitors (21), proton-pump inhibitors (9), angiotensin II receptor blockers (9), NSAIDs (7)
Nausea/vomiting/diarrhoea/ gastroenteritis	57 (3)	Proton-pump inhibitors (15), opiates (14), antibiotics (13), corticosteroids (8), laxatives (7)
Ileus/constipation	44 (3)	Opiates (22), calcium-channel blockers (20), β-blockers (13), antidepressants (8), proton-pump inhibitors (8)
Chest pain	42 (2)	ACE-inhibitors (25), β-blockers (7), antiplatelets (5), α-blockers (4)
Confusion/drowsiness/delirium	32 (2)	Opiates (13), dopaminergics (12), benzodiazepines (9), antidepressants (7), antiepileptics (4), antipsychotics (4)
Hypoglycaemia or hyperglycaemia	30 (2)	Insulin (21), oral antihyperglycemics (12)
Other (e.g. cardiovascular events, dehydration, intoxications)	146 (9)	Diuretics (34), corticosteroids (28), dopaminergics (14), antiplatelets (14), ACE inhibitors (12), vitamin K antagonists (11), opiates (9), β-blockers (8), digoxin (7), NSAIDs (6), antiepileptics (6), antidepressants (6), calcium-channel blockers (6)

ACE, angiotensin-converting enzyme; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

[a]In 1 medication-related hospitalisation (total *n* = 1536), >1 cause could be identified (total *n* = 1687).

[b]One medication-related hospitalisation (total *n* = 1536) could be associated with >1 medication (total *n* = 2750).

[c]Also includes patients with a fracture following collapse.

TABLE 5 Unadjusted drug burden index[a] per high-risk patient

Study group	Intervention group		Usual care group		Usual care plus group	
Study period	Pre	Post	Pre	Post	Pre	Post
High-risk patients, *n*[b]	3106	3091	3232	3292	3185	2974
DBI per patient, mean (SD)	0.48 (0.64)	0.50 (0.63)	0.53 (0.63)	0.54 (0.64)	0.78 (0.68)	0.56 (0.67)
DBI categorised, *n* patients (%)						
0	1485 (48)	1425 (46)	1379 (43)	1354 (41)	1331 (42)	1233 (42)
0–1	1158 (37)	1173 (38)	1311 (41)	1342 (41)	1218 (38)	1177 (40)
>1	463 (15)	493 (16)	542 (17)	596 (18)	636 (20)	564 (19)

DBI, drug burden index; SD, standard deviation

[a]Including all chronically used anticholinergic or sedative medications, excluding ATC-D, ATC-L, ATC-P, ATC-S and ATC-V.[33]

[b]Due to missing data, not all high-risk patients as included in the primary outcome analyses were included here.

Studies measuring the impact of NDP-led care on surrogate clinical outcomes (e.g. glycated haemoglobin, blood pressure and cholesterol levels) and the quality of medication use (e.g. appropriateness of prescribing and medication adherence) are more frequent, and generally demonstrate positive effects.[7,35] However, heterogeneity amongst interventions complicates valid comparison of results. Studies about

TABLE 6 Adjusted treatment effect on lowering drug burden index in high-risk patients[a]

Comparison of treatment effects (95% confidence interval)		*P*-value
Intervention group *vs usual care* group	−0.02 (−0.07–0.02)	.291
Intervention group *vs usual care plus* group	−0.01 (−0.06–0.04)	.609

[a]Using a linear mixed model, see Appendix 1.

TABLE 8 Adjusted ratios of average healthcare costs in high-risk patients[a]

Ratio of healthcare costs in intervention group *vs usual care* group (95% confidence interval)		*P*-value
Primary care costs	1.08 (0.99–1.17)	.073
Secondary care costs	0.92 (0.65–1.29)	.622
Medication costs	1.04 (0.98–1.10)	.172

[a]Using linear mixed models, see Appendix 1.

specific interventions and targeting specific medications or specific conditions are more likely to show positive results than studies on complex interventions targeting multiple medications and/or multiple conditions.[36-40] We think, however, that comprehensive medication therapy management is typically needed in high-risk patients, in whom multiple medications and conditions impact each other.[41]

Measuring clinical effects of such NDP-led comprehensive medication therapy management, a complex intervention, is challenging. Full integration of NDPs in general practice seems key to enlarge effect on pharmaceutical care outcomes.[35] Also, taking integral responsibility for the patient's pharmacotherapy and providing follow-up consultations to monitor the patient is recognised to be essential.[42,43] Furthermore, education is needed to equip the NDPs with the necessary clinical knowledge, consultation skills and experience to work as part of the multidisciplinary general practice team.[44,45] We believe that these 3 aspects (the NDPs being fully integrated in the team, taking integral responsibility for the patient's pharmacotherapy and participating in additional education) enable the NDPs to significantly improve the quality of pharmaceutical care.

