ORIGINAL ARTICLE

Interprofessional Medication Management in Patients With Multiple Morbidities

A Cluster-randomized Trial (the WestGem Study)

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SUMMARY

Background: Medication reviews and medication management are being used more and more around the world to improve medication safety. Both of these tools were originally conceived as pharmaceutical care activities and have recently been developed into interdisciplinary approaches. We studied the efficacy of interprofessional medication management for multimorbid patients that takes their medical conditions, but also their general living situation into account.

Methods: A comprehensive medication management was performed, which involved the collection of information on the drugs each patient took, the way they were stored, the patient's drug intake and handling, and any problems that arose with pharmacotherapy. The interventional approach was evaluated over a period of 15 months in a cluster-randomized controlled trial with a stepped wedge design. The primary endpoint was the quality of pharmacotherapy, as assessed with the Medication Appropriateness Index (MAI). A mixed model was used to analyze efficacy.

Results: 162 patients were enrolled in the study; 142 were included in the intention-to-treat analysis (53.3% women, mean age 76.8 ± 6.3 years). The mean total MAI score decreased significantly ($p \leq 0.001$) from the control phase (29.21, 95% CI [26.09; 32.33]) to the intervention phase (22.27 [19.00; 25.54]), with an effect strength (Cohen's d) of -0.24 [-0.36 ; -0.13]. The number of drug-related problems declined as well.

Conclusion: In this study, interprofessional collaboration increased medication safety. Working across disciplinary boundaries allowed for a decrease in drug-related problems and brought up aspects outside the purview of the primary care physician.

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Internationally, medication management is increasingly becoming an established instrument to improve the quality of therapy and medication safety (1). It is used especially in patients with complex poly-medication, several treating physicians, and a high probability of developing drug-related problems (2, 3). The latter term describes events or circumstances in drug treatment that actually or potentially prevent the achievement of therapeutic goals (4).

Medication management is based on methods of pharmaceutical care; in recent years, it has become a patient-oriented approach that is implemented in structurally different ways (for example, under the supervision of either physicians or pharmacists, or a cooperation of both professions) (5–9). In Germany, the Federal Union of German Associations of Pharmacists (*Bundesvereinigung Deutscher Apothekerverbände*, ABDA) makes a distinction between isolated medication analysis (according to the definition of the Pharmaceutical Care Network Europe, PCNE) (*eFigure 1*) and medication management with longitudinal patient care (10–12).

Systematic reviews and meta-analyses based on controlled studies have described the effectiveness of medication management in outpatient care, especially with regard to quality improvements in medication therapy and medication safety as well as to changes in diverse clinical parameters (13–18). Instruments for measuring the quality of medication therapy—such as a Medication Appropriateness Index (MAI)—allow for the standardized evaluation of the overall therapy (19–22). However, on the basis of these results, conclusions about the effectiveness of medication management can only be drawn to a limited degree for the German healthcare context. A recent systematic review by Viswanathan et al. pointed out the great variance of the achieved results, which is caused by the composition of the interventions and their structural basis (18). As far as we are aware, the results of interventional studies of the cooperation between physicians and pharmacists in the outpatient setting in Germany are currently lacking.

On this background, the Westphalian study on a medication therapy management and home care based intervention under gender specific aspects in elderly multimorbid patients (WestGem) was conducted as an

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interdisciplinary project. The focus was on evaluating the effectiveness of interprofessional medication management in the outpatient care setting. The authors' primary hypothesis was the expectation that the patient's participation in medication management would lead to a change of the quality of medication therapy.

Method

Study design

The proof of efficacy was undertaken in the setting of a controlled, cluster-randomized trial, using a stepped wedge design. Compared with the usual parallel group structure, this design allows for each cluster to start in the control group and the intervention is introduced into the clusters at intervals (in steps).

In the WestGem study, an independent biometrician randomized the participating general practices (clusters) to three (changing) cohorts. After a control period, the cohorts switched to the intervention phase at intervals of three months each. The cohort allocation was disclosed only at the time of the changeover.

During the control phase, patients received standard care; in the intervention phase they additionally participated in medication management.

The intervention phase, depending on the timing of the changeover, was six to 12 months, with a subsequent follow-up period of 3 months. Data were collected at the time of inclusion into the study (T0); at the end of the recruitment phase (T1); and after 3 (T2), 6 (T3), 9 (T4), and 15 months (T6).

The study was entered into the current controlled trials register (ISRCTN41595373). The ethics committee at the Medical Association of Westphalia-Lippe (AKZ-2013–292-f-s) approved the study. The published study protocol provides a detailed description of the WestGem study (23).

Intervention

The complete intervention consisted of two overlapping strands of action that were complementary to standard care:

1. medication management, and
2. care provided by the *Pflege- und Wohnberatung* (PuW, home-care specialists), using a case management concept according to the German Society for Care and Case Management (*Deutsche Gesellschaft für Care und Case Management*, DGCC) (24).

For the purpose of medication management, primary care physicians (PCP) started off by sending information from their patient records to the home-care specialists (*eTable 3*). The home-care specialists arranged a home visit, conducted an assessment of the patient situation they found—including, among others: drugs taken, adherence, medication handling and storage, reported problems with medication therapy—and communicated this to the pharmacist, along with the information provided by the primary care physician. The pharmacist then undertook a comprehensive medication review (PCNE type 3). This included drugs taken, medication documented by

primary care physicians, available laboratory data, diagnostic data, and insights into every patient's personal situation as elicited in patient interviews. The results of the analysis were summarized in a letter of recommendation and sent to the home-care specialists, who in turn added information on the patient's home situation and passed them on to the primary care physicians. Implementing the recommendations was the responsibility of each primary care physician. Details about such patient-related advice from physician to pharmacist and detailed information on the second strand of action can be obtained from the authors.

