Osteoporos Int (2014) 25:1807–1812
DOI 10.1007/s00198-014-2659-8

SHORT COMMUNICATION

Proactive pharmaceutical care interventions decrease patients' nonadherence to osteoporosis medication

A. G. G. Stuurman-Bieze · E. G. Hiddink · J. F. M. van Boven · S. Vegter

Received: 3 January 2014 / Accepted: 13 February 2014 / Published online: 26 February 2014

Abstract
Summary Using a protocolled intervention program, pharmacists can decrease nonadherence to osteoporosis medication, by continuous monitoring and tailored counseling sessions, starting at treatment initiation. In the usual care group, 32.8 % of patients initiating osteoporosis medication discontinued or were nonadherent, compared to 19.0 % of patients in the intervention group.
Purpose While community pharmacies have been shown to offer a promising platform for osteoporosis management in patients with osteoporosis, more research is needed to determine pharmacists' effects on improving adherence. The aim of this study was to determine the effects of a community pharmacists' intervention program on the 1-year discontinuation and nonadherence rates of patients initiating osteoporosis medication.
Methods This intervention study included 937 patients, recruited from 13 Dutch community pharmacies, initiating osteoporosis medication. The intervention group (N=495), received the Medication Monitoring and Optimization (MeMO) intervention, comprising of continuous monitoring of patients' adherence to their osteoporosis medication and tailored counseling sessions with nonadherent patients. Results were compared to an internal (n=442) reference group, receiving usual pharmacy care. Primary study outcomes were therapy discontinuation and nonadherence; results were adjusted for potential confounders using Cox proportional hazard analysis. Secondary outcome was patients' satisfaction.
Results In the usual care group, 32.8 % of patients initiating osteoporosis medication discontinued or were nonadherent, compared to 19.0 % of patients in the intervention group (P<0.001). Ninety-three percent of the respondents were satisfied with the pharmacies' services provided. Notably, 31 % mentioned that the pharmacy was the only place where they received information on various aspects of administration and acting of their medication.
Conclusion Pharmacists can decrease nonadherence and discontinuation with osteoporosis medication by providing tailored counseling sessions and continuous monitoring of drug use. Pharmaceutical care programs, such as MeMO, contribute to more optimal use of osteoporosis medication.

Keywords Adherence · Bisphosphonates · Osteoporosis · Persistence · Pharmaceutical care · Pharmacist intervention

A. G. G. Stuurman-Bieze (✉)
West Pharmacy, Europalaan 124, 8303 GL Emmeloord, The Netherlands
e-mail: ada@fstuurman.nl

A. G. G. Stuurman-Bieze · E. G. Hiddink
Health Base Foundation, Houten, The Netherlands

E. G. Hiddink · J. F. M. van Boven · S. Vegter
Unit of PharmacoEpidemiology & PharmacoEconomics, Department of Pharmacy, University of Groningen, Groningen, The Netherlands

E. G. Hiddink
PharmaPartners BV, Oosterhout, The Netherlands

Introduction

Osteoporosis is a chronic progressive disease that has a significant impact on morbidity, mortality, and quality of life [1]. In recent years, preventive medication to treat (corticosteroid-induced) osteoporosis have demonstrated efficacy in several randomized controlled trials (RCT) and meta-analyses [2].

However, efficacy shown in RCTs may not fairly represent effectiveness in real-life settings. Mainly, real-life effectiveness may be reduced by the low adherence and high extent of early discontinuation seen with osteoporosis therapy [3, 4]. Low adherence and persistence with osteoporosis medication are associated with increased fracture risks [5], thereby putting

a high clinical and economic burden on patients and society [6, 7]. Consequently, as higher adherence is associated with reduced fractures and related cost savings [8], efforts to improve adherence are likely to be cost-effective strategies.