4.2 | Interpretation of results

Differences in rates of medication-related hospitalisations should be interpreted with caution. We found a stronger increase of total acute hospitalisations in the *usual care* group than in the other 2 groups, when comparing the intervention year to the baseline year (see Table 2). Even after detailed analysis of the data, we could not explain this difference. It might be related to the practice population, or simply to chance. Nonetheless, as the number of total acute hospitalisations is closely related to the primary outcome, this quite marked increase of hospitalisations in the *usual care* group could have influenced (part of) the intervention effect.

Interestingly, medication-related hospitalisation outcomes in intervention and *usual care plus* practices did not differ. We think that this is related to characteristics of the *usual care plus* practices that we did not take into account at the time of inclusion. The additional training in performing clinical medication review (the inclusion criterion for *usual care plus*) appeared to be no standalone feature but rather an expression of an already highly integrated pharmaceutical care-model. In the *usual care plus* practices, there was a strong pre-existing collaboration between GPs and community pharmacists, with joint information systems, regular (in)formal face-to-face meetings between GPs and pharmacists and a common focus upon medication therapy management. The main difference with the NDP-intervention practices was that in these practices NDPs were formally co-located in general practices and extensively trained in clinical knowledge, skills and communication.[12]

Regarding the DBI, we found no difference between the intervention and control groups. When interpreting this finding, several issues

TABLE 7 Crude costs per high-risk patient, in euros

Study group	Intervention group		Usual care group	
Study period	Pre	Post	Pre	Post
High-risk patients, *n*[a]	2525	2574	2553	2474
Primary care costs[b], median (IQR)	403 (232–560)	428 (246–602)	422 (233–581)	364 (228–560)
Secondary care costs[c], median (IQR)	977 (188–3359)	840 (122–3249)	1148 (191–4269)	843 (93–3545)
Medication costs[d], median (IQR)	841 (441–1581)	868 (450–1479)	857 (435–1532)	749 (400–1383)

IQR, interquartile range

[a]Due to using a different data source for these analyses, not all high-risk patients included in the primary outcome analyses were included here.

[b]Primary healthcare costs included consultations and home visits by GPs and general practice-based nurse specialists, additional proceedings, module fees and registration fees.

[c]Secondary healthcare costs included hospital care as remunerated in DOTs (these are defined remunerations for combinations of diagnoses and treatments, that particularly last longer than 1 day but maximally a year). Only those DOTs starting during the study period were included.

[d]Medication costs included medications prescribed both in primary and secondary care.

should be considered. First, due to technical difficulties in extracting the medications used per patient, we had missing data on DBI scores in both the pre and post periods (in 17% and 18% of high-risk patients, respectively). Such large proportions of missing data put the comparison of DBIs at risk, minimising chances to find small differences. Second, we included all high-risk patients in the analysis, while not all patients received the intervention by the NDP, possibly diluting a potential effect.

Few studies used DBI-scores to evaluate effects of NDP-led interventions. A study in the Netherlands, researching effects of an intervention by a community pharmacist in collaboration with a GP, did also not find an effect on DBI scores — even while this intervention was specifically tailored on improving the DBI.[26] On the contrary, 2 studies from Australia did find positive effects on DBI-scores following medication therapy management interventions by pharmacists in collaboration with GPs.[46,47] However, in 1 of these studies,[46] total group effects were researched instead of an in-patient lowering of DBIs. The other study[47] did report an in-patient decrease of DBI-scores, but this reduction of 0.12 did not meet the 0.5 reduction we consider clinically relevant. So, effect of NDP-led care on reducing DBI-scores remains subject of research.