Setting and study population

The study was conducted in two regions in the Westphalia-Lippe area. In a first step, all general practices in the regions were invited to participate in the study. Subsequently, patients were recruited from September 2013 to December 2013 (*eBox 1*).

We included patients who met the inclusion and exclusion criteria listed below and who had given written consent to participating in the study:

Inclusion criteria

- Age ≥ 65 years
- A minimum of three chronic disorders affecting two different organ systems
- At least one cardiovascular disease
- At least one visit to the PCP in each of the preceding three-month intervals
- Five or more long-term drug treatments (>3 months) with systemic effects
- Ability to complete questionnaires, with assistance if required

Exclusion criteria

- Life expectancy of less than 12 months (assessed by the treating primary care physician)
- Participation in another clinical study

Study endpoints

The primary outcome measure of the study and the goal parameter for medication management was the quality of medication therapy, measured by using the MAI score (*eBox 2*). The 10 criteria of this score enable standardized assessment of the medication (25–27).

Secondary endpoints were the number of drug-related problems (DRPs), potentially inadequate medication (PIM), patients' quality of life, everyday life skills/competencies, and gait stability/risk of falling.

The attained level of social support was measured as the endpoint to evaluate intervention component 2 (results not shown) (28).

Data collection and measuring instruments

Data were collected by using different documentation media (for a detailed description, see [23]). For the endpoints explained in the Results section, *eTable 1* shows a summary of the fundamentals and instruments of documentation.

TABLE 1

Sociodemographic and clinical characteristics of the intention-to-treat patient cohort in total and considered separately by time of changeover

	Total	Cohort 1: Start of intervention after end of recruitment period	Cohort 2: Start of intervention after 3 months	Cohort 3: Start of intervention after 6 months
	N = 142	n = 59	n = 40	n = 43
Sex [n (%)]				
Male	66 (46.5)	31 (52.5)	10 (25)	25 (58.1)
Female	76 (53.3)	28 (47.5)	30 (75)	18 (41.9)
Age (years)				
M ± SD	76.8 ± 6.3	76.4 ± 6.1	78.5 ± 6.2	75.5 ± 5.4
Family status [n (%)]				
Single	4 (2.9)	2 (3.4)	2 (5.9)	0 (0)
Married	82 (60.3)	38 (64.4)	12 (35.3)	32 (74.4)
Divorced	8 (5.8)	1 (1.7)	5 (14.7)	2 (4.6)
Widowed	42 (31)	18 (30.5)	15 (44.1)	9 (21)
Illness severity				
Number of disorders [M ± SD]	12.7 ± 5.7	12.61 ± 6.1	12.3 ± 4.6	13.2 ± 6.3
CIRS-G severity index [M ± SD]	1.63 ± 0.4	1.75 ± 0.5	1.7 ± 0.3	1.4 ± 0.3
Glomerular filtration rate in mL/min*				
M ± SD	65.2 ± 27.4	70.1 ± 29.9	55.1 ± 24.3	67.9 ± 24.9
Chronic disorders [n (%)]				
Essential hypertension (I10)	109 (76.8)	52 (88.1)	27 (67.5)	30 (69.8)
Lipid metabolism disorder (E78)	77 (54.2)	32 (54.2)	23 (57.5)	22 (51.2)
Chronic ischemic heart disease (I25)	57 (40.1)	23 (39.0)	12 (30.0)	22 (51.2)
Diabetes mellitus type 2 (E11)	50 (35.2)	31 (52.5)	10 (25.0)	9 (20.9)
Atrial flutter and fibrillation (I48)	29 (20.4)	14 (23.7)	6 (15.0)	9 (20.9)
Number of drugs documented by primary care physician				
M ± SD	9.4 ± 3.1	10.3 ± 3.6	9 ± 2.8	8.8 ± 2.4
Proportion of potentially inadequate medication according to PRISCUS list [n (%)]				
Proportion of patients with a prescription	37 (26.1)	16 (27.1)	12 (30.0)	9 (20.9)
Proportion of patients with more than one prescription	6 (4.2)	2 (3.4)	--	4 (9.3)

N, total number within sample; n, number of subgroups; M, mean value; SD, standard deviation;

*calculated by using the Cockcroft-Gault formula, without correcting for body weight

Sample size calculation and statistical analysis

The sample size estimate was done according to Woertman et al. (29). The required sample size to achieve a power of $1-\beta = 80\%$, a two-sided significance level of $\alpha = 5\%$, an effect size of Cohen's $d=0.25$, and after defining all required variables ($ICC=0.05$; for more see [23]), was 240 patients.

