

Proactive Pharmaceutical Care Interventions Improve Patients' Adherence to Lipid-Lowering Medication

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Abstract

Background: Lipid-lowering drugs are effective preventive medication for patients at risk of cardiovascular complications. However, medication adherence is suboptimal, thereby decreasing therapy effectiveness. Pharmaceutical care interventions may increase therapy adherence. **Objective:** To assess the effect of a proactive pharmaceutical care intervention program, Medication Monitoring and Optimization (MeMO), on therapy discontinuation and adherence with lipid-lowering drugs as well as patients' satisfaction with the intervention program. **Methods:** This prospective intervention study included 1002 patients initiating lipid-lowering drug therapy from 9 Dutch community pharmacies. In the intervention group (n = 500), the MeMO program was used, comprising continuous monitoring of patients' adherence to lipid-lowering drugs and personal counseling with nonadherent patients. The intervention group was compared with a historical reference group (n = 502) receiving usual care. Outcomes were therapy discontinuation and adherence. **Results:** Discontinuation rates with lipid lowering drugs in the first year after drug initiation were 13.6% for the intervention group and 25.9% in the usual care group; continued but non-adherent use was 3.2% and 7.6% in these groups. Patients in the MeMO program had a decreased risk to discontinue medication of 51% (95% confidence interval: 34%-63%). Results were not affected by potential confounders. Patient satisfaction with MeMO was very high; one quarter of patients mentioned that they only received information about their medication from their pharmacy. **Conclusions:** Improving adherence to lipid lowering drugs can be achieved by a proactive pharmaceutical care program. Pharmacists can contribute to optimal use of chronic medication, which is likely to reduce healthcare costs.

Keywords

adherence, discontinuation, lipid-lowering drugs, pharmaceutical care, pharmacist intervention, statins

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Introduction

Lipid-lowering drugs are used as preventive medication for patients with cardiovascular disease and diabetes mellitus or other patients at risk for cardiovascular complications.^{1,2} The efficacy of statins has been demonstrated in many randomized clinical trials.³⁻⁶ Although prescribed as chronic medication, the use of lipid-lowering drugs is often discontinued, and medication adherence is often low. In the Netherlands, around 33% of statin users discontinue their medication within 1 year after treatment initiation.⁷ In other countries, adherence is also low.⁸⁻¹² Immediate discontinuation after a single fill contributes disproportionately to statin nonadherence.¹³ Optimal use of statins and other cardiovascular medication significantly decreases the number of myocardial infarction-related hospitalizations as well as the probability of a second myocardial infarction.¹⁴⁻¹⁷

Community pharmacies are a promising platform for monitoring and improving therapy adherence and the provision of pharmaceutical care.¹⁸⁻²³ In 2006, the Medication Monitoring and Optimization (MeMO) program was introduced in community pharmacies in the Netherlands, using the pharmacy information system Pharmacom. MeMO facilitates the application of patient-centered pharmaceutical care around chronic, preventive medication. This