While in previous research, community pharmacies have been shown to offer a promising platform for improving osteoporosis management in patients with osteoporosis, more research is needed to determine pharmacists' effects on improving adherence [9]. 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 in the active signaling of nonadherence and the application of patient-centered pharmaceutical care around chronic, preventive medication. This intervention program was shown in other studies to be both effective and cost-effective in patients initiating lipid-lowering drugs [10, 11].

The aim of the current study was to determine the effects of the MeMO strategy on the 1-year discontinuation and nonadherence rates of patients initiating osteoporotic medication.

Methods

The MeMO program

The MeMO program has been extensively described in a previous study [10]. In short, the program in community pharmacies consisted of an initial phase and a continuous phase. At the first dispense of osteoporosis medication, the pharmacy provided structured counseling on aspects regarding administration, effectiveness, and possible side-effects. The importance of continuous use was highlighted. It was actively monitored if patients returned for their second and third prescription on time. At the second dispense (usually after 2 weeks), a second counseling session was provided. The information focused on patients' first experiences with (fear of) adverse effects and drug administration problems. After the third dispense, the continuous phase of the program started: proactive detection of low adherence or discontinuation. Every 3 months, pharmacists actively searched for patients who should have redeemed a new prescription for their osteoporosis medication (according to their medication history, allowing a margin of 30 days), but had not yet done so. These patients were contacted and intervened if warranted. Reasons for not intervening included drug stockpiling, holidays, or therapy switches (i.e., simultaneous discontinuation of corticosteroids).

Participating pharmacists

The program was implemented in 13 community pharmacies. Before implementation of the MeMO program, all pharmacies provided verbal and written information at the first dispense of new medication. However, a structured protocol was not always used; only four (31 %) out of the 13 pharmacies participating in this study used a protocol at the first dispense of osteoporosis medication. None of the pharmacies performed targeted searches to identify nonadherent patients.

Program implementation

Pharmacists participating in the MeMO program followed an osteoporosis treatment and prevention training, including strategies to cope with therapy nonadherence. The training was organized by the Health Base foundation. In February 2006, all pharmacists started the MeMO program.

Every 3 months, participating pharmacists received email updates and reminders from the research group. Both quantitative and qualitative results of their patient selections and interventions were reported to the research group. A representative number of questionnaires were sent out to the pharmacists to detect problems related to the MeMO program implementation and pharmacists' opinions and experiences with contacting patients and prescribers. On a regular basis, the research group monitored how pharmacies recorded their interventions performed in the MeMO program.

Inclusion and exclusion criteria

All patients who initiated osteoporosis medication like bisphosphonates, raloxifene, strontium, or a fixed combination of a bisphosphonate and vitamin D and/or calcium (Anatomic therapeutic chemical (ATC) codes M05B and G03XC01) and were registered in the participating pharmacies between March 2006 and March 2007 were included in the intervention group. Treatment initiation was defined as not having used any osteoporosis medication for at least 1 year before inclusion.

Study design

The study design was a prospective intervention study in 13 Dutch community pharmacies. Patients initiating osteoporosis medication in 2006/2007 were followed for 1 year. The intervention group consisted of patients receiving pharmaceutical care from the MeMO program. The intervention group was compared to a historical internal reference group receiving usual care, comprising of the first dispense counseling only. Patients in the reference group were recruited from the same 13 pharmacies and consisted of patients who initiated osteoporosis medication in 2004.

Study outcomes

The primary study outcomes were discontinuation and nonadherence. Discontinuation was defined as permanently

stopping osteoporosis medication. Adherence was calculated using the proportion of days covered (PDC) methods. Here, the number of pills dispensed (multiplied by 7 for weekly dosing or 30 for monthly dosing, where appropriate) was divided by the total number of days of use (from first to last prescription). Nonadherent patients were defined as having an adherence less than 80 %, a threshold often used in previous studies [12]. Potentially medically appropriate reasons for discontinuation or nonadherence were assessed using patients' medical history or contacting the patient or prescriber. Appropriate reasons for therapy discontinuation or nonadherence included simultaneous discontinuation of corticosteroids, previous stockpiling and when a patient had moved. A change in dosing regimen or a switch to other osteoporosis medication was not considered therapy discontinuation.