The endpoints were evaluated on the basis of an intention-to-treat population. We started with a descriptive data evaluation; results were presented as means and standard deviations. In order to analyze the effectiveness of medication management we developed a mixed model and evaluated this with a signifi-

cance level of 5%. In order to determine the mere effects of the intervention, we conducted a model specification by considering so-called contrasts, which evaluated the mean change in MAI scores between the control and intervention phases at defined follow-up points (eBox 3). These results are shown as the "mean difference in contrast" with 95% confidence intervals and as effect sizes (Cohen's d). All secondary endpoints were evaluated in analogy to the primary endpoint. For the latter we conducted additional sensitivity analyses (eBox 3). The significance level for all non-confirmatory tests was 5% and was intended to be exploratory. We used SPSS Statistics 23 (IBM Corp,

Alteration of Medication

Appropriateness Index Scores over the study period, separated according to changeover groups

Explanation of documentation time points:

T0, baseline data collection at time of inclusion in the study;
T1, data collection at the end of the recruitment period;
T2, 3 months after the end of the recruitment period;
T3, 6 months after the end of the recruitment period;
T4, 9 months after the end of the recruitment period;
T5, 12 months after the end of the recruitment period;
T6, 15 months after the end of the recruitment period

FIGURE

Armonk, NY, USA) and STATA 14 (StataCorp, College Station, Texas, USA).

Results

Characteristics of the study population

Of the 70 primary care physicians we approached, 13 responded to our invitation; 12 were included in the study and were allocated randomly to the three study cohorts (C1: start after the end of the recruitment period, C2: start after three months, and C3: start after 6 months).

On the assumption of 856 potential study participants, 480 patients were approached about participating in the study (*eBox 1*). 162 patients consented in writing to participate (4–24 per practice). The intention-to-treat population comprised 142 patients. The CONSORT flowchart in *eFigure 2* provides an overview of the flow of patients throughout the study.

The mean age of the ITT cohort was 76.7±6.5 years, and the collective included 76 (53.5%) women. 33.6% of study participants were living alone at the time of the study. *Table 1* describes relevant sociodemographic and clinical characteristics.

Medication therapy at baseline

When reconciling the primary care physicians' documentation with patients' drug intake at home, we found deviations in 4.8±3.5 medical drugs per patient at baseline, in terms of dosages differing from those prescribed, modified intake modalities, or continued use of drugs that should have been discontinued. 60.3% of drugs affected by deviations were lacking in the primary care physician's documentation and resulted from

medication obtained elsewhere or self-medication. The total number of drugs documented by primary care physicians was 9.4±3.5, the number of drugs actually taken was 10.5±3.6.

The mean number of drug-related problems at baseline was 7.3±3.4 per patient. The most common cause for the occurrence of drug-related problems was the choice of substance (49.8%) (*eTable 2*). The mean observed number of interaction effects per patient was 5.5±3.9; 26.8% of such interactions were categorized as clinically relevant and 32.7% as partially clinically relevant.

Primary endpoint

The analysis of the Medication Appropriateness Index (MAI) showed that the mean baseline score in patients in cohort 1 was reduced from 30.15±24.14 to 14.09±14.80 points after 15 months. In cohort 2 it was reduced from 43.27±30.39 to 24.47±16.17 points, and in cohort 3 it was reduced from 26.07±17.33 to 18.44±14.67 points (*Figure*). *Table 2* summarizes the numbers and proportions of prescriptions categorized as inappropriate according to the MAI criteria.

The difference in scores between the control period and the first intervention period reached significance with a mean of −4.51 units (95% confidence interval [−6.66; −2.36], $P<0.001$; effect size $d=-0.24$, [−0.36; −0.13]). An additional medication review showed a reduction in the mean MAI score compared with patients who had had one assessment by additional −0.99 units [−3.96; 1.97], $P=0.510$; $d=-0.04$, [−0.17; 0.08]. Sensitivity analyses (*Table 3*) showed that the change in the mean MAI score was mainly due to an improved

TABLE 2

Numbers and proportions of inappropriate prescriptions, coded by domain of the Medication Appropriateness Index (MAI) score

Domain of MAI score considered	Total		Cohort 1: Start of intervention after end of recruitment period		Cohort 2: Start of intervention after 3 months		Cohort 3: Start of intervention after 6 months	
	Baseline (N = 1261)	After 15 months (N = 1283)	Baseline (n = 582)	After 15 months (n = 585)	Baseline (n = 312)	After 15 months (n = 311)	Baseline (n = 367)	After 15 months (n = 387)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
1. Is there an indication for the drug?	197 (15.6)	96 (7.5)	87 (14.9)	30 (5.1)	61 (19.6)	34 (10.9)	49 (13.4)	32 (8.3)
2. Is the medication effective for the condition?	261 (20.7)	131 (10.2)	102 (17.5)	39 (6.7)	88 (28.2)	45 (14.5)	71 (19.3)	47 (12.1)
3. Is the dosage correct?	353 (28.0)	203 (15.8)	133 (22.9)	63 (10.8)	124 (39.7)	70 (22.5)	96 (26.2)	70 (18.1)
4. Are the directions correct?	358 (28.4)	201 (15.7)	138 (23.7)	61 (10.4)	117 (37.5)	71 (22.8)	103 (28.1)	69 (17.8)
5. Are the directions practical?	322 (25.5)	154 (12.0)	132 (22.7)	42 (7.2)	99 (31.7)	57 (18.3)	91 (24.8)	55 (14.2)
6. Are there clinically significant drug–drug interactions?	251 (19.9)	170 (13.3)	118 (20.3)	74 (12.6)	71 (22.8)	45 (14.5)	62 (16.9)	51 (13.2)
7. Are there clinically significant drug–disease/condition interactions?	87 (6.9)	52 (4.1)	32 (5.5)	18 (3.1)	33 (10.6)	17 (5.5)	22 (6.0)	17 (4.4)
8. Is there unnecessary duplication with other drug(s)?	82 (6.5)	43 (3.4)	40 (6.9)	20 (3.4)	29 (9.3)	13 (4.2)	13 (3.5)	10 (2.6)
9. Is the duration of therapy acceptable?	218 (17.3)	114 (8.9)	84 (14.4)	28 (4.8)	77 (24.7)	43 (13.8)	57 (15.5)	43 (11.1)
10. Is this drug the least expensive alternative compared to others of equal utility?	118 (9.4)	86 (6.7)	46 (7.9)	32 (5.5)	39 (12.5)	27 (8.7)	33 (9.0)	27 (7.0)