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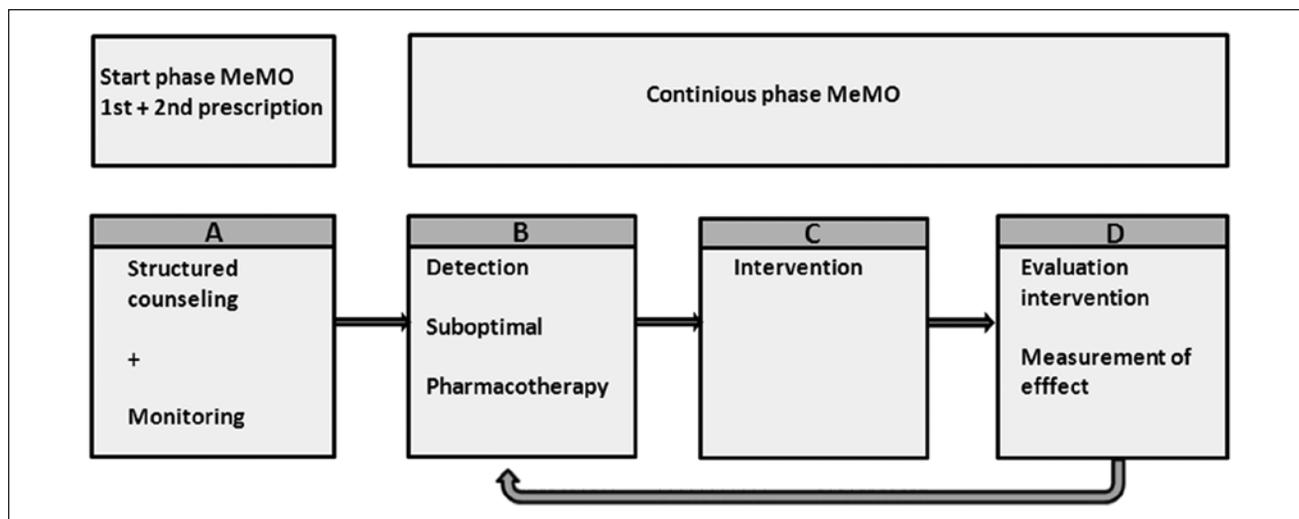


Figure 1. MeMO program: initiation, monitoring, intervention, and evaluation phase. Abbreviation: MeMO, Medication Monitoring and Optimization.

intervention program was shown in earlier studies to be both effective and cost-effective in patients initiating osteoporotic therapy.^{24,25}

The primary aim of this study was to assess the effectiveness of the proactive pharmaceutical care intervention MeMO on the discontinuation rate and adherence of patients initiating lipid-lowering drugs. The effectiveness of the program in a subgroup of patients with an increased risk for cardiovascular events will also be examined. The secondary aim was to assess patient satisfaction with this intervention program.

Methods

Study Design

The study was a prospective intervention study in 9 Dutch community pharmacies. Patients were followed for 1 year. Results in the intervention group were compared with a historical reference group receiving usual care, recruited from the same 9 pharmacies. Historical controls were used because these could be gathered from the same pharmacies. Randomization at patient level was impractical because of the nature of the intervention program; using contemporary control pharmacies was also not feasible because other patient care programs may have been ongoing elsewhere that would bias the measure of usual care.

The MeMO program is presented schematically in Figure 1; the 4 different phases of the program are described below.

Initiation: Structured counseling and monitoring while dispensing new medication. When patients redeemed a prescription for a lipid-lowering drug for the first time, the pharmacy

provided verbal and written information about the drug's mechanism of action, effectiveness, possible side effects, and the proper use of the new medication (first dispense counseling, FDC).²⁶ When patients redeemed their second prescription, medication use was evaluated with the patient, focusing on adverse effects and medication use problems (second dispense counseling, SDC).²⁶ In the Netherlands, FDC and SDC are considered usual care; these were, therefore, also performed in the usual care group. In the MeMO-program, FDC and SDC counseling was carried out according to a standardized protocol and recorded in the pharmacy information system. If patients did not redeem their second prescription on time, they were called (or approached per letter if telephone calls remained unanswered) to ask them about their drug use and if any problems had occurred. Patients' third prescriptions were also monitored to detect potential low adherence.

Proactive detection of low adherence or discontinuation of chronic medication. Every month, users of lipid-lowering drugs were identified, based on their prescription history, who should have redeemed a new prescription but had not yet done so, using a margin of 30 to 60 days after the theoretical end day of their previous prescription. Medication profiles of these patients were assessed to determine whether or not intervention was warranted. Reasons for not intervening were drug stock piling, absence, and changes in pharmacotherapy or new severe comorbidities.

Pharmaceutical patient-centered-care interventions. Patients identified in phase B were selected for the intervention. The pharmacy contacted the patient to clarify the reason(s) for discontinuation. To obtain this information, pharmacists were provided with a protocol, which included questions

about the use and intake of medication and satisfaction with and perceived effectiveness of their medication as well as questions about (fear of) side effects and (fear of) dependence on medication.