Regarding costs, we hypothesised in advance to find a shift in costs from secondary to primary care in intervention practices compared to *usual care*, as we expected fewer medication-related hospitalisations. However, the cost comparison did not confirm this hypothesis. This might be related to the fact that we used cost reimbursement data of a health insurance company as the basis of the calculations. We could not individually link these data to our general practice database, hence individual cost comparison of medication-related hospitalisations was impossible. In addition, although such cost reimbursement data reflect actual expenditures, they do not precisely cover the actual provided care — at least not regarding secondary healthcare costs. In the Netherlands, secondary care is remunerated through so-called *DOTs* (defined remunerations for combinations of diagnoses and treatments), instead of through individual medical actions. Hence, any existing differences might be blurred, as remuneration data lack precision. This idea, that in our study actual existing differences might be blurred, is further supported by 2 studies reporting an (expected) reduction of costs after introduction of an NDP in primary care in the UK, based on measurements of actual used care-elements.[48,49] Based only on prescribing changes, Snell *et al.*[48] expected reductions in costs of about £90 (equivalent to about €99) per high-risk patient per year (resulting from a total of £46,000 costs savings and £9000 additionally spent on medication after introduction of NDPs in primary care). Including total primary care costs and taking investments into account, Bush *et al.*[49] reported that every £1 invested in NDP-care, would result in £4.73 savings; in total, saving on average £3052 per GP practice per month (about €3364). Few studies reporting on cost-effects of NDP-led care suggest that NDP-led care might reduce costs. We did not find such results, maybe due to the fact that we used cost reimbursement data instead of measurements of actual used care-elements. Future research including cost-effectiveness analyses may provide more insight.

4.3 | Strengths and limitations

This study has several strengths. We covered a large patient population with in total 11 928 registered high-risk patients. The intervention was multifaceted, tailored to the needs of each general practice and performed in a real-life setting. We used a structured methodology to systematically identify medication-related hospitalisations (assessment by a multidisciplinary team, consensus meetings with experts and cross-checking of data) to limit the risk of subjectivity in judgement.

This study also has several limitations. The fact that we chose not to randomise puts the comparison at risk of bias, even though we corrected for several relevant baseline differences. We think, however, that randomisation would have put optimal performance of the NDPs at risk. A second limitation concerns the sample size calculation of the study. During our study, a new study reported an increased prevalence of medication-related hospitalisations: 10.4%[2] instead of the 4.5%[28] we used in our original calculations. In addition, the original sample size calculation was not adjusted for clustering. Future research should take these 2 elements into account. Third, regarding the primary outcome, the hospitalisations we identified were *possibly* medication-related, including various levels of certainty about the causality. To assess *definite* causality (if that is even possible), data including interviews with involved doctors, pharmacists and patients would have been necessary.[50] In addition, we could not measure *preventability* of the medication-related hospitalisations due to the nature of available data. Fourth, flaws in the electronic medical records extraction resulted in the omission of an unknown number of deceased patients in our database. As the number of high-risk patients is the numerator in our primary outcome, these missing data may influence the absolute rates of medication-related hospitalisations among elderly with polypharmacy. However, as data collection was similar in all study groups, these missing data probably did not affect the between-group comparison. Fifth, we included all high-risk patients registered in the participating practices, instead of only patients who had a clinical medication review or consultation with the NDP. This might have diluted the measured effect. Last, the intervention period lasted only a year. Even though we added in advance a 3-month start-up period, this year might have been too short to show the full potential of the intervention.

4.4 | Future research

Integration seems key to improve the quality of pharmaceutical care. This may either be done by introduction of the NDP, or by developing more *usual care plus* practices. The latter would involve investment in existing infrastructure and collaboration, which is likely to be a time consuming and nontransparent improvement process. In contrast, the integration of an NDP in general practice is a well described organisational intervention with a potentially rapid implementation process. Cost-effectiveness of both models should be investigated and implementation research should be continued. An intervention study with matched control patients could provide more insight into the effects of NDP-led care.

5 | CONCLUSION

In practices with NDP-led care, we found a lower rate of medication-related hospitalisations compared to *usual care*. No difference with *usual care plus* was found. High-risk patients will benefit most from integrated pharmaceutical care. Full integration of an NDP in clinical practice, adequate training and integral responsibility are key conditions of success for this new concept of pharmaceutical care provision.

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COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

A.J.L., D.L.M.Z., A.A.d.B., M.L.B., J.J.d.G. and N.J.d.W. participated in the design of the study; D.L.M.Z. and N.J.d.W. were the guarantors of the study. A.C.M.H. and V.M.S. were engaged in the data collection. A.C.M.H., V.M.S., .A.J.L., J.M.P., M.L.B., D.L.M.Z. and N.J.d.W. were involved in assessment of the data. Data analyses were performed by V.M.S. and A.C.M.H., who also drafted the paper. All authors contributed to the interpretation of the findings and critical review of the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (V.M.S.). The data are not publicly available due to privacy restrictions. Related documents such as study protocol, statistical analysis plan, et cetera, are available on request as well.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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