Note: The MAI score was calculated according to the method described by Hanlon et al. 1992 (27) and Samsa et al. 1994 (25). The table shows the numbers and proportions of drugs that were assessed as inappropriate in the individual domains of the MAI score.

N, total number in sample; n, number in subgroups

The domains of the MAI score are slightly different in the German version of this article (<http://www.aerzteblatt.de/pdf.asp?id=183308>) in the sense that they are not phrased as questions. For this English-language version, we decided to use the original questions as formulated by Hanlon et al.

quality of the prescribed medication and not due to a change in the number of drugs.

Secondary endpoints

The number of drug-related problems dropped (-0.45 , $[-0.81; -0.09]$; $P=0.014$; $d=-0.13$, $[-0.23; -0.03]$). The second medication review showed no additional reduction. Depending on the category of cause, up to 60% of drug-related problems were solved (*eTable 1*). Medication management did not show any effect for additional endpoints in this analysis (*Table 3*).

Discussion

Results in the context of the published literature

The study showed a statistically significant effect of the intervention on the quality of medication therapy; the number of drug-related problems decreased as well. Both aspects are regarded as indicators in medication safety (30).

As far as we are aware, our study is the first published investigation that generates insights into the effectiveness of interprofessional medication management covering a variety of diseases in the outpatient set-

ting in Germany. A study by Wolf et al. (2015) also found positive effects on the reported parameters for inpatient psychiatric care and outpatient follow-up care (30). A study in patients with Parkinson's disease, reported by Henrichsmann and Hempel (2015), showed an improvement in symptoms (31). International studies have shown similar trends for effects, but different effect sizes, which can be partly explained with a disease-specific focus of the medication management (9, 18, 32). Furthermore, in our study, the type and number of implemented pharmaceutical recommendations affected the observed change in the quality of medication therapy. The process evaluation yielded a mean implementation rate of pharmaceutical suggestions of 54.9%; the rate increased the longer physician and pharmacist had been cooperating (33). The identified number of drug-related problems corresponds to comparable studies (34, 35). The drug-related problems that were included were based on the physicians' documentation only, in order to assess the control period and the first intervention period on the basis of the same data.

The achieved improvement in the quality of medication therapy can be regarded as an important and obvious step

TABLE 3

Results of the intention to treat-analysis for primary and secondary endpoints

	Study phase		Mean difference in contrast [95% CI]	Effect size* ¹ in contrast [95% CI]
Primary outcome measure				
	Control phase	Intervention phase 1		
MAI sum score per patient	29.21 [26.09; 32.33]	22.27 [19.00; 25.54]	−4.51* ² [−6.66; −2.36]	−0.24 [−0.36; −0.13]
	Intervention phase 1	Intervention phase 2		
MAI sum score per patient	22.27 [19.00; 25.54]	19.08 [15.47; 22.69]	−0.99 [−3.99; 1.97]	−0.04 [−0.17; 0.08]
Secondary outcome measure				
	Control phase	Intervention phase 1		
Number of DRP per patient	6.98 [6.27; 7.66]	5.87 [5.23; 6.54]	−0.45* ³ [−0.81; −0.09]	−0.13 [−0.23; −0.03]
Number of PIM prescribed	0.39 [0.34; 0.44]	0.32 [0.26; 0.38]	−0.04 [−0.09; 0.01]	−0.08 [−0.19; 0.03]
SF-12 – physical sum scale	38.47 [37.45; 39.49]	38.26 [37.17; 39.34]	−0.25 [−1.65; 1.15]	−0.02 [−0.16; 0.11]
SF-12 – psychological sum scale	46.30 [45.04; 47.57]	46.06 [44.76; 47.36]	−0.96 [−2.74; 0.82]	−0.07 [−0.20; 0.06]
ADL (according to Barthel index)	94.83 [93.75; 95.91]	94.99 [93.84; 96.14]	0.46 [−0.90; 1.82]	0.04 [−0.08; 0.16]
iADL (according to Lawton and Brody)	6.64 [6.50; 6.78]	6.40 [6.24; 6.55]	−0.20 [−0.43; −0.02]	−0.12 [−0.26; 0.01]
Mobility test according to Tinetti	22.20 [21.10; 23.30]	21.66 [20.55; 22.78]	−0.37 [−1.13; 0.40]	−0.06 [−0.18; 0.06]
Sensitivity analysis MAI score* ⁴				
Mean MAI score per patient and medication	3.01 [2.71; 3.30]	2.30 [2.00; 2.61]	−0.48* ² [−0.67; −0.29]	−0.27 [−0.38; −0.16]
Number of prescribed drugs per patient	9.77 [9.51; 10.04]	9.83 [9.54; 10.12]	0.09 [−0.18; 0.36]	0.04 [−0.07; 0.15]

If not noted otherwise, values shown are means with 95% confidence intervals.