Subsequently, patients were provided with extensive tailored information about their medication, treatment goals, and advices on staying adherent. Where deemed relevant by the pharmacist, a therapy switch was proposed to the prescriber.²⁴ All interventions were recorded in the pharmacy information system.

Evaluation intervention and measurement of effect. After the intervention, results of the intervention were monitored. If no improvement (where improvement was defined as redeeming a new prescription and subsequently continuing with >80% adherence) was seen, a new intervention was initiated directed at the patient or the prescriber. If a new prescription was redeemed, drug use was monitored again according to phase B of the MeMO program.

Program Implementation and Trial Monitoring

Pharmacists participating in the MeMO program followed a 2-day cardiovascular risk management training, including topics on therapy adherence. The training was organized by the Health Base foundation and the PharmaPartners College; both institutes facilitate the Pharmacom system. In October 2008, the first group of pharmacies started the MeMO program (group 1); in January 2010, another group of pharmacists started the MeMO program (group 2). Two intervention periods were used to minimize the influence of media campaigns or new health policies, specifically a burst of media attention in the Netherlands on side effects of statins, which caused a temporary nationwide decline in statin adherence.²⁷ The MeMO-program was not changed in the second period.

Participating pharmacists received monthly e-mail updates and reminders from the research group. Pharmacists reported quantitative and qualitative results of their patient selections and interventions to the research group. Several questionnaires were sent out to the pharmacists to detect problems related to the MeMO program implementation and opinions and experiences about their contact with the patients and prescribers. The research group also monitored, on a quarterly basis, how pharmacies recorded the interventions performed in the MeMO program.

Inclusion and Exclusion Criteria

All patients who initiated lipid-lowering drug therapy (anatomic therapeutic chemical [ATC] code C10%) and were registered in the participating pharmacies between October 2008 and March 2009 (group 1) or between January 2010 and June 2010 (group 2) were included in the intervention

group. Treatment initiation was defined as not having used any lipid-lowering drugs for at least 1 year before inclusion. The usual care group consisted of patients from the same pharmacies who initiated lipid-lowering drugs 2 years before the start of the MeMO program.

Study Outcomes

The study outcomes were discontinuation and nonadherence. Drug duration use was calculated between the date of patient's first prescription and the date of patient's last prescription. For patients who had discontinued therapy, the point at which no more prescriptions were redeemed was assessed, specifically whether this was after the first, second, third, or later prescription. Adherence was calculated by dividing the number of pills dispensed by the total number of days of use (from first to last prescription). Nonadherent patients were defined as those having an adherence of less than 80%, a threshold often used in many previous studies.^{28,29} Pharmacists identified possible medically appropriate reasons for discontinuation or nonadherence by assessment of patient medical history, contacting the patient, or contacting the prescriber. A change in dosing regimen or a switch to another lipid-lowering drug was not considered to be discontinuation.

Patient Satisfaction Survey

After the third prescription, patients in the MeMO program of the second pharmacy group received a satisfaction survey. Patients were asked about their opinion on services of the pharmacy (see the appendix) This survey was similar to a survey previously used.³⁰ Patients were anonymous in the survey, but results could be traced to their pharmacy.

Statistical Analysis

Patient baseline characteristics were described and compared using the Student *t* test and Fisher exact tests, where appropriate. Using an intention-to-treat analysis, study outcomes were described and compared as well. Patients who initially discontinued therapy but restarted with a resulting overall adherence of more than 80% were described separately. Discontinuation was also assessed using Kaplan-Meier survival analysis. Patients were censored when they left their pharmacy, died, discontinued therapy for medically appropriate reasons, or reached the end of study follow-up, whichever came first. The end of follow-up was after 465 days: 365 days + 90 days (duration of prescription) + 10 days (safety margin). Differences in discontinuation between groups were tested using the log-rank test. Cox proportional hazard analysis was used to estimate effect sizes and correct for potential confounders. Subgroup analyses were performed for patients at high risk for cardiovascular events,

Table 1. Inclusion Periods of Patients.