The secondary outcome was patients' satisfaction with the MeMO program. The questionnaire used was previously described and used in the MeMO lipid-lowering drugs study [10]. Questions focused on satisfaction with the pharmacy service and medication counseling. Questionnaires were filled out anonymously.

Statistics

Baseline characteristics were described and compared using Student's *t* tests and Fisher's exact tests, where appropriate. Study outcomes were described and compared using an intention to treat analysis. Patients who initially discontinued therapy but restarted with a resulting overall adherence of over 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 (e.g., simultaneous discontinuation of corticosteroids), or reached the end of study follow-up. Follow-up ended after 365 days. Cox proportional hazard analysis was used to estimate effect sizes and to correct for potential confounders. All statistical analyses were performed with SPSS 19.0.

External validation

An external dataset was used to validate the appropriateness of the historical reference group. Drug-dispensing data were obtained from the IADB.nl database [13]. This database contains prescriptions of over 500,000 pharmacy patients in the Netherlands, regardless of patients' insurance, prescriber, or reimbursement status of the drug. The database is validated and has been used in previous adherence and persistence studies [3, 14]. In this dataset, the discontinuation and nonadherence rates of patients initiating osteoporosis medication between 2004 and 2010 were determined using the same definitions as in the MeMO program. These data were compared to the usual care group to verify consistency and to detect potential changing patterns of drug use over time.

Results

Patient population

Between March 2006 and March 2007, 495 patients redeemed the first prescription for osteoporosis medication and were followed for at least 1 year. The usual care group included patients initiating osteoporosis therapy from January 2004 till December 2004. During the inclusion period of the usual care group, 442 patients redeemed the first prescription. Patient characteristics of both groups are presented in Table 1.

Populations in both groups did not differ significantly regarding age or gender. The number of patients with GP as the first prescriber, type of medication, with a weekly dosing regimen, and patients using corticosteroids simultaneously did differ significantly (Table 1)

Discontinuation and nonadherence

The discontinuation and nonadherence rates in the usual care group and the MeMO intervention group in the first year after start of osteoporosis medication are presented in Fig. 1.

In the first year after treatment initiation of osteoporosis medication, 123 (27.8 %) usual care patients discontinued therapy, compared to 78 (15.8 %) patients in the intervention group ($P<0.001$). A total of 22 (5.0 %) usual care patients and 16 (3.2 %) intervention patients continued use but were nonadherent ($P=0.18$).

In total, in the usual care group, 32.8 % of patients initiating osteoporosis medication discontinued or were nonadherent,

Table 1 Patient characteristics ($N=937$)

	Usual care	Intervention	*P* value
Patients (*N*)	442	495	
Female (*N*, %)	347 (78.5 %)	381 (77.0 %)	0.583
Age (mean±SD)	67.0 (13.9)	67.0 (15.2)	0.97
GP as first prescriber (%)	201 (45.5 %)	240 (48.5 %)	<0.001
Specialist	150 (33.9 %)	246 (49.7 %)	
Unknown	91 (20.6 %)	9 (1.8 %)	
Alendronate	239 (54.1 %)	325 (65.7 %)	<0.001
Risedronate	183 (41.4 %)	144 (29.0 %)	
Other bisphosphonates	18 (4.1 %)	20 (4.0 %)	
Strontium	0 (0 %)	5 (1.0 %)	
Raloxifene	2 (0.5 %)	1 (0.2 %)	
Daily dosing	60 (13.6 %)	34 (6.9 %)	<0.001
Weekly dosing	382 (86.4 %)	445 (89.9 %)	
Monthly dosing	0 (0 %)	16 (3.2 %)	
Patients with simultaneous use of corticosteroids	174 (39.4 %)	233 (47.1 %)	0.02