Note: The results shown correspond to a mixed model with a particular model specification, which clarifies the mere effect of medication management. For the primary outcome measures the values shown are the effects of the first intervention phase (that is, effects of an initial changeover to the intervention) as well as the effects that were achieved additionally by means of a second medication analysis (intervention phase 2). For all secondary outcome measures, only the results of the control phase and intervention phase 1 are shown.

DRP, drug-related problems; ADL, activities of daily life; iADL, instrumental activities of daily life; CI, confidence interval; MAI, Medication Appropriateness Index; PIM, potentially inappropriate medication

^{*1}corresponds to Cohen's d; ^{*2}statistically significant at a significance level of $p \leq 0.001$; ^{*3} $p = 0.014$; ^{*4}For a description of the sensitivity analysis, see eBox 3

towards increased medication safety, even though current literature does not provide a clear correlation between a MAI score reduction and patient outcomes (18, 19, 21, 32). We are therefore investigating in secondary analyses which change on the MAI score leads to a clinically significant improvement in patient relevant endpoints.

Strengths and limitations

We were able to compile a detailed dataset for 142 multimorbid patients with polymedication, allowing precise insights into patients' entire life and healthcare situation. The stepped wedge design we used furthermore enables a comprehensive evaluation of the process. The study does, however, include a random regional sample, which includes medical practices that were willing to participate. For this reason, we cannot exclude the possibility of a selection bias (for example, certain prescribing profiles, specialized practices). The differences in the structure of patients in the practices underlines this assumption. It is unlikely, however, that the patient selection was done by the physicians themselves as the included study participants had been drawn randomly from the total number of all relevant patients in a given practice.

The low number of cases in the study is a further limitation. In spite of our recruitment effort we were not able to reach our target of 240 patients. This would have required a longer recruitment period, which was not feasible because of the restricted funding period. The case number was not sufficient especially for the evaluation of the patient-relevant secondary endpoints.

Another limitation of our study was the approach in determining the MAI score. The pharmacists had been blinded when calculating scores as to which cohort a patient was allocated to, but they were involved in some cases in conducting the medication reviews. They can therefore not be regarded as completely independent. For reasons of comparability between the control and the intervention phase, the MAI score is solely based on the physicians' patient files. The drugs the patients were actually taking were not regarded. This means that we were able to assess individual criteria (Table 2) to a limited extent only.

As far as the generalizability of the intervention and translation to routine healthcare practice is concerned, it should be borne in mind that the participating pharmacists were particularly qualified for the medication reviews (for example most pharmacists had attained a

doctorate in clinical pharmacy and were particularly specialized in medication management). The participation of the home-care specialists in the medication management process is a similar limitation. The home-care specialists conducted the so-called “brown bag review” (the inspection of all medication packages that patients had collected) on behalf of the pharmacists and therefore took over an pharmaceutical core activity. This was necessary because the terms of the funding program prohibited pharmacists from direct patient contact as a means to prevent a competitive advantage.

Conclusions

Interprofessional medication management has proved effective in outpatient care in terms of quality improvement of medication therapy in elderly multimorbid patients with polymedication. Furthermore, the number of drug-related problems was reduced. Larger follow-up studies should adapt the intervention to a wider and optimized community setting. The authors’ own secondary analyses demonstrated, for example, that not all patients benefitted equally from participating in medication management (33). In view of the resource implications associated with the interdisciplinary management of patients, criteria for how to select suitable patients might be conceived. For example, the number of drugs taken and the deviation between drugs prescribed and actually taken by the patient were significant factors determining a patient’s individual response to medication management.

Studies with longer follow-up periods should furthermore investigate the effect of medication management on patient relevant endpoints.

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Conflict of interest statement

Pharm D Rose has received conference delegate fees, travel expenses, and accommodation costs, as well as honoraria for preparing scientific continuing medical educational events, from Bayer, Boehringer Ingelheim, Medac, MSD, and Omnicell.

Pharm D Walthering has received lecture honoraria from Medac, MSD, and HRA-Pharma.

Prof. Köberlein-Neu, Prof. Mennemann, Stefanie Hamacher, Corinna Schaffert, and Prof. Jaehde declare that no conflict of interest exists.

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KEY MESSAGES

- Medication management is an internationally established interprofessional and patient-oriented service.
- Our study showed a statistically significant effect of interprofessional medication management on the quality of drug therapy in Germany, which was measured using the Medication Appropriateness Index (MAI).
- The number of drug-related problems (DRP) was reduced by the intervention.
- The study revealed a profound discrepancy between the medications prescribed and those actually used by patients.
- The study results showed that interprofessional and comprehensive medication management leads to improved medication safety in outpatient care in Germany.

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Supplementary material
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Supplementary material to:

Interprofessional Medication Management in Patients With Multiple Morbidities
A Cluster-randomized Trial (the WestGem Study)

by Juliane Köberlein-Neu, Hugo Mennemann, Stefanie Hamacher,
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eBOX 1

Recruitment of patients and PCPs in detail

For the purpose of recruiting participating practices, all primary care physicians in the two regions received letters providing information on the planned study and invitations to participate between March and August of 2013. The selection of study practices was therefore not random but was based on the primary care physicians' voluntary decision.