Pharmacies (n)	Inclusion Period (Usual Care)	Patients (n)	Inclusion Period (Intervention)	Patients (n)	End Follow-up Period
1 to 4 (n = 503)	October 2006 to March 2007	288	October 2008 to March 2009	215	October 2010
5 to 9 (n = 499)	January 2008 to June 2008	214	January 2010 to June 2010	285	January 2012
N = 1002		502		500	

identified based on comedication (diabetes: ATC A10%; antithrombotics: ATC B01AA% and B01AC%). All statistical analyses were performed with SPSS 19.0.

External Validation

Drug-dispensing data were obtained from the IADB.nl database.^{31,32} This database comprises prescriptions of approximately 500 000 individuals in the Netherlands, regardless of patients' insurance, prescriber, or reimbursement status of the drug and has been used in previous adherence studies.^{33,34} The 9 intervention pharmacies were not included in this database. The discontinuation and adherence of incident users of lipid-lowering drugs between 2006 and 2010 was determined in this data set using the same definitions as in the MeMO program. These data were then compared with those of the usual care group of the intervention pharmacies to detect potential changing patterns of drug use.

Results

Program Implementation

Before the start of the training session, all pharmacies provided verbal and written information at first dispense of a new prescription but not always according to a structured protocol; 55% of the pharmacies used a protocol at first dispense of lipid-lowering drugs. None of the pharmacies performed targeted searches to identify nonadherent patients. All participating pharmacies implemented all phases of the MeMO program, as described in Figure 1.

During regular evaluation by the research team, the pharmacists indicated that the MeMO program was relatively simple to implement, and the interventions and contacts with patients and prescribers were, in general, good and constructive. Data from the pharmacy information system showed that counseling at first and second prescription was continuously performed during the whole study period.

Patient Population

During the inclusion periods of the 2 groups of participating pharmacies, 500 patients redeemed a first prescription with lipid-lowering drugs such as statins, ezetrol, or the combination ezetrol/simvastatin. During the inclusion periods of the usual care groups, 502 patients redeemed a first prescription, shown

in Table 1. Patient characteristics of both groups are presented in Table 2.

Populations in both groups did not differ significantly regarding age, gender, or first prescriber. There was a trend for higher increased risk for cardiovascular events in the usual-care group (66.9% vs 61.0%, $P = .056$). The number of prescriptions for simvastatin was significantly increased in the intervention group (83.2% vs 66.3%, $P < .001$).

Discontinuation and Nonadherence

The discontinuation and adherence rates in the usual care group and the MeMO intervention group in the first year after start of a lipid-lowering drug are presented in Figure 2.

In the first year after treatment initiation of lipid-lowering drugs, 130 (25.9%) usual care patients discontinued therapy, compared with 68 (13.6%) patients in the intervention group ($P < .001$); 38 (7.6%) usual care patients and 16 (3.2%) intervention patients continued use but were nonadherent ($P = .003$). In total, in the usual care group, 33.5% of patients initiating lipid-lowering drugs discontinued or were nonadherent, compared with 16.8% of patients in the intervention group ($P < .001$). The point in time when patients' last prescription was redeemed is presented in Table 3.

The rate of drug discontinuation was significantly lower in the intervention group compared with the usual care group: hazard ratio = 0.49; 95% confidence interval [CI] = 0.37-0.66. Therefore, the MeMO program decreased the risk for discontinuation by 51% (95% CI = 0.34-0.63) compared with usual care. Multivariate correction for age, gender, and increased risk for cardiovascular events did not influence this effect (data not shown).

The effect of the MeMO program did not differ significantly over time (proportional hazards assumption test, $P = .792$). However, the absolute risk to discontinue therapy was the highest in the first month (Figure 3). Thus, the MeMO program achieved the largest absolute reduction in stoppers in the first month after therapy initiation.