GP general practitioner, *SD* standard deviation

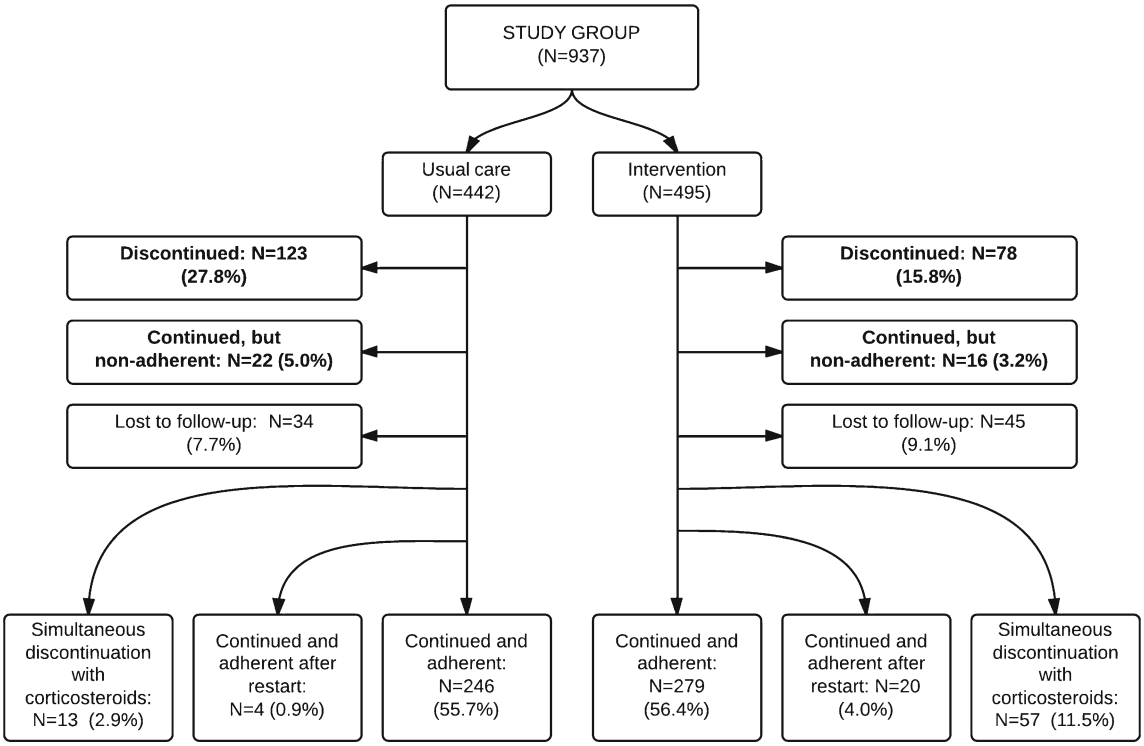

Fig. 1 Flow diagram of use of osteoporosis medication 1 year after initiation

compared to 19.0 % of patients in the intervention group ($P<0.001$) (Fig. 2).

Thirteen (2.9 %) usual care patients and 57 (11.5 %) intervention patients discontinued simultaneously bisphosphonate and corticosteroid therapy, which was started together ($P<0.001$). Note that this is a positive outcome, however not part of our primary study endpoint which was nonpersistence and nonadherence without medical appropriate reasons.

Effects of the MeMO program

The rate of drug discontinuation or nonadherence was significantly lower in the intervention group compared to the usual care group, hazard ratio 0.54 (95 % confidence interval (CI) 0.42–0.70).

Multivariate correction for medication, dosing regimen, prescriber, and comedication of corticosteroids did not influence this effect; hazard ratio 0.54 (95 % CI 0.41–0.72).

The absolute risk to discontinue therapy was the highest in the first month (Fig. 2). Thus, the MeMO program achieved the largest absolute reduction in stoppers in the first month after therapy initiation.