Patients were recruited from September 2013 to December 2013. In order to avoid or minimize selection bias in recruiting patients, we selected participants in two steps:

- 1) The staff in each participating practice compiled a list of all patients who met the inclusion and exclusion criteria. The exception was the inclusion criterion "signed consent form"; this became relevant only in the second stage of recruitment. The patient list was pseudonymized and handed over to an independent statistician, who, on the basis of the practice lists, drew a random sample comprising 40 patients each and sent this to the participating primary care physician as a recruitment list.
- 2) The selected potential participants subsequently received an invitation to participate in the study from their primary care physician, which included information and a consent form. Furthermore, the contents of these documents were discussed in a personal consultation, and if patients were willing to participate they gave written consent at this stage. A new sample of patients was drawn from the original pool of participants, if fewer than 20 patients of the first recruitment list had consented.

eBOX 2

MAI score calculation

The MAI score was chosen as the primary endpoint as it ensures a comprehensive and evaluated assessment of the quality of drug therapy. The score provides 10 criteria for the evaluation of each drug taken by the patient (*Table 2*). These were operationalized by using assessment instructions and examples, and assessed by using a 3-point scale (1–appropriate, 2–marginally appropriate, 3–inappropriate). Subsequently the assessments were dichotomized and the criteria were weighted. Criteria that were deemed appropriate or marginally appropriate for a medication were given a value of "0." Criteria judged to be "inappropriate" were coded as "1" (27). They were subsequently weighted according to the publication by Samsa et al. (1994) (25):

The MAI sum score per medication was calculated by adding up the values per criterion. The highest achievable score per drug was 18 points; a higher point score expressed an increasing degree of inappropriateness. A total score for each patient was developed by adding up the generated scores per drug (25, 27).

In order to determine the appropriateness of medication therapy using the MAI score in a valid and reliable fashion, extensive clinical information about the patient is required—for example their prescription history (26). By means of information exchanges between primary care physicians, home-care specialists and pharmacists, this was ensured in the WestGem study.

Two pharmacists separately evaluated each patient's MAI score. They were blinded with regard to the patients' group allocation. The physician's documentation formed the basis for the evaluation. In this context, it would not have made sense to base the evaluation on the drugs found in the patient's domestic environment—which would have reflected the drugs actually taken rather better—as information on the actual medication was available only for the intervention phase. This means that any comparison with the control group would have been impossible.

eBOX 3

Further descriptions of the evaluation of the outcome measures

Allocation to the control and intervention phase

Medication management in the WestGem study included the professional dimension—that is, the relationship between physicians and pharmacists—as well as the patient dimension—the interaction between physicians and patients. This multistep, complex study characteristic could have caused the treatment effect in the intervention phase to become noticeable only after long time delays. In order to take into account this aspect in allocating patients to the intervention and control phases, study participants were allocated to the intervention phase not at the time of the changeover from the control to the intervention phase but at the next but one documentation time point after that. We cannot exclude the possibility that some patients already displayed treatment effects at this point, although they were still in the control phase. This bias is negligible, however, as it would lead to underestimation of the intervention effect.

Further explanations regarding the mixed model

To analyze the effectiveness of medication management, we developed a mixed model using the MAI sum score at documentation follow-up points 2 to 7 as dependent variables. In addition to the baseline MAI score, the timings of the documentation, the treatment status (control phase / intervention phase with medication review / intervention phase with two medication reviews), and the interaction between the timing of the documentation and the treatment status as fixed effects. We considered the allocation of a patient to a practice as a random effect. The time dependence of the MAI score owing to repeated measurements was modeled by using a heterogeneous first-order autoregressive covariance structure.

To evaluate the pure effect of the intervention—that is, the changeover from the control phase to the intervention phase and from the intervention phase with one assessment to the intervention phase with a second assessment—we considered only the time points in the mixed model for which scores were available from the corresponding comparison phases. The mixed model was extended by so-called contrasts that compare MAI scores at the relevant time points.

- Contrast 1 for the comparison between the control phase and intervention phase 1—that is, the fundamental changeover into the intervention and the associated initial assessment: documentation 4 and 5
- Contrast 2 for the comparison between intervention phase 1 and intervention phase 2—that is, the changeover into intervention phase 2, which is done by means of a second assessment: documentation 6 and 7 (sensitivity analysis).

Explanations regarding the sensitivity analysis

The mixed model for the primary endpoint takes into account as the dependent variable the MAI sum score per patient: the MAI scores of individual medications were added up, as is shown in eBox 2. This means that the appropriateness of the entire therapy can be shown. As a result of adding of scores, the MAI scores are determined, on the one hand, from the appropriateness of each single drug and, on the other hand, from the number of drugs. This applies as well for the development of the MAI sum score per patient over the study period, which results from either a reduction in the number of drugs, changes in the appropriateness of the prescribed drugs, or the interaction between those two factors.