Discontinuation and nonadherence in the usual care group compared with the intervention group was 34.4% versus 19.1% ($P < .001$) in the first group of participating pharmacies, and 32.2% versus 15.1% ($P < .001$) in the second group of pharmacies. The effectiveness of the MeMO program did not differ significantly between the 2 pharmacy groups ($P = .330$).

Table 2. Patient Characteristics.

	Usual Care	Intervention	P Value
Total patients (n)	502	500	
Female, n (%)	209 (41.6%)	227 (45.4%)	.251
Age (years) at first prescription (mean ± SD)	60.9 ± 11.7	61.3 ± 11.2	.552
GP as prescriber, n (%)	328 (65.3%)	342 (68.4%)	.502
First prescription lipid-lowering drug			<.001
Simvastatin	333 (66.3%)	416 (83.2%)	
Pravastatin	16 (3.2%)	15 (3.0%)	
Atorvastatin	95 (18.9%)	37 (7.4%)	
Rosuvastatin	47 (9.4%)	22 (4.4%)	
Fluvastatin	3 (0.6%)	1 (0.2%)	
Ezetrol/Combinations	8 (1.6%)	9 (1.8%)	
Other lipid-lowering drugs	None	None	
Increased risk of cardiovascular event, n (%)	336 (66.9%)	305 (61.0%)	.056

Abbreviation: SD, standard deviation.