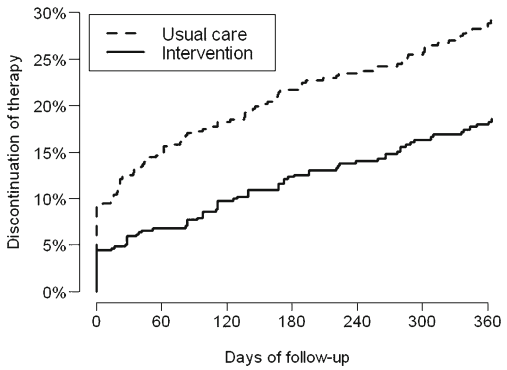

Fig. 2 Kaplan-Meier curve showing the percentage of patients discontinuing osteoporosis medication or continuing with low adherence (<80 %) for usual care and intervention (MeMO) patients in the first year after treatment initiation

Reasons for discontinuation

Several reasons for therapy discontinuation or nonadherence were signaled during counseling sessions. Common reasons for therapy discontinuation mentioned by patients were (fear of) side effects (e.g., gastro intestinal side effects), lack of knowledge on duration of use, confusion related to daily or weekly use, no perceived effects of medication, general resistance against use of medication, or discontinuation recommended by their physician.

External validation

Seven thousand four hundred thirty-five patients initiating osteoporosis medication between 2004 and 2010 were identified in the IADB.nl database. In 2004, the percentage of patients who discontinued treatment and/or were nonadherent in the first year of use was 33.4 % and was comparable ($P=0.$

82) with the usual care group in 2004 which was (27.5+5.0) 32.8 % (Fig. 1). Between 2004 and 2010, the percentage of patients who discontinued treatment or were nonadherent in the first year of use, was 33.9 % (SD 1.9) on average (data not shown).

Patients' and pharmacists' satisfaction

One hundred forty-five of the 230 questionnaires that were sent out were returned (response rate 63 %). About 93 % of the respondents were (very) satisfied with the pharmacies' services that were provided. Eighty-seven percent considered the information that was given as very important. Notably, 31 % mentioned that the pharmacy was the only place where they had received information on medication effectiveness, administration and the importance of therapy adherence. Fifty-four percent of patients had also received this information from their physician or nurse.

During regular evaluation by the research group, 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. Details regarding patients' and pharmacists' satisfaction have been described previously (in Dutch) [15].

Discussion

Results of the current study show that the MeMO program significantly decreased the number of patients discontinuing osteoporosis medication (or continuing with suboptimal adherence), from 32.8 to 19.0 % in the first year after treatment initiation. Simultaneous discontinuation with corticosteroids increased from 2.9 to 11.5 %. Continuous pharmaceutical care programs, such as MeMO, which focus on protocolled medication counseling at therapy initiation and monitoring after follow-up prescriptions, have beneficial impact on therapy adherence. Moreover, protocolled patient counseling at medication dispenses and active monitoring of prescriptions leads to clear, uniform, and complete information for all patients, independent of the pharmacy employee performing the interventions.

In general, our study indicates that adherence and persistence in patients using osteoporosis medication were suboptimal. These findings do, taken into account methodological differences, well correspond with findings from other Dutch adherence studies [3, 4]. Previous studies of pharmacists' interventions in osteoporosis care are limited. Other studies primarily focused on optimization of bisphosphonate use in patients using high-dose oral corticosteroids [16], optimization of calcium/vitamin D intake [17], or identification of patients at risk [18]. One pharmacy intervention study found significantly higher adherence after 6 months and 1 year, however persistence did not increase significantly [19]. An important difference with our study is that their study population consisted of women who were recently hospitalized due to a fracture and of whose baseline persistence was already relatively high, allowing less room for improvement.

A systematic review summarized adherence enhancing interventions in osteoporosis patients and showed that three out of the five included studies showed improved adherence and one study showed improved persistence [20]. In the study that improved persistence, usual care persistence was 39 % and intervention persistence was 57 % (effect size 0.36) [21]. However, this study did not only include educational sessions but also a switch in medication from weekly to monthly medication.