As our main analysis did not differentiate between the described effects, we conducted a supporting sensitivity analysis, which considered the mean MAI score per patient as the dependent variable in the mixed model. This means that the individual assessments per drug were not added together in the overall score for a patient but the mean MAI score per patient and medication was calculated. All other specifications of the model were retained. Furthermore, we checked whether the number of drugs had reduced to a significant degree. This approach enabled us to estimate whether the observed development of the MAI score had been determined only by a reduction or an increase in the number of drugs, or if additionally the appropriateness of the individual medication had changed as a result of the intervention.

eFIGURE 1

Definition of medication review (from Pharmaceutical Care Network Europe) (12)

eFIGURE 2

CONSORT flowchart

MAI, medication appropriateness index; T, timing of documentation

Documentation times: T0, baseline collection at inclusion into study; T1, data collection at end of recruitment period; T2, 3 months after end of recruitment period; T3, 6 months after end of recruitment period; T4, 9 months after end of recruitment period; T5, 12 months after end of recruitment period; T6, 15 months after end of recruitment period

Explanations regarding study drop-out at patients' own volition, unrelated to the intervention, according to exit questionnaire: move into care home/moving in with children and therefore changing primary care physicians; change in family situation (for example, death of spouse) and no more time for the study; extended inpatient stays including rehabilitation. From the reasons given in the exit questionnaires we were not able to establish any connection to the intervention.

Definition of the intention-to-treat (ITT) group: all randomized patients whose written consent had been filed, who met all inclusion and exclusion criteria, and for whom the MAI score was determined at least at baseline were included in the ITT analysis. All patients in this group were evaluated within the group they had been randomized to.

Definition of the per protocol (PP) group: all patients within the ITT set who had received medication management according to the cluster they had been randomized to, and for whom, in addition to the baseline MAI score, at least two further MAI scores had been collected after the change from control group to intervention group.

eTABLE 1

Description of the complete intervention

Medication management (initial and follow-up assessment)		
Substeps of the intervention	Content	Participating professionals (qualification)
I. Data passed on to home-care specialists	Among others, patient characteristics, diagnoses, prescribed and known medication, quality of life as judged by patient (SF-12), risk of falls (Tinetti), intolerances and allergies	12 primary care physicians (specialist in primary care medicine or internal medicine)
II. Visit to patient in his/her domestic environment	Drugs actually taken by patient, drug intake modalities, drugs prescribed by physician or self-medication (according to patient), location/storage of drugs, patients' health literacy concerning their medication, therapeutic motivation Time spent on discussing medication with patient: – Initial assessment: 30–45 min – Subsequent assessment (see VII.): 15–30 min	3 home-care specialists (social pedagogue with diploma certificate, gerontologist, healthcare scientist)
III. Data handed over to pharmacist (anonymized)	Patient's medical history provided by primary care physician, information on brown bag review (or home medicines review) and patient assessment by home-care specialists	3 home-care specialists (social pedagogue with diploma certificate, gerontologist, healthcare scientist)
IV. Medication review	Medication review: drug interactions, contraindications, appropriateness or therapeutic goal, drug or therapeutic duplications, potentially inadequate medications, etc. Time spent on medication analysis and preparing the letter of recommendation depending on the degree of complexity: – Initial assessment: 1–4 hours – Subsequent assessment (see VII.): 1–3 hours	6 pharmacists as main assessors (5 Pharm.D) 2 pharmacists as reviewers (1 Pharm.D)
V. Recommendations of home-care specialists communicated to primary care physician	If required, recommendations were added by the home-care specialists (for example, regarding potential aids)	3 home-care specialists (social pedagogue with diploma certificate, gerontologist, healthcare scientist)
VI. Feedback from primary care physician	Primary care physician provides feedback on the implementation of recommendations (evaluation of each recommendation): a. Recommendation rejected, because it is deemed to be medically wrong, b. recommendation rejected for other reasons, c. recommendation rejected for reasons of cost/budget, d. recommendation accepted, e. recommendation partly accepted	12 primary care physicians (specialist in primary care medicine or internal medicine)
VII. Follow-up assessment (after 6 months)	See initial assessment	

The intervention we developed included the processes of medication management as used internationally, the different advisory services of the home-care specialists and the medical expertise of the treating primary care physician. The table shows substeps for medication management. Detailed descriptions of case management of the home-care specialists can be requested from the authors.

The home-care specialists undertook the brown bag review (or home medicines review, in the patient's domestic environment) in this study on behalf of the pharmacists. Taking over this task, which is usually the pharmacists' responsibility, independently of whether undertaken as a brown bag review or home medicines review, was necessary because of the rules of the funding program. Personal contact between pharmacists and patients was not permitted. To ensure that a review conducted by a pharmacist and the data collections from The home-care specialists led to comparable results, a standardized data collection instrument including training materials was developed before the study, which was tested in 10 patients over the course of a pre-test. Direct contact (by telephone) between primary care physician and pharmacist was possible at all times.