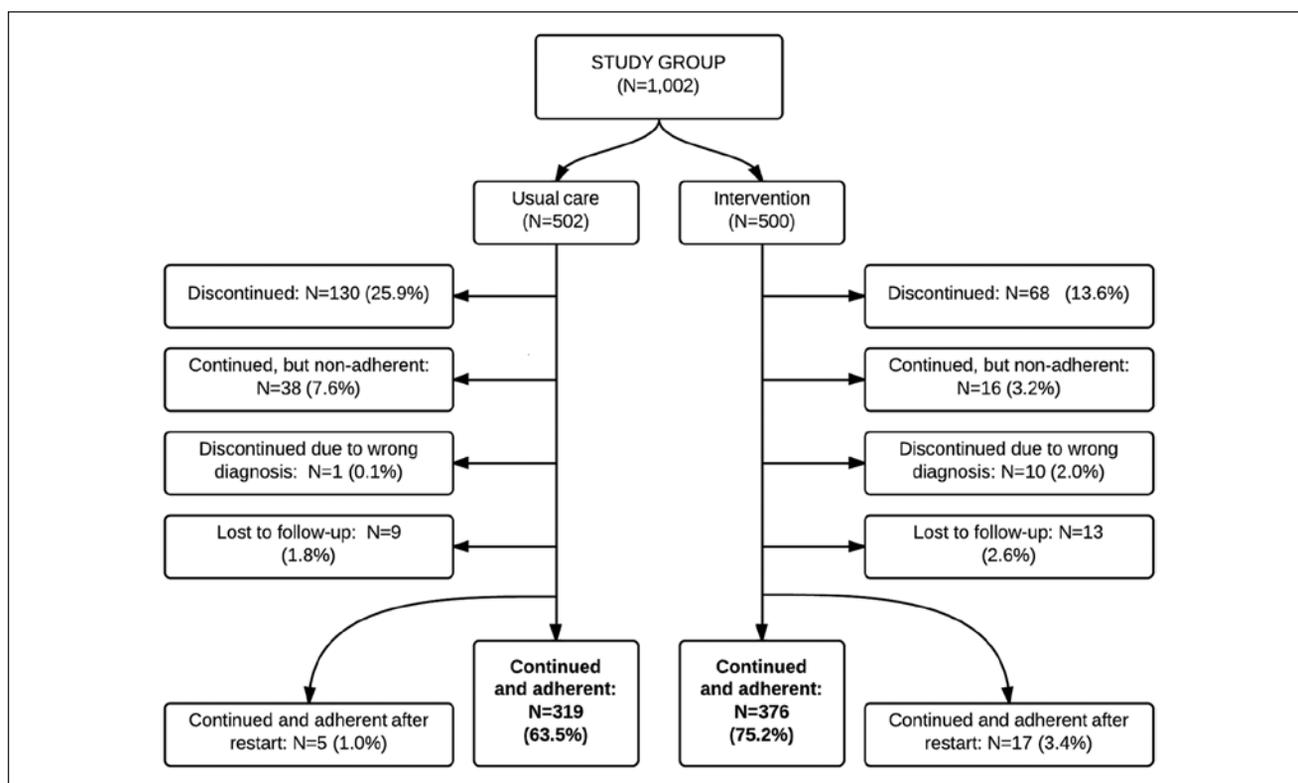


Figure 2. Flow diagram showing the outcomes of patients receiving usual care (left) or the MeMO intervention (right). Outcomes were analyzed 465 days after treatment initiation.

Abbreviation: MeMO, Medication Monitoring and Optimization.

Subgroup Analysis of High-Cardiovascular-Risk Group

A total of 336 usual care patients and 305 intervention patients used glucose-lowering drugs and/or antithrombotics and were thus classified in the high-cardiovascular-risk group (Table 2).

In this group of patients, the percentage of patients with sub-optimal pharmacotherapy (ie, patients who discontinued or were nonadherent) decreased significantly from 32.2% to 15.1% ($P < .001$). The effect of the MeMO program was not significantly different between patients with and without increased risk for cardiovascular incidents ($P = .773$).

Table 3. Time of Last Prescription of Lipid-Lowering Drug in the First Year After Treatment Initiation.

Time of Last Prescription	Usual Care, n = 502	Intervention, n = 500	P Value
No prescription 14 days after treatment initiation	10.0 %	4.8 %	.002
No prescription after 90 days	17.1 %	8.4 %	<.001
No prescription within 365 days	24.1 %	13.2 %	<.001

External Validation

The number of incident users of lipid-lowering drugs in the IADB.nl database between 2006 and 2010 and their discontinuation and adherence rates during the first year of use are presented in Table 4. The percentage of patients who discontinued treatment or were nonadherent in the first year of use in the IADB.nl database is comparable with that in the 2 usual care groups (34.4% in pharmacies 1 to 4 and 32.2% in pharmacies 5 to 9) in the same periods ($P = .608$ and $.882$).

Reasons for Discontinuation

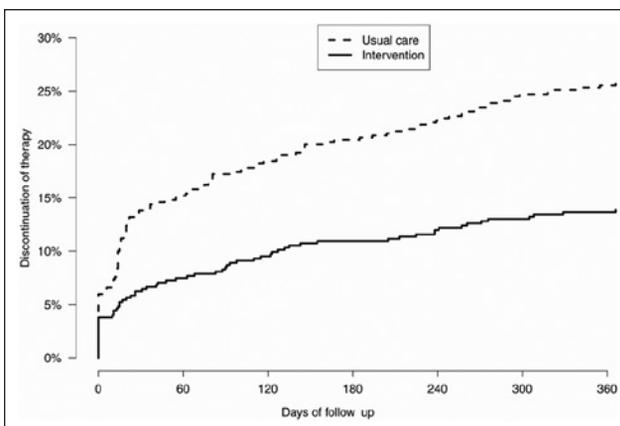
Personal counseling sessions revealed several reasons for therapy discontinuation or nonadherence. Common reasons were side effects or fear of side effects (diarrhea, fatigues, or muscle pain), lack of knowledge regarding duration of use, problems with daily use, feeling no effects of their medication, resistance against use of medication in general, or their physician telling them that their medication was no longer needed.

Switching

Pharmacy dispensing records showed that 67 patients (13.4%) in the intervention group and 65 patients (12.9%) in the usual care group switched to another type of lipid-lowering drug. Of these, 15 patients (22.4%) in the intervention group and 23 patients (35.4%) in the usual-care group eventually discontinued or became nonadherent ($P = .125$).