In a recently described MeMO program, focusing on lipid-lowering drugs, the percentage of drug discontinuation or low adherence in the first year decreased from 33.5 % in the usual care group to 16.8 % in the intervention group [10]. In this particular study, the same early difference in discontinuation rate was observed. In both studies additional monitoring of follow-up prescriptions via the pharmacy information system, using the MeMO program, led to an improvement of adherence in the first year of use. Based on average time investment for pharmaceutical care interventions, the MeMO programs for lipid lowering drugs has shown favorable cost effectiveness [11].

In both studies, patients' satisfaction was measured. Patients were very satisfied with the pharmacy and the counseling they received regarding their new medication. This counseling was considered important, especially the explanation of the use and the importance of regularly intake. Almost one third of all respondents in the osteoporosis survey (compared to one quarter in de lipid-lowering survey) mentioned that the pharmacy was the only place where they received information regarding the use and acting of their medication. This lower percentage for patients in the lipid-lowering drugs program may be explained by the higher percentage of patients included in regional integrated care programs for diabetes patients (usually receiving lipid-lowering drugs).

Participating pharmacies had access to complete patients' prescription records.

Historical controls were drawn from the same pharmacies as patients in the intervention group, increasing internal validity. Furthermore, validity of the control group was confirmed using a large Dutch dispensing database.

Although for all patients extensive medication prescription data were available, diagnoses and bone mineral density records were not directly accessible. When required, these were obtained from the patient or prescriber. Although most Dutch patients redeem all of their prescriptions at the same pharmacy, we cannot exclude the possibility that patients may have incidentally redeemed prescriptions from another pharmacy. In this study, we tried to minimize this possibility by active verification at the patient and/or surrounding pharmacies.

Based on results from this study, community pharmacists are stimulated to implement the MeMO strategy for patients initiating osteoporosis medications as part of their daily practices. Active periodical searches for all patients who seem to discontinue their medication are recommended. Careful assessment of the reasons for discontinuation is needed. Note that legitimate reasons to discontinue include the simultaneous discontinuation of use of high-dose oral corticosteroids or reaching the maximal recommended duration of use of 5 years (sometimes up to 10) [22]. Data exchange with other healthcare professionals may provide important additional clinical data, thereby adding to the quality of tailored interventions. Pharmaceutical care as provided by the MeMO program should be embedded in the integral multidisciplinary care for patients with osteoporosis.

Conclusion

Pharmacists can decrease nonadherence and discontinuation with osteoporosis medication by protocolled medication reviews, tailored counseling sessions, and continuous monitoring of drug use. Pharmaceutical care programs, such as MeMO, contribute to more optimal use of osteoporosis medication.

Acknowledgments We thank all community pharmacists for their participation in this study. We would also like to acknowledge Ellen Vergouwen (PharmaPartners BV staff) who took care of data collection and technical support.

Funding/support The osteoporosis treatment and prevention training was cofunded by Merck Sharp and Dohme (MSD). MSD did not have any influence on the study design, the MeMO intervention program or the contents of the manuscript.

Conflicts of interest None.