eTABLE 2

Basis and instruments of documentation of the endpoints shown

Endpoint	Data collection instrument	Basis of documentation or evaluation	Person in charge of documentation/calculation	Documentation time point						
				T0	T1	T2	T3	T4	T5	T6
Quality of medication therapy	Medication Appropriateness Index (MAI) (27)	Patient file (prescribed drugs)	Docu: physician Calculation: pharmacist	x	x	x	x	x	x	x
Drug-related problems	Classification according to PCNE version 6.2 (36)	Patient file (prescribed drugs)	Docu: physician Calculation: pharmacist	x	x	x	x	x	x	x
Drug interactions	ABDA database as in 02/2015; additional evaluation in the individual case scenario ^{*1}	Patient file (prescribed drugs)	Docu: physician Calculation: pharmacist	x	x	x	x	x	x	x
Adjustment of prescribed vs. actually taken drugs	Standardized instruments developed during the initial phase of the study	Patient file, brown bag review	Docu: physician, HCS Calculation: pharmacist	x		x ^{*2}	x ^{*2}	x ^{*2}	x ^{*2}	x
Potentially inadequate medication	According to PRISCUS (37)	Patient file (prescribed drugs)	Docu: physician Calculation: pharmacist	x	x	x	x	x	x	x
Quality of life	SF-12 (38); EuroQoL (EQ-5D) (39) ^{*3}	Telephone interview	Docu: Patient/ interviewer	x		x	x	x	x	x
Everyday competence	ADL (40), iADL (e1)	Telephone interview	Docu: Patient/ interviewer	x		x	x	x	x	x
Gait stability and risk of falling	Mobility test according to Tinetti (e2)	Physician's CRF	Docu: physician	x		x	x	x	x	x
Social situation ^{*3}	Assessing the social situation (SoS) according to Nikolaus (28)	Telephone interview	Docu: Patient/ interviewer	x		x	x	x	x	x
Sociodemographic data	Batteries of questions from socio-economic panel (e3)	Physician's CRF, telephone interview	Docu: physician, patient/interviewer	x			x			x
Illnesses/disorders	ICD-10	Patient file	Docu: physician	x	x	x	x	x	x	x
Severity of illnesses/disorders	CIRS-G (cumulative illness rating scale – German) (e4)	Physician's CRF	Docu: physician	x	x	x	x	x	x	x
Glomerular filtration rate	Cockcroft-Gault formula (e5)	Patient file	Docu: physician Calculation: pharmacist	x	x	x	x	x	x	x

T0, 0, Baseline data collection at the time of inclusion into the study; T1, data collection at the end of the recruitment period; T2, 3 months after the end of the recruitment period; T3, 6 months after the end of the recruitment period; T4, 6 months after the end of the recruitment period; T5, 12 months after the end of the recruitment period; T6, months after the end of the recruitment period. ABDA, Federal Union of German Associations of Pharmacists; ADL, activities of daily life; iADL, instrumental activities of daily life; CRF, case report form; docu: documentation; HCS, home-care specialists

^{*1} First of all, a drug interaction test with the ABDA database was conducted. The results were subdivided into 8 degrees of severity (from “no measures” to “contraindicated”). Whether and to what extent an interaction was relevant to the treatment was decided by the pharmacists after careful pharmacological considerations. The ABDA database includes interactions only as pairs, for example. If more than two substances affect the same cytochrome-P-450 isoenzyme or organ system, the relevance of the interaction was graded higher. Similarly, parameters for individual patients—such as laboratory test results, diagnoses, and sociological information—were included in assessing the relevance. Possible and sensible measures were suggested for each interaction and alternative effective substances were suggested that were less problematic in terms of the interaction, and that were as close as possible to the desirable outcome. For the evaluation of the interactions we distinguished between “relevant,” “partly relevant,” and “not relevant.” “Relevant” in this sense described an interaction that, according to the pharmacist's perspective, required concrete action. “Partly relevant” included interactions if certain risk factors (for example, diabetes mellitus, renal failure) contributed to the usefulness of a measure. “Not relevant” described interactions that merely required monitoring.

^{*2} Post-baseline values are available specifically for each cohort at the corresponding changeover (initial assessment) and at the time of the follow-up assessment (6 months after initial assessment).

^{*3} Results not shown.

eTABLE 3

Reasons for the occurrence/observation of drug-related problems

Category of reason with examples from Pharmaceutical Care Network Europe (PCNE)	Total		Cohort 1: Start of intervention after end of recruitment period		Cohort 2: Start of intervention after 3 months		Cohort 3: Start of intervention after 6 months	
	Baseline (N = 1588)	Solved DRPs	Baseline (n = 688)	Solved DRPs	Baseline (n = 425)	Solved DRPs	Baseline (n = 475)	Solved DRPs
	N (%)	%	n (%)	%	n (%)	%	n (%)	%
1. Selection of substance (inappropriate drug, unsuitable combination, too many substances for the indication)	791 (49.8)	26.0	323 (46.9)	38.7	216 (50.8)	27.8	252 (53.1)	8.3
2. Galenic formulation (inappropriate galenic formulation)	6 (0.4)	0	2 (0.3)	0	3 (0.7)	0	1 (0.2)	0
3. Selected dosage (dosage too low/too high/not frequent enough)	312 (19.6)	30.1	134 (19.5)	44.0	82 (19.3)	18.3	96 (20.2)	20.8
4. Duration of treatment (duration of treatment too short/too long)	25 (1.6)	32.0	13 (1.9)	46.2	6 (1.4)	33.3	6 (1.3)	0
5. Problems with use (timing of intake inappropriate, medication taken too often/too rarely, wrong medication taken)	320 (20.2)	27.2	135 (19.6)	45.2	88 (20.7)	18.2	97 (20.4)	10.3
6. Logistics (medication not available, incorrect medication dispensed)	10 (0.6)	60.0	8 (1.2)	62.5	2 (0.5)	50.0	0 –	0
7. Patient (forgets to take medication, medication kept in inappropriate place)	21 (1.3)	28.6	13 (1.9)	46.2	3 (0.7)	0	5 (1.1)	0
8. Other reason	103 (6.5)	33.0	60 (8.7)	56.7	25 (5.9)	0	18 (3.8)	0

DRP, drug-related problems; N, total number in sample; n, number in subgroups