Patients' Satisfaction Survey

In total, 135 of the 250 surveys that were sent out were returned (response rate = 54%). The sample included about the same number of women and men, and the average age was 64 years. More than 92% of the respondents were (very) satisfied with the pharmacy, particularly with the accuracy, the expertise, and the verbal information that was provided. In general, patients were satisfied with the

**Figure 3.** Kaplan-Meier curve showing the number of patients discontinuing lipid-lowering drugs for usual care and intervention patients (MeMO) in the first year after treatment initiation. Abbreviation: MeMO, Medication Monitoring and Optimization.**Table 4.** Persistence of Patients Initiating Lipid-Lowering Drugs in the IADB.nl Database.

Year	Incident Users of Lipid-Lowering Drugs	Users Who Continue Treatment With Adherence >80% (%)	Users Who Discontinue or Are Nonadherent to Treatment (%)
2006	5632	67.1	32.9
2007	4452	63.7	36.3
2008	3783	68.5	31.5
2009	4006	70.6	29.4
2010	3513	71.3	28.7

information about their new medication (77%), and this information was considered (very) important (88%).

The vast majority of patients (74%) mentioned that their knowledge about their medication was increased because of the information provided, especially regarding the administration of their medication, the method of action of their drug, and the importance of adherence. In addition, 9 patients (7%) were eager for even more information.

One quarter of the respondents indicated that the pharmacy was their only source of information regarding the method of action or administration of their lipid-lowering drug, whereas 62% did also receive this information from their physician or their nurse practitioner.

Also, 75% of the respondents indicated that the information provided by their pharmacy helped them take their medication according to the regimen prescribed, and 52% were more satisfied with their pharmacy after the counseling session they received when they started their lipid-lowering drug.

Discussion

After introduction of the MeMO program, the number of patients who discontinued use of lipid-lowering drugs in the first year decreased significantly from 24.1% to 13.2%. At the end of the follow-up period, 33.5% of patients in the usual-care group and 16.8% of the patients in the MeMO group had discontinued their medication or had low adherence. In the MeMO intervention group, structured patient counseling at dispensation of medication and active monitoring of prescriptions were introduced. The way of working according to this protocol is expected to lead to clear, uniform, and complete information for every patient, independent of the pharmacy employee.

In a previously described MeMO program focusing on osteoporotic patients, the percentage of drug discontinuation also halved from 31.7% (in 2004, usual care group) to 16.1% (in 2006, intervention group).²⁴

The implementation and application of the complete patient-centered pharmaceutical care strategy in the pharmacy were supported by the number of interventions recorded in the pharmacy information system and the monthly reports regarding the assessment of medication profiles until the end of the follow-up period.

Figure 3 and Table 3 show that a clear difference in discontinuation rate was already observed after 14 days. After 90 days, the difference was even clearer; this difference indicates that structured counseling at initiation of medication therapy and monitoring at second (after 14 days) and third (15-90 days) prescription has a high impact on the improvement of therapy adherence. In previous research, the importance of second dispense counseling was already highlighted.³⁵ However, it is also recommended to extend this counseling with additional monitoring of the second (and third) prescription to further improve therapy adherence. Additional monitoring of follow-up prescriptions via the pharmacy information system, using the MeMO program, leads to an even greater improvement of adherence in the first year of use.

Results from the patient satisfaction survey showed that patients were in general very satisfied with the pharmacy and the counseling they received regarding their new medication. This counseling was considered important; one quarter of all respondents mentioned that the pharmacy was the only place where they received information regarding the use and method of action of their medication.

Strengths

This study has several strengths. First, participating pharmacies had complete access to patients' prescription records because although in the Netherlands patients may consult several physicians, they usually have all their prescriptions filled at the same community pharmacy; even when prescriptions are dispensed by another community, hospital, or polyclinic pharmacy, their home pharmacy will be notified.^{31,36} Second, the patients from

the intervention group and the patients from the usual care group were recruited from the same pharmacies, improving internal validity. Third, an intention-to-treat analysis was used, meaning that all patients starting lipid-lowering drugs in the inclusion periods were used for analysis. Fourth, the use of 2 inclusion periods is likely to have reduced the influence of media or societal campaigns or new regulations. Finally, the percentages of drug discontinuation and nonadherence to lipid-lowering drugs in the usual care group were comparable to observations in the same years in the IADB.nl database, which is representative of the overall Dutch population, thus increasing external validity.