References

1. Lips P, van Schoor NM (2005) Quality of life in patients with osteoporosis. Osteoporos Int 16(5):447–455
2. Freemantle N, Cooper C, Diez-Perez A, Gitlin M, Radcliffe H, Shepherd S, Roux C (2013) Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. Osteoporos Int 24(1):209–217
3. van Boven JF, de Boer PT, Postma MJ, Vegter S (2013) Persistence with osteoporosis medication among newly-treated osteoporotic patients. J Bone Miner Metab 31(5):562–570
4. Netelenbos JC, Geusens PP, Ypma G, Buijs SJ (2011) Adherence and profile of non-persistence in patients treated for osteoporosis—a large-scale, long-term retrospective study in The Netherlands. Osteoporos Int 22(5):1537–1546
5. Imaz I, Zegarra P, Gonzalez-Enriquez J, Rubio B, Alcazar R, Amate JM (2010) Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. Osteoporos Int 21(11):1943–1951
6. Landfeldt E, Lundkvist J, Strom O (2011) The societal burden of poor persistence to treatment of osteoporosis in Sweden. Bone 48(2): 380–388
7. Hiligsmann M, Rabenda V, Bruyere O, Reginster JY (2010) The clinical and economic burden of non-adherence with oral bisphosphonates in osteoporotic patients. Health Policy 96(2):170–177
8. Hiligsmann M, Rabenda V, Gathon HJ, Ethgen O, Reginster JY (2010) Potential clinical and economic impact of nonadherence with osteoporosis medications. Calcif Tissue Int 86(3):202–210
9. Elias MN, Burden AM, Cadarette SM (2011) The impact of pharmacist interventions on osteoporosis management: a systematic review. Osteoporos Int 22(10):2587–2596
10. Stuurman-Bieze AG, Hiddink EG, van Boven JF, Vegter S (2013) Proactive pharmaceutical care interventions improve patients' adherence to lipid-lowering medication. Ann Pharmacother 47(11):1448–1456
11. Vegter S, Oosterhof P, Van Boven JF, Stuurman-Bieze AG, Hiddink EG, Postma MJ (2014) Improving adherence to lipid-lowering therapy in a community pharmacy intervention program: a cost-effectiveness analysis. J Manag Care Pharm in press
12. Yeaw J, Benner JS, Walt JG, Sian S, Smith DB (2009) Comparing adherence and persistence across 6 chronic medication classes. J Manag Care Pharm 15(9):728–740
13. Visser ST, Schuiling-Veninga CC, Bos JH, de Jong-van den Berg LT, Postma MJ (2013) The population-based prescription database IADB.nl: its development, usefulness in outcomes research and challenges. Exp Rev Pharmacoecon Outcome Res 13(3):285–292
14. Vegter S, Nguyen NH, Visser ST, de Jong-van den Berg LT, Postma MJ, Boersma C (2011) Compliance, persistence, and switching patterns for ACE inhibitors and ARBs. Am J Manag Care 17(9):609–616
15. Stuurman-Bieze AG, Hiddink EG (2010) Apotheekteam verbetert therapietrouw osteoporosemedicatie door gestructureerde medicatiebegeleiding en geautomatiseerde opsporing van suboptimale farmacotherapie. PW Wetenschappelijk Platf 4(7/8): 128–135 [article in Dutch]
16. McDonough RP, Doucette WR, Kumbera P, Klepser DG (2005) An evaluation of managing and educating patients on the risk of glucocorticoid-induced osteoporosis. Value Health 8(1):24–31
17. Crockett JA, Taylor SJ, McLeod LJ (2008) Patient responses to an integrated service, initiated by community pharmacists, for the prevention of osteoporosis. Int J Pharm Pract 16:65–72
18. Yuksel N, Majumdar SR, Biggs C, Tsuyuki RT (2010) Community pharmacist-initiated screening program for osteoporosis: randomized controlled trial. Osteoporos Int 21(3):391–398
19. Lai PS, Chua SS, Chew YY, Chan SP (2011) Effects of pharmaceutical care on adherence and persistence to bisphosphonates in postmenopausal osteoporotic women. J Clin Pharm Ther 36(5):557–567
20. Gleeson T, Iversen MD, Avorn J, Brookhart AM, Katz JN, Losina E, May F, Patrick AR, Shrank WH, Solomon DH (2009) Interventions to improve adherence and persistence with osteoporosis medications: a systematic literature review. Osteoporos Int 20(12):2127–2134
21. Cooper A, Drake J, Brankin E (2006) PERSIST investigators: treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. Int J Clin Pract 60(8):896–905
22. Elders PJM, Dinant GJ, Van Geel T, Maartens LWF, Merlijn T, Geijer RMM, Geraets JJXR (2012) NHG-Standaard Fractuurpreventie (tweede herziening). Huisarts Wet 55:452–458