Limitations

This study also faced some limitations. For most analyses, only medication prescription data were available; diagnoses and lab records were not directly accessible but had to be obtained via the patient or prescriber. In further research, it is recommended to include cholesterol values and diagnoses. The assessment of persistence is based on medication records from the home pharmacy. However, patients may have incidentally redeemed one of their prescriptions from another pharmacy. By active verification, this possibility was minimized. Although we collected data on reasons for discontinuation, we did not quantify these reasons. These data would be valuable for further research.

This study showed that patients with increased risk for cardiovascular events had higher adherence to their medication. Especially in these patients, higher adherence to lipid-lowering drugs is associated with lower health care costs.^{14,15,17} In the MeMO program, all patients discontinuing their lipid-lowering drugs were identified by monthly selections. In daily practice, medication profiles of all these patients are assessed, and interventions are undertaken to improve medication adherence. The participating pharmacists reported that the interventions also resulted in long-term users having a lower discontinuation rate.

Based on average time investment for the pharmaceutical care interventions, the MeMO program for osteoporosis has shown to be cost-effective.²⁵ Further research needs to be conducted to assess the cost-effectiveness for this current MeMO program for lipid-lowering drugs.³⁷

Currently, MeMO programs for oral antidiabetic medication, platelet aggregation inhibitors, and inhalation medication for asthma and COPD are being implemented, and effectiveness will be assessed.

Conclusion

Using the MeMO program, pharmacists improve adherence to chronic lipid-lowering medication by structured first- and second-dispense counseling and active monitoring of drug use. In this way, pharmacists contribute to an optimal use of patients' chronic medication, which is likely to contribute to the quality of life of patients and to a reduction in health care costs.

Appendix

Patient Satisfaction Survey (Translated From the Original Dutch Version)

Question	Choose an Answer
How satisfied are you with the information the pharmacy provided you regarding your medication against high cholesterol?	<ul style="list-style-type: none"> • Very satisfied • Satisfied • Not satisfied/Not unsatisfied (neutral) • Unsatisfied • Very unsatisfied
How important do you think it is that the pharmacy provides information about, in this case, medication against high cholesterol?	<ul style="list-style-type: none"> • Very important • Important • Not important/Not unimportant (neutral) • Unimportant • Very unimportant
Could you state why you are satisfied with the information you received in the pharmacy? (Multiple answers possible)	<ul style="list-style-type: none"> • I now better understand how my medication works • I now better know how I should use my medication • I now understand better how important it is to use my medication regularly • I enjoyed the conversation in the pharmacy • I am not satisfied with . . .
Were you told, apart from the pharmacy, how to use your medication against high cholesterol? (Multiple answers possible)	<ul style="list-style-type: none"> • No, only in the pharmacy • From the doctor • From the nurse or GP assistant • From someone else, namely . . .
Were you told, apart from the pharmacy, how your drug against high cholesterol works? (Multiple answers possible)	<ul style="list-style-type: none"> • No, only in the pharmacy • From the doctor • From the nurse or GP assistant • From someone else, namely . . .
Do you expect that the counseling from the pharmacy will help you to use your medication continuously (for as long as you are prescribed this drug)? (Multiple answers possible)	<ul style="list-style-type: none"> • Yes • Yes, but I already intended to • No, I stopped using the medication • I don't know
Are you more satisfied now you received counseling in the pharmacy about your medication against high cholesterol?	<ul style="list-style-type: none"> • Yes • No • I don't know

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Ada G. G. Stuurman-Bieze and Eric G. Hiddink are employees of the Health Base foundation that developed the MeMO intervention program. Job F. M. van Boven and Stefan Vegter declare no conflicts of interest.

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